ISSN: 1309-470X
e-ISSN: 1309-5994

ACIBADEM
MEHMET ALİ AYDINLAR ÜNİVERSİTESİ
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ACIBADEM ÜNİVERSİTESİ

SAĞLIK BİLİMLERİ DERGİSİ

Volume:16, Issue:1, January 2025

ACIBADEM ÜNİVERSİTESİ

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Volume: 16, Issue: 1, January 2025

ISSN: 1309-470X
e-ISSN: 1309-5994

YAYIN TÜRÜ
Hakemli Süreli Yayın
(Dergi, yılda 4 sayı olarak Ocak, Nisan, Temmuz, Ekim aylarında yayımlanır)

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ACIBADEM ÜNİVERSİTESİ

Volume: 16, Issue: 1, January 2025

HEALTH SCIENCES JOURNAL

ISSN: *1309-470X*
e-ISSN: *1309-5994*

JOURNAL TYPE
Refereed Periodicals
(The journal is published four times a year in January, April, July and October)

JOURNAL OWNER
On behalf of Acıbadem Mehmet Ali Aydınlar University
Rector, Prof. Dr. Ahmet Şahin

EDITOR
Prof. Dr. Enis Özyar

DEPUTY EDITOR
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Acıbadem University Health Sciences Journal Acıbadem University, School of Medicine Kayışdağı Cad. No: 32 34752 Ataşehir / İstanbul
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e-mail : editor@acibadem.edu.tr

Acıbadem University Health Sciences Journal
İndexed in ULAKBİM TR Dizin, EBSCO, Google Scholar, Crossref, ROAD Directory of Open Access Scholarly Resources, Turkish Medline, Academi index ve İndex of Academic Journals and Türkiye Atıf Dizini.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1569618

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Bioelectronics, Bioengineering / Biyoelektronik, Biyomühendislik

Clinical Validation of a Custom Wearable Patch for Accurate and Comfortable Vital Sign Monitoring in Pediatric Patients

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Received: 18.10.2024
Accepted: 11.11.2024

ABSTRACT

Background/Purpose: Measuring vital signs in pediatric patients requires special consideration and adaptation due to varying anatomy and wide age range. In addition, children's anxiety, uncooperativeness, and high activity levels further complicate measurements, necessitating devices and algorithms designed to minimize the inaccuracies and discomfort. In this work, the performance of a custom wearable patch mounted on the mid-sternum was validated in uncontrolled settings on a cohort including 84 pediatric patients.

Methods: Three-minute-long electrocardiogram (ECG), seismocardiogram (SCG) and photoplethysmogram (PPG) signals were acquired using the custom patch. First, pre-processing and signal smoothing algorithms were employed to suppress the out-of-band and motion noise. Two different tasks were then studied: (i) Heart rate (HR) and respiration rate were derived from the ECG, PPG and SCG signals individually. During HR derivation from the SCG, a novel Teager-energy-based HR estimation algorithm was proposed. (ii) Clinical relevance of the SCG signals was shown through mapping the SCG characteristics to body mass index (BMI) and blood pressure values.

Results: While the best HR estimation was achieved through the PPG-infrared signal with an absolute error of 2.2±2.1 bpm, the best respiration estimation was achieved with PPG-Red signal with an error of 2.6±2.2 breaths/min. On the other hand, regression models resulted in a minimum of 85% confidence interval, revealing that the SCG characteristics indeed have salient correlation with the BMI and blood pressure values.

Conclusion: Overall, the proposed patch and corresponding algorithms could potentially be leveraged for measuring vital signs from pediatric patients in clinical settings by minimizing the inaccuracies and discomfort encountered.

Keywords: Biomedical signal processing; Hemodynamic parameters; Wearable systems; Electrocardiogram; Seismocardiogram; Photoplethysmogram

ÖZET

Amaç: Pediatrik hastalarda yaşamsal parametrelerin ölçülmesi, değişken anatomi ve geniş yaş aralığı nedeniyle özel dikkat ve adaptasyon gerektirmektedir. Buna ek olarak, çocukların anksiyetesi, yeterince işbirliği yapmaması ve yüksek aktivite seviyeleri ölçümleri daha da karmaşık hale getirmektedir. Bu nedenle hataları ve kullanıcı rahatsızlığını en aza indirmek için tasarlanmış cihazlara ve algoritmalara büyük bir ihtiyaç vardır. Bu çalışmada, 84 pediatrik hastayı içeren bir kohort üzerinde, kontrolsüz ortamlarda, orta sternuma yerleştirilen özel bir giyilebilir yamanın performansı valide edilmiştir.

Yöntem: Yama kullanılarak üç dakikalık elektrokardiyogram (EKG), sismokardiyogram (SCG) ve fotopletismogram (PPG) sinyalleri kaydedilmiştir. İlk olarak, bant dışı ve hareket gürültüsünü bastırmak için ön işleme ve sinyal yumuşatma algoritmaları kullanılmıştır. Ardından iki farklı analiz üzerinde çalışılmıştır: (i) Nabız ve solunum hızı, EKG, PPG ve SCG sinyallerinden ayrı ayrı türetilmiştir. SCG'den nabız türetme sırasında, yeni bir Teager-enerji tabanlı HR tahmin algoritması önerilmiştir. (ii) SCG sinyallerinin klinikte kullanılabilirliği, SCG özelliklerinin vücut kitle indeksi (BMI) ve kan basıncı değerleriyle eşleştirilmesiyle değerlendirilmiştir.

Bulgular: En iyi nabız tahmini 2.2±2.1 bpm mutlak hata ile PPG-kızılötesi sinyali ile elde edilirken, en iyi solunum tahmini 2.6±2.2 nefes/dak hata ile PPG-Kırmızı sinyalinden elde edilmiştir. Öte yandan, regresyon modelleri minimum %85 güven aralığıyla sonuçlanmış ve SCG özelliklerinin BMI ve kan basıncı değerleri ile belirgin bir korelasyona sahip olduğunu ortaya koymuştur.

Sonuç: Önerilen yama ve ilgili algoritmalar, klinik ortamlarda karşılaşılan yanlışlıkları ve rahatsızlıkları en aza indirerek pediatrik hastaların yaşamsal belirtilerini ölçmek için potansiyel olarak kullanılabilir.

Anahtar Kelimeler: Biyomedikal sinyal işleme; Hemodinamik parametreler; Giyilebilir sistemler; Elektrokardiyogram; Sismokardiyogram; Fotopletismogram

Each year, pediatric clinics around the world admit millions of young patients, encompassing a diverse spectrum of medical needs and conditions. Based on the National Health Interview Survey reported by the Centers for Disease Control and Prevention, 95.0% of the children had a visit with a health care professional in 2023 (1). The clinical assessments during these visits often involve assessing vital signs like heart rate, respiration, blood pressure, and temperature, along with heart, lung, and vascular evaluations. Such assessments support accurate diagnosis, monitor treatment, and help ensure the well-being of pediatric patients globally (2-4).

Measuring vital signs in pediatric patients presents unique challenges, as devices designed for adults may not be suitable for children's smaller size, wider age range (from newborns to adolescents) and anatomical features (5). Indeed, pediatric devices tend to be less advanced and available compared to adult devices, often trailing by up to around 10 years in technological development (6). Second, children may be anxious or uncooperative during vital sign assessments, introducing motion artifacts and affecting the reliability of readings (2). It has been found that 91% of children reported fear related to medical procedures, with 28% associating clinical exams with pain and 29% being scared of nursing activities (7). Thus, devices and algorithms for pediatric population should be designed in a way that the discomfort and inaccuracies are minimized.

Physiological signals like the electrocardiogram (ECG), seismocardiogram (SCG) and photoplethsmogram (PPG) are essential in wearables, as they directly originate from the underlying physiology. The ECG assesses the heart's electrical activity, while the SCG detects vibrations originating from heart contractions, with peaks and valleys reflecting cardiac events like aortic opening (AO), mitral closing (MC), etc. (8). Recent studies have utilized the SCG signal for various applications, ranging from estimating hemodynamic parameters to assessing valvular heart diseases (9-14). Finally, the PPG detects changes in light absorption caused by variations in arterial blood volume during the cardiac cycle. Analyzing PPG provides insights into blood oxygen levels, blood pressure, and vascular resistance (15-18). Thus, integrating physiological signals into wearable devices is a major advancement in healthcare, enhancing preventive care and supporting better health outcomes worldwide (19).

In this work, *for the first time*, the performance of a custom wearable patch was investigated in *uncontrolled settings* on a cohort including 84 pediatric patients visiting Koc University Hospital. The study involved the continuous acquisition of 3-minute-long ECG, tri-axial SCG and PPG (red and infra-red) signals. After pre-processing, heart rate (HR) and respiration rate were calculated using novel signal processing pipelines. Clinical relevance was assessed by performing regression analyses that mapped SCG features to body mass index (BMI) and blood pressure values.

Material and Methods

In this work, we adapted our previously developed custom wearable patch and, *for the first time*, validated its clinical performance in uncontrolled settings on a cohort including 84 pediatric patients visiting Koc University Hospital from March to April 2024. Figure 1 shows the patch's hardware layers and attachment locations.

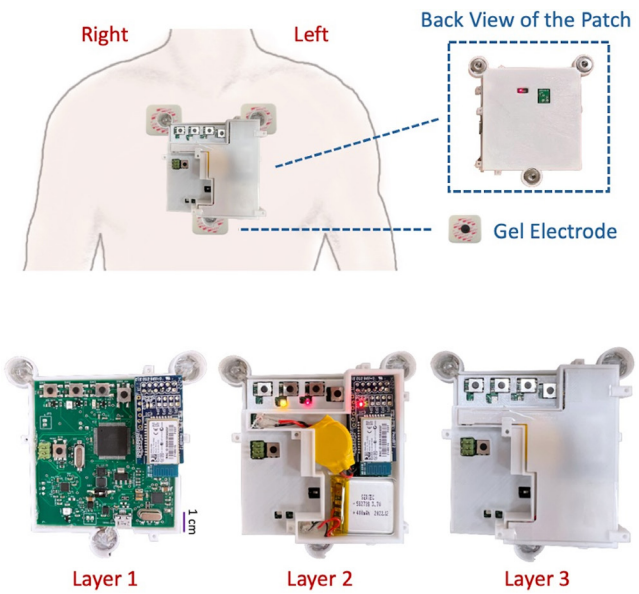


Figure 1: The wearable patch used in data collection

2.1 Custom Hardware

The SCG and PPG were acquired using an ADXL355 accelerometer (at 500 Hz) and a MAX30102 sensor (at 200 Hz), respectively. The ECG was recorded with an AD8232 analog front-end integrated circuit, through three gel electrodes to form Einthoven's triangle. Skin temperature was measured using an LMT70A sensor. The ECG and temperature were sampled at 500 Hz and 25 Hz with 10-bit resolution. As the microcontroller, ATMEGA2560 was used. Data was written to a file on a microSD card, with file naming controlled by the DS3231 real-time clock. The system ran on a 400 mAh Lithium-Polymer battery, charged via an LTC4062 charger, with hardware interrupts for optimized power management. The hardware and firmware specifications are detailed in (20).

2.2 Data Collection Protocol

The study was conducted under a protocol approved by the Koc University Institutional Review Board (2023.408.IRB2.089) and all parents/guardians have provided their written consent. 84 children were participated in the study. Before data collection, the baseline values for the body temperature, oxygen saturation (SpO2), heart rate (HR), and systolic and diastolic blood pressures (SBP and DBP) were measured. The demographics and baseline hemodynamic parameters are presented in Table I.

Table 1. Subject demographics (mean ± std)

Age (years) 9.1 ± 4.3	**Weight** (kg) 33.9 ± 18.3	**Height** (cm) 131.4 ± 26.3
BMI (kg/m^2) 18.1 ± 3.9	**Gender** 50.0 % Female 50.0 % Male	**Chronic Disease** 26.6 % Yes 71.4 % No
Heart Rate (bpm) 103.8 ± 22.7	**Temperature** (Celsius) 37.0 ± 0.6	**SpO_2** (%) 96.7 ± 3.6
Respiration Rate (breaths/min) 23.4 ± 4.1	**Systolic BP** (mmHg) 109.4 ± 14.0	**Diastolic BP** (mmHg) 74.4 ± 12.5

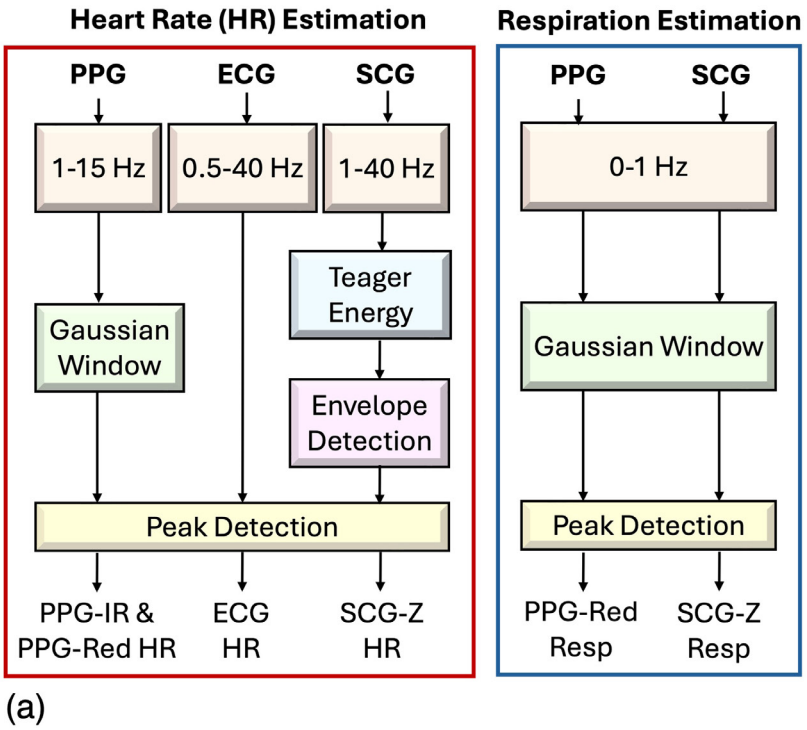
Data collection took place in a room in pediatric clinic without specific environmental restrictions, as factors like sound, humidity, and lighting did not impact the signals. The patch was placed on the mid-sternum using three gel electrodes, and to minimize motion artifacts, subjects sat still in a relaxed state for three minutes. The ECG, SCG and PPG signals were acquired continuously with sampling rates of 500, 500 and 200 Hz, respectively. The start and end moments of the three-minute period were determined by gently tapping on the patch, generating two distinct peaks on the SCG signals. The challenges regarding the clinical implementation are covered in the Discussion section.

Analyses were conducted on the entire dataset, followed by sub-group analyses based on:

- *Age groups:* Pre-school ($y < 6$, $n = 20$, 4.2 ± 1.3), Elementary-school ($6 \leq y < 11$, $n = 37$, 8.0 ± 1.2), Middle-school ($11 \leq y < 14$, $n = 8$, 11.3 ± 0.7), and High-school ($14 \leq y \leq 18$, $n = 19$, 15.7 ± 1.3).
- *Gender:* 42 subjects each for female and male groups.
- *Chronic disease status:* 24 subjects with chronic disease and 60 without

2.3 Signal Pre-Processing

After data collection, signal processing pipelines for estimating hemodynamic parameters were developed (Figure 2(a)). The signals were filtered with Kaiser window FIR bandpass filters to reduce noise while maintaining signal integrity. To calculate the heart rate, cut-off frequencies of 1-15 Hz for PPG, 0.5-40 Hz for ECG, and 1-40 Hz for SCG were used as per the literature (21, 22). Figure 3 shows representative four-second segments of filtered ECG, SCG, and PPG signals from one subject.



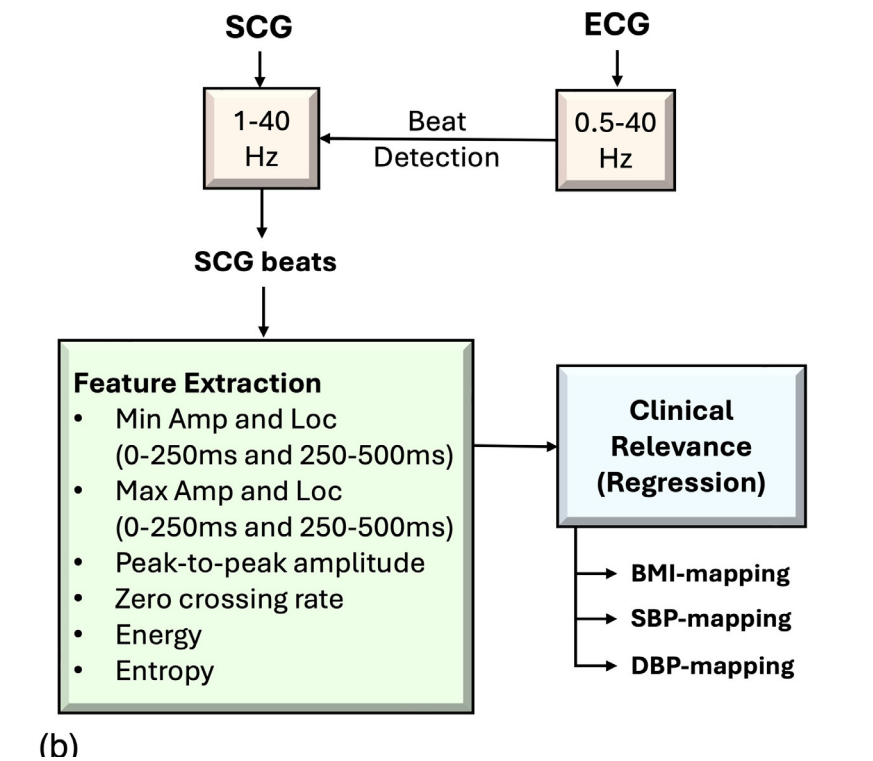


Figure 2: (a) Pre-processing and signal processing pipelines for the estimation of hemodynamic parameters, **(b)** Pre-processing and signal processing pipelines for the clinical relevance assessment tasks, *Min: minimum, Max: maximum, Amp: amplitude, Loc: location, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure*

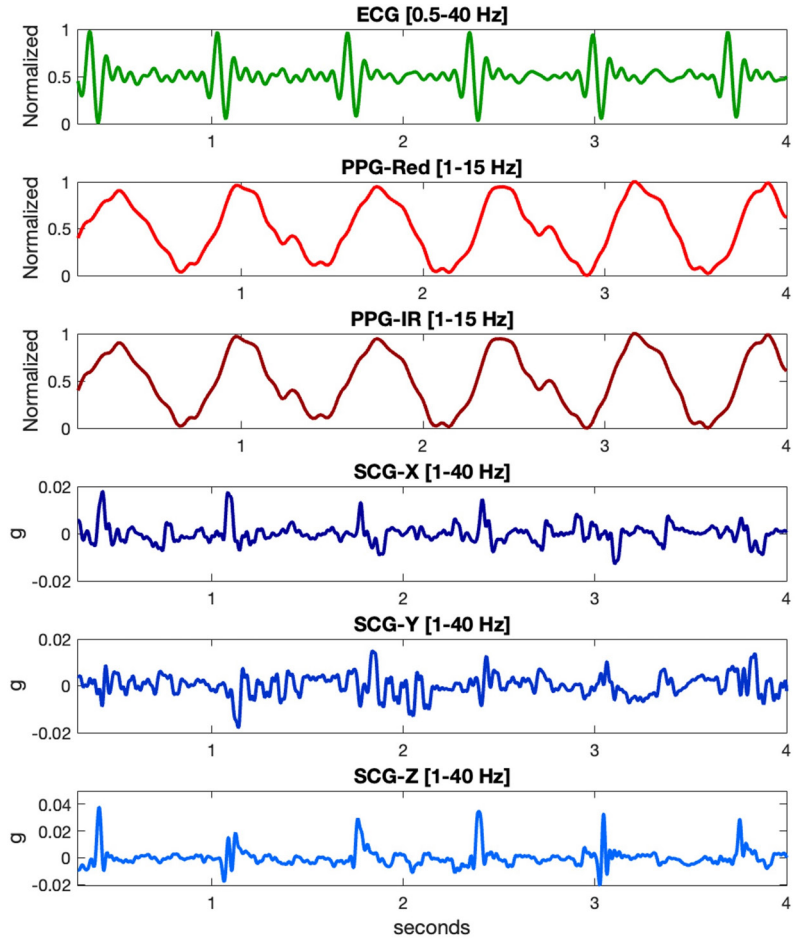


Figure 3: Four-second long segments of the collected signals

On the other hand, the frequencies below 1 Hz represent the respiration information corresponding to the respiration-induced chest movements (23). Hence, while extracting respiratory information from the SCG and PPG signals, the original raw signals were filtered using an upper cut-off frequency as 1 Hz. The PPG and SCG signals were then Gaussian filtered to remove the motion artifacts for ease of peak detection. The Gaussian window was applied to the signal, averaging the points to smooth high-frequency noise while retaining signal characteristics. The Gaussian window and width factor (alpha) values were determined heuristically to ensure that the signals were not over-smoothed (losing fiducial points) or under-smoothed (having redundant fluctuations). For the PPG and SCG signals, the window size and width factor pairs were selected as (25, 2.3) and (250, 2.3), respectively, in alignment with the corresponding sampling rates.

2.4 Estimation Hemodynamic Parameters

2.4.1 Estimation of Heart Rate from ECG and PPG Signals

To compute the HR values from the collected signals, the following steps were implemented:

1) As the reference values, the baseline HR measurements acquired prior to data collection were used.

2) For the ECG-based computation, the filtered signal (0.5-40 Hz) was first normalized. Then, the R-peaks were detected with a simple peak detection algorithm (minimum peak height: 0.6, minimum peak distance: 0.33 of the sampling rate). The consecutive R-peak intervals formed an RR difference vector, which was used to calculate heart rate (HR) in beats per minute (bpm) using Equation 1.

3) For the PPG-based computation, the time intervals between the consecutive peaks on the filtered (1-15 Hz) and Gaussian-windowed red and infrared PPG signals were computed, and stored as a PP difference vector, similar to the ECG case.

4) Equations 2 and 3 were used to calculate the mean absolute error (MAE) and percentage error, where 'actual' refers to the reference HR values and 'calculated' refers to the HR values derived from the ECG, PPG-red, and PPG-infrared signals *(Fs: sampling rate, std: standard deviation)*.

$$HR = \frac{60*Fs}{mean(RR)} \quad (1)$$

$$MAE = |actual - calculated| \quad (2)$$

$$\%\ error = \frac{|actual-calculated|}{actual} * 100 \quad (3)$$

2.4.2 Teager-Operator-based Heart Rate Estimation from SCG Signals

The Teager energy operator, derived from the energy of an oscillator, detects instantaneous changes in signals, such as amplitude variations, frequency shifts, or discontinuities (24). In our previous work, the Teager operator was leveraged to locate the clicks in the joint sound signals acquired from the children with juvenile idiopathic arthritis (25). When an SCG signal is considered, detecting the aortic opening (AO) points using a simple peak detection algorithm can be challenging as (i) there are additional neighboring peaks representing mitral closing (MC) and aortic closing (AC) moments, and (ii) there are added noise due to motion artifacts and signal variability, which make AO points more subtle. Hence, we hypothesized that the Teager energy operator could accurately locate AO points, even when simple peak detection algorithms fail.

For any discrete-time signal , the Teager energy () at time is calculated using the three consecutive samples of the signal as in Equation 4.

$$\Psi_{TE}[n] = x[n]^2 - x[n+1]x[n-1] \quad (4)$$

In this work, the Teager energy of the filtered SCG-Z signal (1-40 Hz) was calculated (Equation 4). The upper envelope of the Teager operator was then generated to emphasize significant peaks representing the AO points (26). The time intervals between consecutive spikes were computed, and their mean value was used to calculate the HR (Equation 1). Error calculations were done using Equations 2 and 3.

2.4.3 Estimation of Respiration

To calculate the respiration rate, two different approaches (SCG-Z-based and PPG-Red-based) were used. PPG-Red was chosen over PPG-IR, as it is less prone to motion artifacts due to relatively lower wavelength. As previously explained, both signals were filtered between 0-1 Hz and smoothed with a Gaussian window. Peak-to-peak intervals were then calculated, with the peak-valley transitions corresponding to exhalation-inhalation cycles, where each peak-to-peak duration represents a full respiration cycle. The resulting peak-to-peak vector was then used in an equation similar to Equation 1, and respiration rate in breaths/min was calculated. The errors were again calculated using Equations 2 and 3.

2.4.4 Investigating the Clinical Relevance of SCG

The clinical relevance of SCG signal characteristics was assessed by correlating them with physiological parameters (Figure 2(b)). The R-peaks from the ECG (0.5-40 Hz) were leveraged to divide the SCG-Z (1-40 Hz) into individual beats, each truncated to the minimum R-R interval length. A total of 13,603 SCG-Z beats from 84 subjects were analyzed, extracting 12 temporal features per beat (27): the minimum and maximum amplitudes and corresponding locations within the systolic (0-250ms) and diastolic (250-500ms) portions, peak-to-peak amplitude, energy, entropy and zero-crossing rate. Three XGBoost regression models were trained to map the SCG characteristics to body mass index (BMI), sytolic blood pressure (SBP), and diastolic blood pressure (DBP), with performances validated using 5-fold cross-validation and assessed by mean absolute percentage error (MAPE).

Results

3.4.1 Estimation of Heart Rate from ECG and PPG Signals

The absolute and percentage errors for ECG and PPG-based calculations were presented in Table 2, and the boxplots for absolute errors are shown in Figure 4. While the ECG-derived resulted in an absolute and percentage errors of 4.9 ± 6.7 bpm and 4.7 ± 6.8 %, respectively; these values were 2.5 ± 2.4 bpm and 2.3 ± 1.9 % for the PPG-Red, and 2.2 ± 2.1 bpm and 2.1 ± 1.9 % for the PPG-IR.

3.4.2 Teager-Operator-based Heart Rate Estimation from SCG Signals

Figure 5(a) shows a 10-second SCG signal and its Teager energy plot. While some SCG segments (green box) were clean enough for accurate peak detection, others (yellow box) contained motion noise. Direct peak detection in the noisy regions would thus be unreliable, but the Teager operator successfully identified the AO peaks in these areas, allowing for accurate HR computation. Our algorithm yielded absolute and percentage errors of 4.6 ± 5.4 bpm and 4.4 ± 6.0 %, respectively (Table 2). This result was indeed comparable to the one obtained from ECG and suggests a confidence interval of at least 95%. The corresponding boxplots for absolute errors are shown in Figure 4.

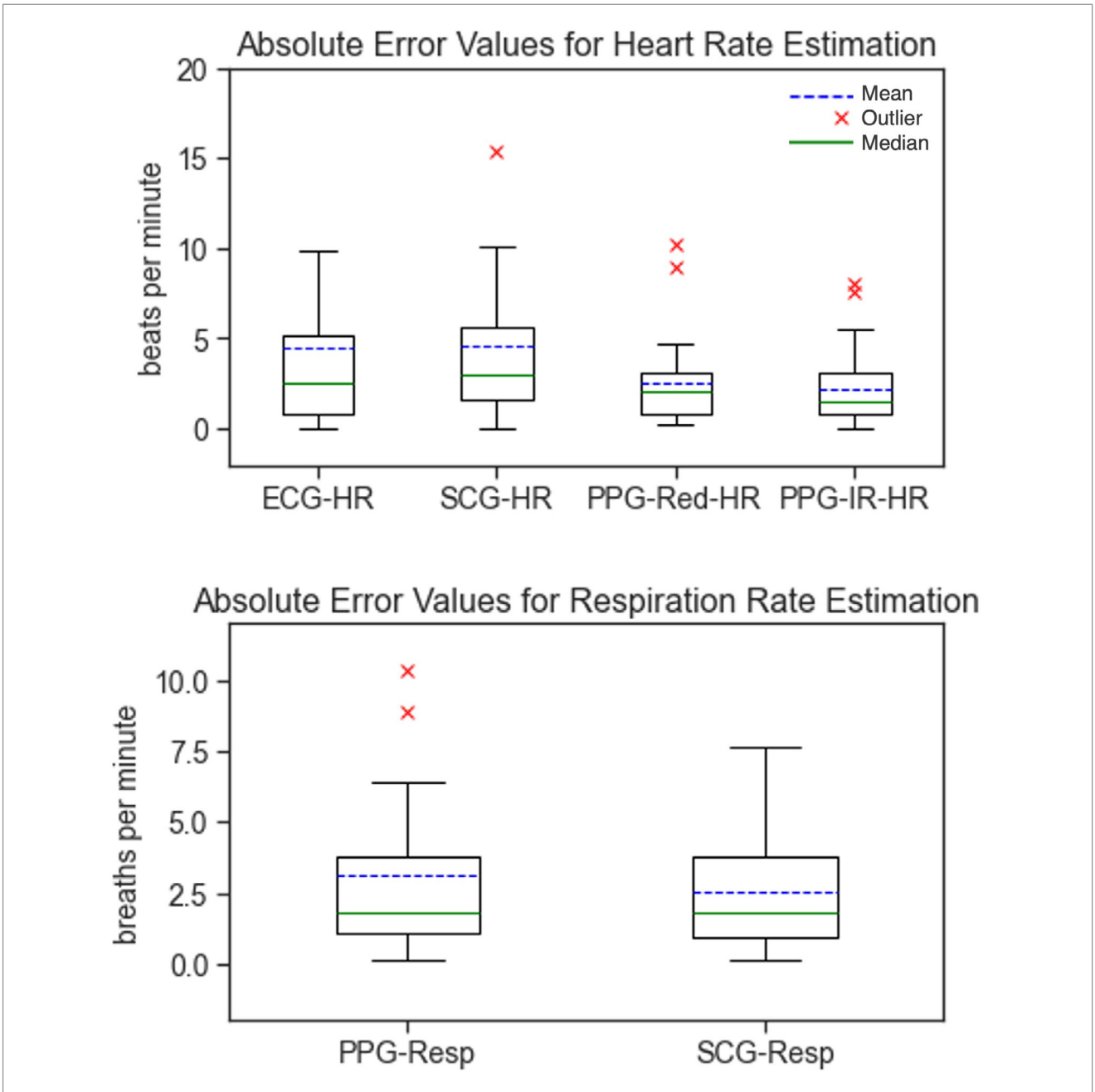


Figure 4: Box plots representing the absolute error values for heart rate and respiration rate estimation tasks.

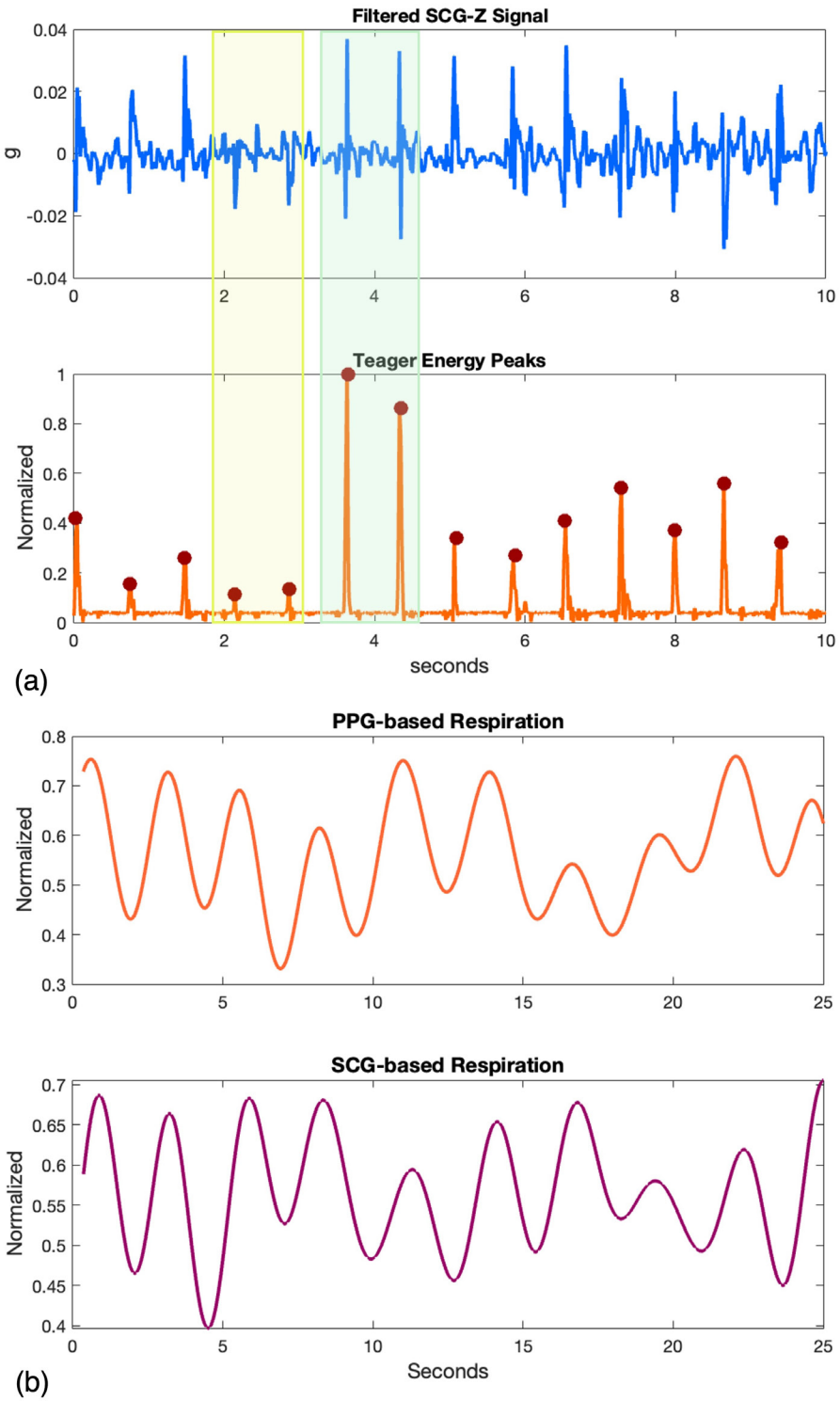


Figure 5: (a) Teager energy operator of a 10-second long SCG segment and detected beats, **(b)** Five-second long respiration signals derived from SCG and PPG signals

3.4.3 Estimation of Respiration

To derive the respiration information, an SCG-Z-based and PPG-Red-based derivation pipelines were used and compared. Sample five-second-long segments from the resulting signals are presented in Figure 5(b). As seen, the oscillation patterns are the same with a slight variance in the amplitude values. This was expected as the sensors are located in different regions on the patch. The estimated respiration rates are presented in Table 2. While the respiration rate estimated from PPG-Red resulted in an absolute error and percentage error of 2.6 ± 2.2 breaths/min and 11.5 ± 10.3 %; these results were 3.1 ± 3.2 breaths/min and 12.9 ± 11.1 % for the SCG-Z-based derivation.

3.4.4 Investigating the Clinical Relevance of SCG

For the BMI-, SBP- and DBP-mapping tasks, the train and test MAPE pairs were (11.3%, 14.4%), (9.7%, 11.5%) and (9.2%, 11.1%), respectively (Table 2). Overall, all models resulted in a minimum of 85% confidence interval, revealing that the SCG characteristics indeed have salient correlation with the BMI, SBP and DBP values.

Table 2. Estimated Cardiovascular Parameters (mean ± std) and results for the regression tasks

	Absolute Error	**Percentage Error**
ECG HR	4.9 ± 6.7 bpm	4.7 ± 6.8 %
PPG-Red HR	2.5 ± 2.4 bpm	2.3 ± 1.9 %
PPG-IR HR	2.2 ± 2.1 bpm	2.1 ± 1.9 %
SCG HR	4.6 ± 5.4 bpm	4.4 ± 6.0 %
PPG-Red Respiration	2.6 ± 2.2 breaths/min	11.5 ± 10.3 %
SCG-Z Respiration	3.1 ± 3.2 breaths/min	12.9 ± 11.1 %
Clinical Relevance (Regression Task)		
	5-fold Train MAPE	**5-Fold Test MAPE**
BMI-mapping	11.3% error (88.7% confidence)	14.4% error (85.6% confidence)
SBP-mapping	9.7% error (90.3% confidence)	11.5% error (88.5% confidence)
DBP-mapping	9.2% error (90.8% confidence)	11.1% error (88.9% confidence)

Sub-group results revealed a general decrease in error rates for both heart rate and respiration rate measurements as age increases (Table 3). When the effect of gender was investigated, male patients showed relatively lower errors in heart rate estimation and regression tasks, while females exhibited lower errors in respiration rate analysis (Table 4). On the other hand, for all analyses, patients with chronic disease resulted in lower errors compared to the ones not having.

Table 3. Sub-group Analysis for Different Age Groups (mean ± std)

		Heart Rate			
		ECG	**SCG**	**PPG-Red**	**PPG-IR**
Pre-School (y < 6)	Abs err	8.1 ± 10.1 bpm	7.3 ± 8.4 bpm	5.1 ± 4.3 bpm	3.3 ± 3.4 bpm
	% error	7.7 ± 11.0 %	6.6 ± 9.1 %	3.9 ± 3.1 %	2.8 ± 2.7 %
Elem-School (6 ≤ y < 11)	Abs err	4.6 ± 6.2 bpm	4.0 ± 4.5 bpm	**1.7 ± 1.3 bpm**	**1.4 ± 1.0 bpm**
	% error	4.2 ± 5.6 %	3.8 ± 4.2 %	1.6 ± 1.1 %	1.3 ± 0.9 %
Mid-School (11 ≤ y < 14)	Abs err	3.6 ± 2.9 bpm	4.7 ± 3.3 bpm	3.2 ± 1.4 bpm	5.9 ± 2.9 bpm
	% error	3.5 ± 2.8 %	4.3 ± 3.2 %	3.0 ± 1.9 %	5.5 ± 3.4 %
High-School (14 ≤ y ≤ 18)	Abs err	**2.9 ± 3.1 bpm**	**3.3 ± 4.3 bpm**	**2.1 ± 1.3 bpm**	**2.3 ± 1.2 bpm**
	% error	3.3 ± 4.3 %	3.9 ± 6.8 %	2.3 ± 1.7 %	2.5 ± 1.6 %

		Respiration Rate	
		SCG	**PPG**
Pre-School (y < 6)	Abs err	5.0 ± 3.0 breath/min	7.3 ± 4.8 breath/min
	% error	19.3 ± 11.5 %	26.4 ± 14.8 %
Elem-School (6 ≤ y < 11)	Abs err	2.1 ± 1.7 breath/min	2.2 ± 1.6 breath/min
	% error	10.1 ± 10.2 %	10.1 ± 7.4 %
Mid-School (11 ≤ y < 14)	Abs err	3.4 ± 2.7 breath/min	2.7 ± 1.4 breath/min
	% error	17.4 ± 12.8 %	14.1 ± 6.4 %
High-School (14 ≤ y ≤ 18)	Abs err	**1.3 ± 0.7 breath/min**	**2.0 ± 2.6 breath/min**
	% error	5.7 ± 3.2 %	8.4 ± 10.8 %

		Clinical Relevance (Regression Task) – 5 fold		
		SBP	**DBP**	**BMI**
Pre-School (y < 6)	Train Mape	4.8 ± 0.6 %	9.2 ± 1.2 %	4.9 ± 0.1 %
	Test Mape	6.5 ± 0.5 %	11.9 ± 0.8 %	6.8 ± 0.5 %
Elem-School (6 ≤ y < 11)	Train Mape	6.2 ± 0.5 %	7.9 ± 0.1 %	9.1 ± 0.1 %
	Test Mape	7.9 ± 0.3 %	10.4 ± 0.5 %	12.0 ± 0.5 %
Mid-School (11 ≤ y < 14)	Train Mape	4.6 ± 0.4 %	3.9 ± 0.1 %	4.4 ± 0.1 %
	Test Mape	5.4 ± 0.2 %	**5.5 ± 0.6 %**	**6.1 ± 0.3 %**
High-School (14 ≤ y ≤ 18)	Train Mape	3.9 ± 0.1%	4.9 ± 0.1 %	8.4 ± 0.1 %
	Test Mape	**5.3 ± 0.3 %**	6.4 ± 0.2 %	11.3 ± 0.5 %

Table 4. Sub-group Analysis for Different Genders and Chronic Disease Conditions (mean ± std)

GENDER-BASED GROUPING		Heart Rate			
		ECG	SCG	PPG-Red	PPG-IR
Female	Abs err	5.2 ± 6.7 bpm	5.2 ± 5.4 bpm	3.0 ± 2.9 bpm	2.3± 2.0 bpm
	% error	5.4 ± 7.7 %	5.4 ± 6.9 %	2.6 ± 2.1 %	2.3 ± 2.1 %
Male	Abs err	**4.5 ± 6.6 bpm**	**3.9 ± 5.5 bpm**	**1.9 ± 1.4 bpm**	**2.2 ± 2.1 bpm**
	% error	4.0 ± 5.7 %	3.3 ± 4.7 %	1.9 ± 1.5 %	1.9 ± 1.6 %

DISEASE-BASED GROUPING		Heart Rate			
		ECG	SCG	PPG-Red	PPG-IR
Chronic Disease	Abs err	**2.7 ± 2.6 bpm**	**3.2 ± 3.7 bpm**	**1.3 ± 1.2 bpm**	**1.7 ± 1.2 bpm**
	% error	2.8 ± 3.6 %	3.6 ± 5.7 %	1.3 ± 1.3 %	1.6 ± 1.1 %
NO Chronic Disease	Abs err	5.9 ± 7.6 bpm	5.2 ± 6.0 bpm	2.8 ± 2.5 bpm	2.4 ± 2.2 bpm
	% error	5.6 ± 7.7 %	4.8 ± 6.1%	2.5 ± 1.9 %	2.2 ± 2.1 %

GENDER-BASED GROUPING		Respiration Rate	
		SCG	PPG
Female	Abs err	**2.5 ± 2.4 breath/min**	**2.9 ± 3.1 breath/min**
	% error	11.6 ± 12.1 %	12.2 ± 11.1 %
Male	Abs err	2.6 ± 2.1 breath/min	3.4 ± 3.3 breath/min
	% error	11.4 ± 8.3 %	13.9 ± 11.0 %

DISEASE-BASED GROUPING		Respiration Rate	
		SCG	PPG
Chronic Disease	Abs err	**1.9 ± 2.3 breath/min**	**0.2 ± 0.1 breath/min**
	% error	10.7 ± 15.1 %	4.3 ± 4.5 %
NO Chronic Disease	Abs err	2.7 ± 2.2 breath/min	3.7 ± 3.3 breath/min
	% error	11.7 ± 9.0 %	15.3 ± 11.2 %

GENDER-BASED GROUPING		Clinical Relevance (Regression Task) – 5 fold		
		SBP	DBP	BMI
Female	Train Mape	9.5 ± 0.4 %	8.4 ± 0.1 %	10.4 ± 0.1 %
	Test Mape	11.2 ± 0.3 %	11.1 ± 0.3 %	13.9 ± 0.5 %
Male	Train Mape	7.5 ± 0.7 %	6.1 ± 0.1 %	9.9 ± 0.1 %
	Test Mape	**9.4 ± 0.2 %**	**8.3 ± 0.2 %**	**12.9 ± 0.3 %**

DISEASE-BASED GROUPING		Clinical Relevance (Regression Task) – 5 fold		
		SBP	DBP	BMI
Chronic Disease	Train Mape	5.9 ± 0.1 %	7.1 ± 0.1 %	10.5 ± 0.1%
	Test Mape	**8.1 ± 0.3 %**	**9.5 ± 0.5 %**	**12.4 ± 5.7 %**
NO Chronic Disease	Train Mape	10.2 ± 0.2 %	9.1 ± 0.1 %	10.5 ± 0.1%
	Test Mape	12.1 ± 1.7 %	11.1 ± 0.4 %	13.6 ± 0.4 %

Discussion

PPG-derived HR trials resulted in lower errors than ECG-derived HR, contrary to the expectations. This may be due to two factors: (i) The ECG signal quality was compromised by motion and contact loss between the skin and electrodes, as children often get nervous and sweat in clinical settings. (ii) PPG signals were smoothed with a Gaussian window, reducing oscillations and noise while preserving key peaks, making peak detection more accurate.

On the other hand, deriving HR from SCG has always been challenging due to the noise from movement and complex waveform. Additionally, it contains multiple neighbouring peaks corresponding to various cardiac phases, making AO point identification difficult. Our proposed approach's superior performance has been compared with the common methods in the literature as well (Table 5). These methods were including direct peak detection, template matching with correlation computation (28) and wavelet decomposition (29). Among these, the closest results were obtained when wavelet decomposition was used, whereas template matching and direct peak detection suffered from inaccuracies due to motion-related variation in the SCG morphology. Hence, given SCG's common use in wearable systems, this Teager-based method can enhance vital parameter monitoring while reducing computational and hardware demands.

Table 5. Comparison with the literature for the SCG-based HR methods

METHOD		Absolute Error	% Error
Direct Peak Detection	Without envelope	6.4 ± 6.2 bpm	6.1 ± 6.2 %
	With envelope	5.9 ± 7.1 bpm	5.8 ± 7.4 %
Template Matching with Correlation Computation (28)		16.1 ± 14.9 bpm	17.3 ± 19.7 %
Wavelet Decomposition (29)	Without envelope	5.6 ± 7.2 bpm	5.7 ± 7.7 %
	With envelope	5.5 ± 7.1 bpm	5.5 ± 7.5 %
Teager Energy Operator	Without envelope	5.8 ± 7.4 bpm	5.6 ± 7.9 %
	With envelope	**4.6 ± 5.4 bpm**	**4.4 ± 6.0 %**

In respiration derivation, both SCG- and PPG-based methods showed similar performance, with the PPG-Red method slightly outperforming SCG-Z. The 3-breath error could be attributed to signal quality, but another factor might be the reliability of the reference measurement. The reference respiration rate was determined using manual breath counting rather than a digital tool, which could have introduced inaccuracies that were reflected in the algorithm's output.

The clinical relevance of SCG was also observable in the BMI and blood pressure mapping models.

The transmission of vibrations from the heart to the accelerometer is influenced by various tissues such as bone, muscle, fat, and skin, whose composition and thickness vary across individuals (30). These anatomical differences impact SCG characteristics, which were observed in our BMI estimation results in parallel. Similarly, the SBP and DBP estimation tasks resulted in satisfactory performance. As previously explained, the peaks and valleys of the SCG signal represent cardiac valve movements, similar to the blood pressure waveform where the valleys mark aortic valve opening (diastolic pressure) and the dicrotic notch corresponds to aortic valve closure. Literature demonstrates that time differences between fiducial points in the ECG, SCG, and PPG signals can be used in pulse arrival time (PAT) and pulse transit time (PTT)-based blood pressure estimation (31-33). However, these approaches require two different signals to derive the blood pressure values. On the other hand, in our work, we showed that the SCG signal features could directly be mapped to blood pressure values, without requiring any additional signals. This might potentially contribute to alleviate the computational or hardware-related needs.

When sub-groups results were investigated, PPG methods showed lower errors across all age groups in all tasks. For

SBP, DBP, and BMI analyses, older children (middle and high school) exhibited lower error rates, suggesting more stable measurements. When gender results were investigated, anatomical differences, particularly the higher fat-to-muscle ratio in females, affect patch placement and signal quality in HR estimation, though this anatomical variation may improve respiration rate accuracy by enhancing chest expansion detection. Lastly, patients with chronic diseases exhibit significantly lower errors across all measurement methods compared to those without chronic conditions, suggesting more coherent signals and improved model performance, likely due to more consistent physiological responses.

Limitations and Challenges

The study was limited by the relatively small sample size and imbalance across age sub-groups, which may affect the generalizability across and comparability within specific demographic categories. Future work should focus on validating the system with larger, more diverse datasets, including subjects with varying clinical conditions and demographics. Additionally, incorporating longitudinal data could offer insights into the system's long-term effectiveness across different pediatric populations.

A key challenge for clinical implementation is ensuring data accuracy and reliability. Factors such as device placement, sensor quality, and patient movement can lead to inconsistent readings. Children's nervousness can result in sweating and excessive motion, causing electrode contact loss, affecting data quality and creating intra- and inter-subject variability. Additionally, some children and parents expressed concerns about the wearable patch's unfamiliarity and potential long-term effects, which may hinder acceptance and implementation. Addressing these concerns requires targeted education and reassurance to improve user confidence and adherence.

Conclusion

In this study, the performance of our custom wearable patch was evaluated in uncontrolled settings with 84 pediatric patients at Koc University Hospital. The first part involved computing hemodynamic parameters such as heart rate and respiration rate from ECG, PPG, and SCG signals. The second part assessed the clinical relevance by using regression analyses to correlate SCG characteristics with BMI, DBP and SBP. Future work will focus on refining the algorithms and validating the patch's effectiveness in disease monitoring and treatment.

Declarations

Funding

This work was supported by the Scientific and Technological Research Council of Turkey (Grant Number: 121E133).

Conflicts of interest/Competing interest

The authors do not have any conflict of interest or competing interest to disclose.

Ethics Approval

The study was conducted under a protocol approved by the Koc University Institutional Review Board (2023.408.IRB2.089) and all parents/guardians have provided their written consent.

Availability of data and material

The data is not publicly available due to ethical reasons.

Authors contributions

B.S.: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review and editing, Visualization, Funding acquisition

Acknowledgements

This work was supported by the Scientific and Technological Research Council of Turkey (Grant Number: 121E133).

The corresponding author would like to thank Dr. Remziye Semerci, Hatice Seyrek and Ferzin Sinem Opak for their support during data collection, and Yusuf Ziya Hayirlioglu for his support during the hardware design.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1492199

A Retrospective Study on Insulin Resistance in Adults with Autoimmune Thyroiditis in Turkish Population: a Clinical and molecular Docking Study

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Received: 31.05.2024
Accepted: 26.08.2024

ABSTRACT

Purpose: This study retrospectively analyzes data to assess the prevalence and severity of insulin resistance in adults with autoimmune thyroiditis, including Hashimoto's thyroiditis. Additionally, 14 compounds from the methanolic extract of G. aparine, traditionally used for hypothyroidism, were docked into the Thyroid Hormone Receptor binding site. Luteolin, Quercetin, and Esculetin were predicted to bind successfully to the receptor.

Methods: Our approach involves a comprehensive review of medical records to evaluate insulin levels, HbA1c values, and other health markers in patients with autoimmune thyroiditis. Molecular docking simulations were performed using the Schrödinger suite, and data analysis was conducted with SPSS version 26. Normality of distribution was verified using the Shapiro-Wilks test and Box Plot diagrams, and correlations between variables were determined using Pearson or Spearman's correlation analysis.

Results: Our analysis showed a significant positive correlation between higher Insulin Resistance (HOMA-IR) scores and increased blood glucose and insulin levels ($p<0.01$). There was also a moderate positive correlation between HOMA-IR scores and both HbA1c and HbA1c (IFCC) levels. In molecular docking simulations, Luteolin and Quercetin provided greater stabilization than Esculetin due to bonds at both ends and larger molecular size, resulting in higher binding scores.

Conclusion: This study highlights the significant impact of insulin resistance in individuals with autoimmune thyroiditis, offering insights for improved diagnosis and treatment. Additionally, molecular docking simulations show that Luteolin, Quercetin, and Esculetin from the traditional medicinal plant G. aparine, used for hypothyroidism, successfully bind to the Thyroid Hormone Receptor. Understanding these associations can enhance clinical strategies and guide further research to improve treatment outcomes.

Keywords: Insulin resistance, Autoimmune thyroiditis, Hashimoto's thyroiditis, Glucose metabolism, HbA1c

ÖZET

Amaç: Bu çalışma, Hashimoto tiroiditi dahil olmak üzere otoimmün tiroiditli yetişkinlerde insülin direncinin yaygınlığını ve şiddetini değerlendirmek için verileri retrospektif olarak analiz etmeyi amaçlamıştır. Ayrıca, geleneksel olarak hipotiroidizm için kullanılan G. aparine'nin metanolik ekstraktından 14 bileşik, Tiroid Hormonu Reseptörü bağlanma bölgesine yerleştirilmiştir. Luteolin, Kuersetin ve Eskuletin'in reseptöre başarıyla bağlanacağı öngörülmüştür.

Yöntem: Yaklaşımımız, otoimmün tiroiditli hastalarda insülin seviyeleri, HbA1c değerleri ve diğer sağlık belirteçlerini değerlendirmek için tıbbi kayıtların kapsamlı bir şekilde incelenmesini içermektedir. Moleküler yerleştirme simülasyonları Schrödinger paketi kullanılarak gerçekleştirilmiş ve veri analizi SPSS versiyon 26 ile yapılmıştır. Dağılımın normalliği Shapiro-Wilks testi ve Box Plot diyagramları kullanılarak doğrulanmış, değişkenler arasındaki korelasyonlar Pearson veya Spearman korelasyon analizi ile belirlenmiştir.

Bulgular: Analizimiz, daha yüksek İnsülin Direnci (HOMA-IR) skorları ile artan kan şekeri ve insülin seviyeleri arasında anlamlı bir pozitif korelasyon göstermiştir ($p<0.01$). Ayrıca, HOMA-IR skorları ile hem HbA1c hem de HbA1c (IFCC) seviyeleri arasında orta derecede pozitif bir korelasyon bulunmuştur. Moleküler yerleştirme simülasyonlarında, Luteolin ve Kuersetin, her iki uçtaki bağlar ve daha büyük moleküler boyutları nedeniyle Eskuletin'den daha fazla stabilizasyon sağlamış ve bu da daha yüksek bağlanma skorları ile sonuçlanmıştır.

Sonuç: Bu çalışma, otoimmün tiroiditli bireylerde insülin direncinin önemli etkisini vurgulayarak, teşhis ve tedavi için iyileştirilmiş yaklaşımlar sunmaktadır. Ayrıca, geleneksel olarak hipotiroidizm için kullanılan tıbbi bitki G. aparine'den elde edilen Luteolin, Kuersetin ve Eskuletin'in Tiroid Hormonu Reseptörüne başarıyla bağlandığını gösteren moleküler yerleştirme simülasyonları yapılmıştır. Bu ilişkilerin anlaşılması, klinik stratejileri geliştirebilir ve tedavi sonuçlarını iyileştirmek için daha fazla araştırmaya yön verebilir.

Anahtar Kelimeler: İnsülin direnci, Otoimmün tiroidit, Hashimoto tiroiditi, Glukoz metabolizması, HbA1c

Hashimoto's thyroiditis, also known as chronic lymphocytic or autoimmune thyroiditis, is a long-term autoimmune condition characterized by the immune system producing thyroid peroxidase (TPO) and/or thyroglobulin (Tg) antibodies that attack the thyroid gland (1, 2). This attack leads to inflammation and a slow decline in thyroid function, often resulting in hypothyroidism, where the thyroid produces insufficient hormones (3). Hypothyroidism can decrease glucose absorption, causing sugar accumulation and increased insulin production, eventually leading to insulin resistance and potentially diabetes (4-7). Comprehensive management of Hashimoto's thyroiditis should address both thyroid function and its metabolic consequences (8). It is imperative to develop a novel therapy with minimal or no side effects that can enhance thyroid function. Plant-based medicines are often considered as the potential options that provide valuable therapy for various diseases with negligible or no side effects (9).

Plants have been a source of natural medicine since ancient times, with 25–48% of drugs today originating from plants or their synthetic derivatives (10). *Galium aparine* L. (GA), also known as Cleavers or "Yogurt herb" due to its use in cheese manufacturing, is common in Anatolia and traditionally used for hypothyroidism. Fourteen compounds were identified in the methanolic extract of *G. aparine* (11). This study also aims to elucidate the molecular mechanism of action using in silico methods, specifically molecular docking simulations.

In this study, our objective was to assess the impact of insulin resistance in adult populations with proven autoimmune thyroiditis. We conducted a retrospective screening using routine blood test results and employed statistical methods to evaluate insulin resistance levels in individuals with autoimmune thyroiditis. By utilizing retrospective screening methods, we aimed to provide valuable insights into the potential relationship between autoimmune thyroiditis and insulin resistance.

To support these findings; we also aimed to perform the mechanism of action at the molecular level using established in silico methods, specifically molecular docking simulations. Our findings will contribute to a better understanding of the metabolic implications of autoimmune thyroiditis and shed light on the importance of assessing insulin resistance in this population.

Material and Methods

Experimental Design

The ethical oversight for this investigation was provided by the Ethics Committee of Biruni University, which granted approval under the protocol number 2022/75-12. This research involved a cohort of 34 participants from whom various biomarkers were measured, including hemoglobin, insulin, HbA1c (hemoglobin A1c), anti-TPO (thyroid peroxidase antibodies), anti-Thyroglobulin, ferritin, vitamin B12, and vitamin D levels.

Molecular Docking

Molecular docking simulations were performed using Schrödinger suite (12). Crystal structure of Thyroid Hormone Receptor with 2.20 Å resolution was obtained from protein databank (PDB ID: 3GWS). The raw 3D structure was initially prepared by adding hydrogen atoms, correcting bond orders and minimizing the system after optimizing step. All compounds to be docked were also prepared using LigPrep (13) module implemented in Schrödinger suite. In order to cover large chemical space, all possible conformations and tautomers were also considered and ionization states at pH 7.0±2 were generated too. Glide's standard precision (SP) method was conducted for docking of all structure into the receptor.

Statistical Analysis

The study used descriptive and inferential statistical methods to analyze biomarkers, summarizing continuous and qualitative variables. SPSS version 26 was used for analysis, with normality assessed using Shapiro-Wilks test and Box Plot graphs, and correlations were evaluated using Pearson or Spearman's analysis ($p < 0.05$). The study excluded participants with thyroid medication, antioxidant supplementation, insulin resistance, autoimmune diseases, pregnancy, thyroid surgery, or thyroid cancer, and used anonymous results for interpretation.

Results

The study explores the link between autoimmune thyroiditis and insulin resistance, using biomarkers and blood test results. It aims to understand the metabolic implications of autoimmune thyroiditis and improve management and treatment strategies for individuals with the condition.

Data from 34 participants at Dr. Savaş Gur's outpatient clinic were analyzed for gender representation. Among them, 14.7% (n=5) were males and 85.3% (n=29) were females, reflecting the higher prevalence of autoimmune thyroiditis in females (Figure 1A). The graphical representation of gender distribution offers a visual overview of the study population, aiding in the interpretation of findings.

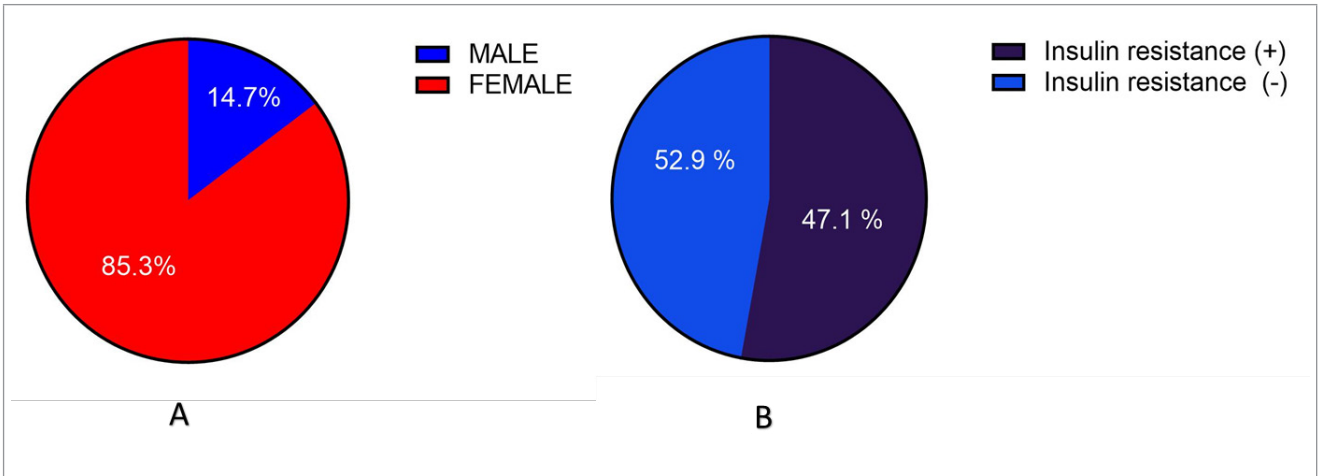

Figure 1: A) The distribution of genders. This figure illustrates the distribution of genders within our study population.
B) Distribution of Insulin Resistance. This figure displays the distribution of insulin resistance among the study participants.

Table 1 provides a comprehensive overview of the clinical measurements obtained from the study participants. The table includes various hematological, metabolic, and immunological parameters along with their corresponding mean and standard deviation values. The average hemoglobin level was 13.25±1.55, insulin resistance (HOMA-IR) was 3.40±2.44, blood sugar was 101.82±38.96, insulin was 13.28±7.57, HbA1c (both in percentage and IFCC units) were 5.58±1.11 and 37.62±12.18 respectively, anti-thyroid peroxidase (TPO) antibodies were 188.98±153.31, anti-thyroglobulin antibodies were 310.89±621.58, ferritin was 67.41±83.14, vitamin B12 was 445.94±193.04, and vitamin D was 24.18±12.68. These descriptive statistics provide valuable insights into the central tendencies and variability of the measured parameters within the study population, serving as a basis for further analysis and interpretation of the data.

Table 1: Distribution of Clinical Measurements

	Mean±Sd	Median (Min-Max)
Hemoglobin	13,25±1,55	13,2 (10,3-17,5)
Insulin resistance HOMA-IR	3,40±2,44	2,7 (0,8-12,4)
Blood sugar	101,82±38,96	94 (71-261)
Insulin	13,28±7,57	10,7 (3,8-32,4)
HbA1c	5,58±1,11	5,3 (4,6-10,8)
HbA1c IFCC	37,62±12,18	34,5 (27-95)
Anti TPO	188,98±153,31	150,9 (8,9-540)
Anti Triglobulin	310,89±621,58	144,5 (15,9-3600)
Ferritin	67,41±83,14	46 (7-460)
Vitamin B12	445,94±193,04	424 (161-969)
Vitamin D	24,18±12,68	21,5 (6-62)

r=Pearson's Correlation Test
***p<0,01*

The data shows that 52.9% of the study population had insulin resistance, while 46.1% did not. Figure 1B visually represents this prevalence. Understanding insulin resistance distribution is crucial for assessing its impact on study outcomes and implications for participant management and treatment.

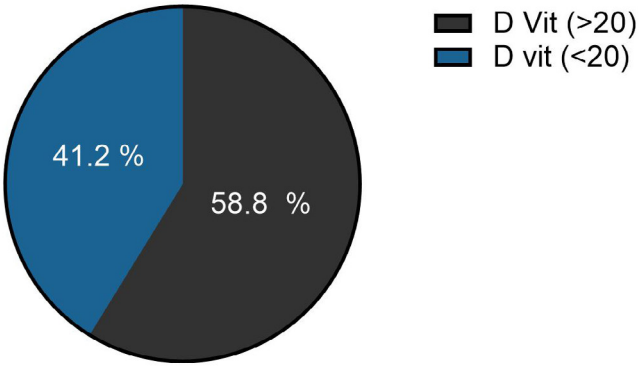

Figure 2: Distribution of Vitamin D. This figure depicts the distribution of vitamin D levels among the patients.

The data indicates that 58.8% of the patients had vitamin D levels greater than 20, while the remaining 41.2% had vitamin D levels less than or equal to 20. Figure 2 provides a visual representation of the proportion of patients with sufficient (above 20) and insufficient (20 or below) vitamin D levels within the studied population. Understanding the distribution of vitamin D levels is crucial for evaluating the prevalence of vitamin D deficiency and its potential impact on the patients' health and well-being.

Table 2 shows a significant positive correlation between higher HOMA-IR values and elevated blood glucose (p=0.556; p=0.001), insulin (p=0.829; p=0.001), HbA1c (p=0.699; p=0.001), and HbA1c (IFCC) levels (p=0.706; p=0.001). These findings suggest that higher HOMA-IR values are linked to increased blood glucose, insulin levels, and long-term glucose control, highlighting the importance of understanding insulin resistance to develop effective treatment strategies.

Table 2: Relationship between Insulin Resistance (HOMA-IR) and Clinical Measurements

	Insulin resistance (HOMA-IR)	
	r	p
Hemoglobin	0,212	***0,229***
Blood sugar	0,556	***0,001****
Insulin	0,829	***0,001****
HbA1c	0,699	***0,001****
HbA1c (IFCC)	0,706	***0,001****
Anti TPO	-0,043	***0,811***
Anti Triglobulin	0,243	***0,166***
Ferritin	-0,107	***0,546***
Vitamin B12	-0,051	***0,776***
Vitamin D	-0,085	***0,633***

Figure 3 shows no significant correlation between insulin resistance (HOMA-IR) and clinical indicators like hemoglobin, anti-TPO, anti-thyroglobulin, ferritin, vitamin B12, and vitamin D ($p > 0.05$). Figure 4 illustrates the relationships between vitamin D and hemoglobin, anti-thyroglobulin, and vitamin B12 levels. These findings suggest the complexity of insulin resistance's etiology and highlight the need for further research to explore additional factors.

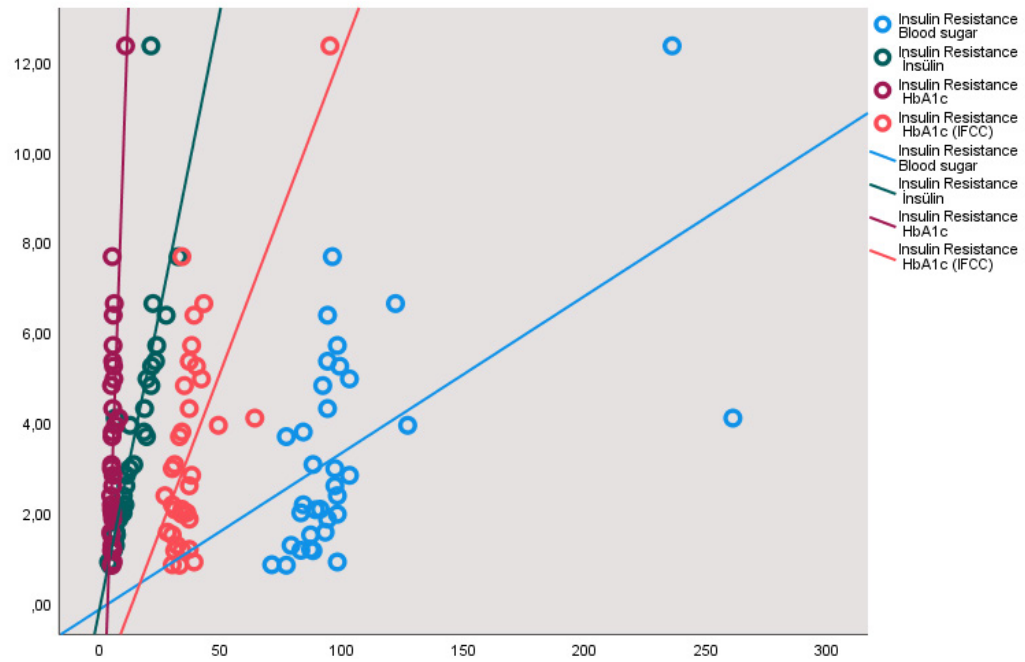

Figure 3: Relationship between Insulin Resistance (HOMA-IR) and blood glucose, HbA1c, and HbA1c (IFCC) measurements.

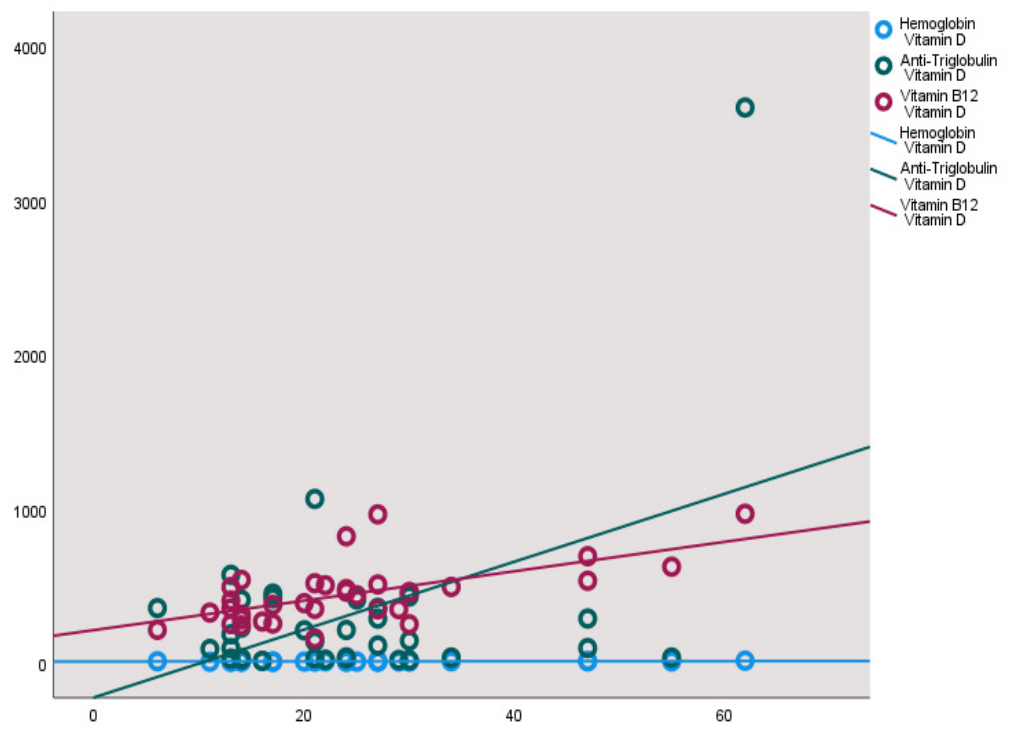

Figure 4: Relationship between Vitamin D and Hemoglobin, Anti Tri globulin and Vitamin B12 measurements

Table 3 shows Vitamin D levels have a weak positive correlation with hemoglobin (p=0.348; p<0.05) and Anti-Thyroglobulin (p=0.448; p<0.01), and a moderate positive correlation with Vitamin B12 (p=0.625; p<0.01). No significant relationships were found between Vitamin D and blood glucose, insulin, HbA1c, HbA1c (IFCC), Anti-TPO, and Ferritin (all p>0.05), highlighting Vitamin D's selective impact on certain clinical measures.

Table 3: The Relationship Between Vitamin D and Clinical Measurements

	Vitamin D	
	r	***p***
Hemoglobin	0,348	*0,044**
Blood sugar	-0,054	*0,762*
Insulin	-0,073	*0,683*
HbA1c	-0,074	*0,678*
HbA1c (IFCC)	-0,072	*0,684*
Anti TPO	0,148	*0,404*
Anti Triglobulin	0,448	*•0,008***
Ferritin	0,040	*0,821*
Vitamin B12	0,625	*0,001***

r=Pearson's Correlation Test
*r•=Spearman's Correlation Test **p<0,01*

In Table 4, Luteolin, Quercetin, and Esculetin show promising binding scores compared to the co-crystallized ligand. Figure 5 illustrates the binding interactions of all four compounds, including T3. A hydrogen bond interaction with Asparagine 331 is observed in all cases, suggesting its crucial role in ligand activity against the Thyroid Hormone Receptor.

Table 4: Docking scores of the native ligand T3 and the studied compounds.

Compound	Docking Score (kcal/mol)
3GWS-Native Ligand, T3	-10.30
Luteolin	-10.19
Quercetin	-9.36
Esculetin	-8.62
Coumarin	-7.61
Monotropein	-7.26
Normetanephrine	-6.77
Chlorogenic-acid	-6.28
p-Coumaric-acid	-6.19
Cinnamic-acid	-5.86
Pyridoxine	-5.72
Spectinomycin	-5.64
Pantothenic-acid	-3.62

The study underscores the need for further research on Vitamin D's health effects, highlighting its limited influence on other parameters in this particular group.

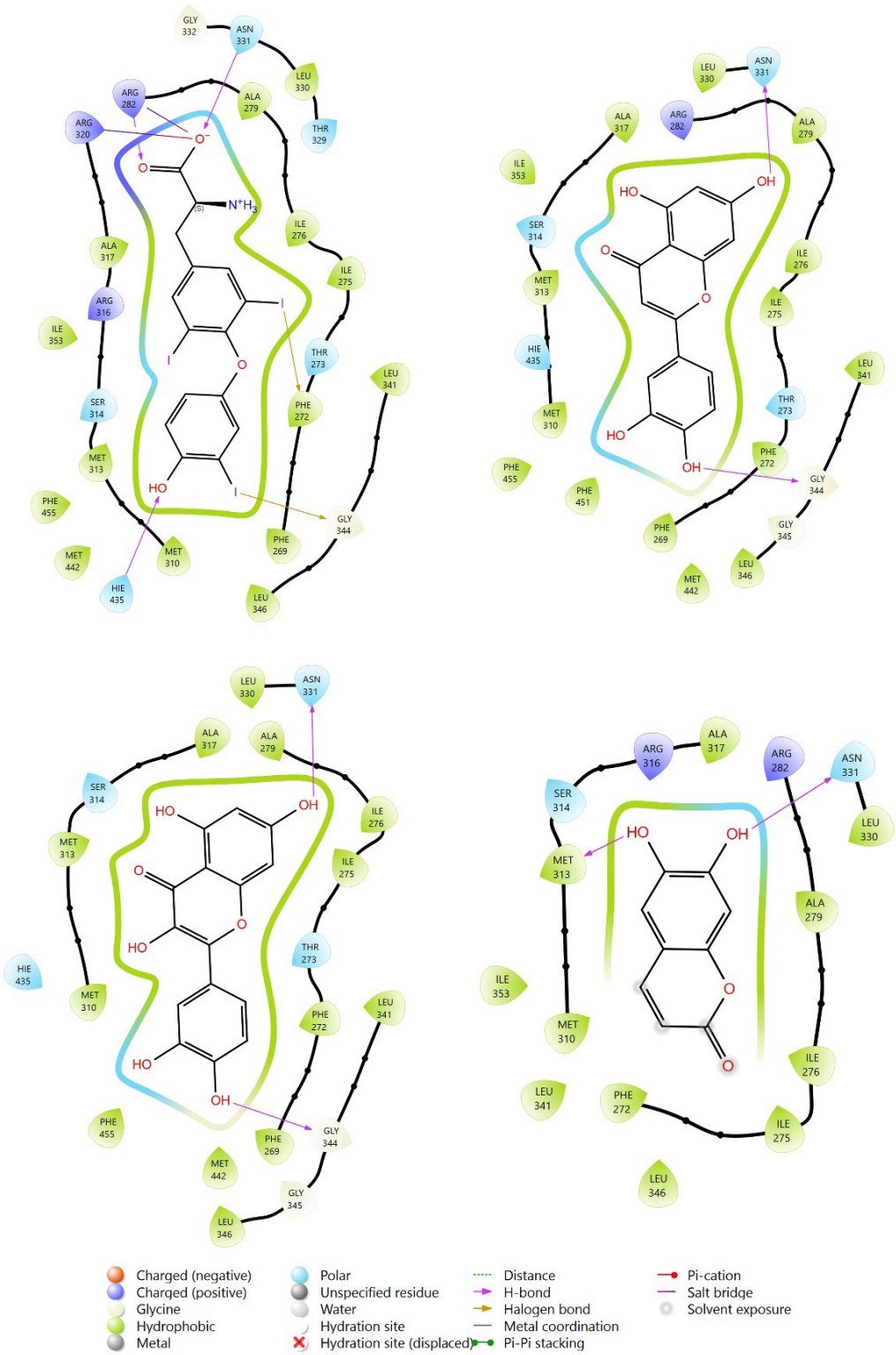

Figure 5: The 2D Ligand interaction diagram of the native ligand (top left), Luteolin (top right), Quercetin (bottom left) and Esculetin (bottom right).

Discussion

This manuscript examines the relationship between autoimmune thyroiditis and insulin resistance in the adult Turkish population. A retrospective analysis of clinical measurements from 34 participants reveals a significant prevalence of insulin resistance, with more than half exhibiting this condition, underscoring the importance of monitoring and managing it to prevent further complications (14). The study also highlights a higher prevalence of autoimmune thyroiditis in females, aligning with existing literature (5).

The research found a positive correlation between insulin resistance and blood glucose, insulin, HbA1c, and HbA1c (IFCC) levels, highlighting the need for enhanced blood glucose monitoring in individuals with autoimmune thyroiditis (15). No significant relationships were found between insulin resistance and hemoglobin, anti-TPO, anti-thyroglobulin, ferritin, vitamin B12, and vitamin D levels, indicating that insulin resistance may not impact these parameters in the context of autoimmune thyroiditis. This highlights the complexity of insulin resistance's role and the need for further research (16).

The study suggests a potential link between vitamin D levels, hemoglobin, anti-thyroglobulin, and vitamin B12 levels (17). This suggests a potential link between vitamin D status and certain health outcomes in autoimmune thyroiditis, but further research is needed to fully understand these associations.

G. aparine is traditionally used for natural therapy, particularly for hypothyroidism. Fourteen compounds were identified in its methanolic extract (11). To elucidate the molecular mechanism, we used in silico tools like molecular docking.

Prior to any computational modelling studies, a validation step is a must (18). In an attempt to validate our docking protocol, co-crystal ligand (T3) was docked into the binding site of Thyroid Hormone Receptor. The predicted binding geometry was then superimposed on the x-ray crystal structure. The room mean standard deviation (RMSD) was found as 0.34, which is an acceptable value. Then, we applied the same protocol (Glide SP) (19) to the docking of compounds reported in *G. aparine* methanolic extract. Amongst them, 12 compounds yielded successful poses. Table 4 shows Luteolin, Quercetin, and Esculetin have promising binding scores compared to the co-crystallized ligand.

Figure 5 demonstrates the binding contacts of all four molecules, including T3, with a hydrogen-bond connection at Asparagine 331 in all instances. This indicates that Asparagine 331 plays an essential role in the activity of the ligands against the Thyroid Hormone Receptor. Luteolin and Quercetin display interactions between hydrogen bonds at both ends, leading to enhanced stability and, due to their larger molecular size, yielding higher binding scores in compared to Esculetin.

The insights from this study have important clinical implications, potentially influencing management and treatment strategies for autoimmune thyroiditis. Further studies are needed to explore the relationships between autoimmune thyroiditis, insulin resistance, and other clinical parameters to improve patient care and outcomes (15).

Conclusion

This study highlights the significant interplay between autoimmune thyroiditis and insulin resistance in the Turkish adult population, with a high prevalence of insulin resistance. Key findings show a crucial link between insulin resistance and blood glucose and HbA1c levels, emphasizing the need for vigilant monitoring. No significant correlation was found between insulin resistance and hemoglobin or vitamin D levels. The study underscores the complexity of autoimmune thyroiditis and its metabolic implications, highlighting the need for a multifaceted management approach.

G. aparine, traditionally used for hypothyroidism, contains Luteolin, Quercetin, and Esculetin in its methanolic extract, which were predicted through molecular docking simulations to bind successfully to the Thyroid Hormone Receptor. These findings, along with the study's insights into the interplay between autoimmune thyroiditis and insulin resistance, emphasize the need for further research to explore underlying mechanisms and develop targeted treatments.

Declaration

Conflicts Of Interest /Competing Interests

The authors declare that they have no conflicts of interest.

Funding Statement

This study had no external funding.

Ethics Approval

This study was approved by the Ethical Committee of Biruni University, which granted approval under the protocol number 2022/75-12.

Authors' Contributions

ESA and SG conceptualized and designed the study. ESA organized the database, performed the statistical analysis, ESA and SG wrote the first draft of the manuscript. ESA edited the final version of paper. All authors approved the final version of the manuscript.

Acknowledgement

The support of Dr. Abdulilah Ece is gratefully acknowledged in computational part. Special thanks to Epigenetic Coaching for their support and encouraging.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1531188

Evaluation the Effect of Tumor-Associated Macrophage-Derived Factors on Pancreatic Cancer Microenvironment Cells

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Received: 23.08.2024
Accepted: 21.11.2024

ABSTRACT

Purpose: The unique tumor microenvironment (TME) of pancreatic cancer (PCa) is a critical factor contributing to its aggressive and incurable nature. Pancreatic stellate cells (PSCs) are among the most abundant stromal cells in the TME, closely associated with tumor progression, metastasis, and chemo-/radioresistance. Tumor-associated macrophages (TAMs) are another important cell type in the TME, playing a vital role in promoting tumor growth and metastasis. Limited research exists on the interaction between PSCs and TAMs, underscoring the need for more studies to better understand the interaction between these two cell types.

Methods: THP-1 monocytic cells were differentiated into macrophages, and differentiation efficiency was confirmed by morphological analysis and Western blot. PSCs were co-cultured with monocytes/macrophages, and changes in the migration and invasion abilities of PSCs were assessed using wound healing and transwell invasion assays, respectively. To investigate the effects of macrophage-derived factors, MCP-1 and Gas6, on PSC-macrophage interactions, these proteins were applied to PSCs, or their receptors (Axl and CCR2) were suppressed using siRNA technology. The effects of Gas6/Axl and MCP-1/CCR2 signaling on PSC cell viability, colony formation, and migration were then evaluated.

Results: While MCP-1 did not induce changes in colony-forming and migration abilities of PSCs, Gas6 treatment resulted an induction. This effect was reduced when the Gas6 receptor Axl was suppressed with siRNA, suggesting that Gas6/Axl signaling may play critical role in macrophage-mediated changes in PSCs.

Conclusion: Further research is needed to fully understand the interaction between PSCs and TAMs in pancreatic cancer.

Keywords: pancreatic cancer, tumor microenvironment, pancreatic stellate cells, macrophages, MCP-1, Gas6

ÖZET

Giriş: Pankreas kanserinin (PKa) karakteristik tümör mikroçevresi (TMÇ), bu kanserin agresif ve ölümcül doğasına aktif şekilde katkıda bulunmaktadır. Pankreatik stellat hücreleri (PSH'ler), TMÇ'de en bol bulunan stromal hücreler arasındadır ve tümör gelişimi, metastaz ve kemoterapi ve radyoterapi direnci ile yakından ilişkilidir. Tümörle ilişkili makrofajlar (TİM'ler), mikroçevredeki bir diğer önemli hücre türüdür ve tümör büyümesini ve metastazı desteklemede kritik rol oynamaktadır. TMÇ'nin bu iki önemli hücre türünün (PSH'ler ve TİM'ler) arasındaki etkileşime odaklanan çalışmalar oldukça sınırlıdır, bu nedenle iki hücre türü arasındaki etkileşimi daha iyi anlamak için daha fazla çalışmaya gereksinim bulunmaktadır. Bu amaçla, çalışmamızda bu iki hücre arasındaki etkileşime ve etkileşimde rol alan faktörlerin tanımlanmasına odaklandık.

Yöntem: İlk olarak THP-1 monositik hücreleri makrofajlara farklılaştırıldı ve farklılaşma etkinliği morfolojik analiz ve Western blot ile doğrulandı. PSH'ler monositler/makrofajlarla birlikte kültüre edildi ve hücrelerin göç ve invazyon yeteneklerindeki değişiklikler sırasıyla yara iyileşmesi ve invazyon analizleri ile değerlendirildi. Makrofaj kaynaklı faktörler olan MCP-1 ve Gas6'nın PSH-makrofaj etkileşimi üzerindeki etkilerini araştırmak için bu proteinler PSH'lere uygulandı veya reseptörleri (Axl ve CCR2) siRNA teknolojisi kullanılarak baskılandı. Daha sonra Gas6/Axl ve MCP-1/CCR2 sinyalizasyonunun PSH canlılığı, koloni oluşumu ve göçü üzerindeki etkileri değerlendirildi.

Bulgular: MCP-1 uygulaması PSH'lerin koloni oluşturma ve göç yeteneklerinde değişiklik yaratmazken, Gas6 hücrelerin oluşturma koloni ve migrasyon yeteneğinde bir artışa neden oldu. Ek olarak, bu etki Gas6 reseptörü Axl siRNA ile bastırıldığında azaldı. Bu bulgular Gas6/Axl sinyalizasyonunun PSH-makrofaj etkileşiminde rol alan sinyal yollarından biri olabileceğine dikkat çekmektedir.

Sonuç: Pankreas kanserinde PSH'ler ve TİM'ler arasındaki etkileşimi net şekilde anlamak için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: pankreas kanseri, tümör mikroçevresi, pankreatik stellat hücreleri, makrofajlar MCP-1, Gas6

Pancreatic cancer (PCa) is one of the deadliest solid tumors, with a 5-year survival rate just above 10% (1). Despite recent technological advancements, PCa remains highly aggressive and lethal. Its rich tumor microenvironment (TME) significantly contributes to tumor progression, metastasis, drug resistance, and evasion of apoptosis and immune system (2-4).

Pancreatic stellate cells (PSCs), the most abundant fibroblastic cells in the PCa stroma, are quiescent under normal conditions but become activated by inflammation. During tumorigenesis, PSCs remain constantly active and play critical roles in tumor progression by creating a supportive microenvironment for cancer cells (5-8). Tumor-associated macrophages (TAMs), defined as macrophages in or around the tumor, are another important cell type in the TME and play critical roles in regulating tumor progression. In general, TAMs can be categorized into two main populations with opposite functions: M1 macrophages have anti-tumorigenic properties, whereas M2 macrophages are pro-tumorigenic (9). M2 macrophages interact bidirectionally with PCa cells and other cells in the TME, promoting tumor growth and progression (10).

Monocyte chemoattractant protein-1 (MCP-1/CCL2), a chemokine mainly released by monocytes/macrophages, regulates the migration and infiltration of monocytes/macrophages and promotes monocyte-macrophage differentiation (11, 12). Growth-arrest-specific 6 (Gas6), another protein in the PCa TME, is known to contribute to cancer cell proliferation and migration (13, 14). Gas6/Axl signaling regulates the TME by inducing TAM polarization toward M2 macrophages (15). Indeed, TAMs express high levels of Gas6 (16), suggesting the existence of a tumor-promoting cycle mediated by Gas6 signaling.

Considering all this information, we focused on investigating the interaction between two important cell types in TME, PSCs and macrophages, and evaluating the potential effects of this interaction on behaviors of PSCs, as well as identifying the factors regulating this interaction. Our results suggest that Gas6/Axl signaling may play an important role in communication between PSCs and macrophages and could serve as a therapeutic target for modulating the TME in the future.

Material and Methods

2.1. Cell Culture

THP-1 acute monocytic leukemia cells were obtained from the ATCC (Manassas, VA, USA). Human pancreatic stellate cells (PSCs) were kindly provided by Dr. Rosa Hwank (MD Anderson Cancer Center). Both cell types were cultured in RPMI-1640 medium supplemented with 10% FBS and 100 U/ml Penicillin/Streptomycin at 37°C in 5% CO_2, and tested for mycoplasma contamination.

2.2. Monocyte-Macrophage Differentiation and Characterization

THP-1 cells were cultured to 70-80% confluency in 75 cm^2 flasks. For mature (M0 type) macrophage differentiation, cells were treated with 10 ng/ml Phorbol 12-myristate 13-acetate (PMA) (Sigma-Aldrich, St. Louis, MO, USA) for 24 h. Then, media were replaced with fresh RPMI-1640 media (without PMA) and M0 cells were cultured in this media. To polarize M0 macrophages into M2 pro-tumorigenic macrophages, IL-4 and IL-13 (25 ng/ml) were added to the flasks for 24h (17). Cell were then examined under phase-contrast microscopy, and CD68, CD163, and CD206 protein expressions were assessed by Western blot to confirm polarization.

2.3. Indirect Co-culture Experiments

Briefly, THP-1 cells were seeded in transwell inserts (0.4 µm pore size, Corning, New York, NY, USA) of 6 well plates at $2x10^5$ cells/well and cultured as monocytes or differentiated into M0/M2 macrophages. PSCs were seeded in separate 6-well plates at a density of $3x10^5$ cells/well and incubated overnight. Then, inserts containing monocytes or macrophages were transferred onto the wells and were co-cultured with PSCs for 48 h. After the co-culture period, the inserts were removed and the cells were subjected to further analyses.

2.4. MCP-1 and Gas6 Treatment

Recombinant human MCP-1/CCL2 protein (R&D Systems, Minneapolis, MN, USA) was dissolved in sterile PBS containing 0.1% bovine serum albumin at 100 µg/ml. Recombinant human Gas6 protein (R&D Systems, Minneapolis, MN, USA) was dissolved in sterile water at 500 µg/ml. PSCs were seeded in 6-well plates at $2x10^5$ cells per well and allowed to attach overnight. Before Gas6 treatment, the medium was replaced with serum-free medium, and cells were incubated overnight. Subsequently, cells were treated with Gas6 (200, 400, 600 ng/ml) for 30 min or MCP-1 (10, 25, 50 ng/ml) for 24 h. The concentration ranges and treatment periods for both Gas6 and MCP-1 were chosen based on the literature (18-20). Treated cells were used for further experiments.

2.5. siRNA Transfection

PSCs were seeded in 6-well plates at a density of $2x10^5$ cells/well. After 24 h, cells were transiently transfected with 100 nM concentrations of control siRNA, eEF2K or AXL siRNA (Sigma-Aldrich, St. Louis, MO, USA) using Hiperfect transfection reagent (Qiagen, Hilden, Germany) in Opti-MEM Reduced Serum Medium (Life Technologies, Carlsbad, CA, USA) according to the manufacturer's protocol. After 6 h of transfection, Opti-MEM media were changed with culture media containing 10% FBS, and cells were incubated for additional 48 h for Western blot analysis.

2.6. Colony Formation Assay

PSCs were seeded in 24-well plates at a density of $2x10^2$ cells/well. Following overnight incubation, cells were treated with MCP-1, Gas6, or siRNAs as described above. After the treatments, media were replaced with fresh media and cells were cultured for 10-14 days until visible colonies formed. Colonies were then stained with crystal violet (0.5% w/v) and counted using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

2.7. Wound Healing Assay

The wound healing assay was used to assess the migration ability of cells. PSCs were plated at a density of $2x10^5$ cells per well in 6-well plates and incubated for 24 h. Subsequently, wounds were created using a 200-µl sterile pipette tip, followed by gentle washing with culture media to remove cellular debris. Cells were then either co-cultured with monocytes/macrophages or treated with Gas6. Wounds were photographed immediately (0 h) and again at 24 and 48 h using a phase-contrast microscope (Nikon Eclipse TE-200-U). At least three random, non-overlapping images were taken from each well.

2.8. Matrigel Transwell Invasion Assay

PSCs were seeded in 6-well plates and co-cultured with monocytes/macrophages as previously described. After 24 h, cells were and suspended in 200 µl of serum-free media and added to Matrigel-coated Transwell inserts (8-µm-pore size; Fisher Scientific). The lower chambers of the inserts were filled with 500 µl of media containing 10% FBS as chemoattractant. After 24 h, invading cells were fixed and stained using a Hema 3 staining kit (Thermo Scientific, Waltham, MA, USA). Cells on the upper side of the membrane were removed by wiping with a cotton swab, and the membranes were photographed. The number of invaded cells was quantified by counting at least six fields per membrane using ImageJ software and results were expressed as the mean number of invaded cells from triplicate measurements.

2.9. Western Blot

Cells were collected and lysed with RIPA lysis buffer. Protein concentration was then measured, and lysates were mixed with Laemmli loading buffer, heated at 95°C for 5 min, and separated by SDS-PAGE using a 4%-15% gradient gel. Proteins were transferred to PVDF membranes, blocked in 5% milk in TBS-T, and probed with primary antibodies: eEF2K, p-eEF2 (Thr56), Src, p-Src (Tyr416), MMP-2, Snail, integrin beta 1, p-Akt (Ser473), Akt, CCR2 (Cell Signaling Technology); CD68, CD163, CD206 (Abcam); MCP-1, Axl, p-Axl (Tyr702) (R&D Systems); Gas6 (Abcam). Membranes were then incubated with HRP-conjugated secondary antibodies and detected using HyGLO Chemiluminescent HRP Antibody Detection Reagent. Each membrane was exposed to film (Kodak) in a dark room for 0.5-10 min. For subsequent detections with different antibodies, membranes were stripped using Restore™ PLUS Western Blot Stripping Buffer (Thermo Scientific, Waltham, MA, USA) for 15 min. β-actin (Sigma-Aldrich, St. Louis, MO, USA) and GAPDH (Cell Signaling Technology, Danvers, MA, USA) were used as loading controls.

2.10. Statistical Analyses

Data were expressed as means or fold changes ± standard deviations (SDs). Statistical analysis was performed using the Student's t-test and one-way ANOVA to determine statistical significance by using GraphPad Prism 9.0 statistical software for Windows. *P* values indicate the probability of the means compared, being equal with $*P<0.05$, $** P<0.01$, $*** P<0.001$, $**** P<0.0001$.

Results

3.1. High CD68 and CD163 expression is associated with poor survival in PDAC patients

Tumor-associated macrophages are known to be associated with the aggressiveness of various cancers, including PCa. Kaplan-Meier survival curves were generated for macrophage markers, CD68 (pan-macrophage marker) and CD163 (M2-pro-tumorigenic marker), in PDAC patients with low and high expression levels. As shown in **Fig. 1A**, patients with high CD68 and CD163 expression have significantly shorter overall survival.

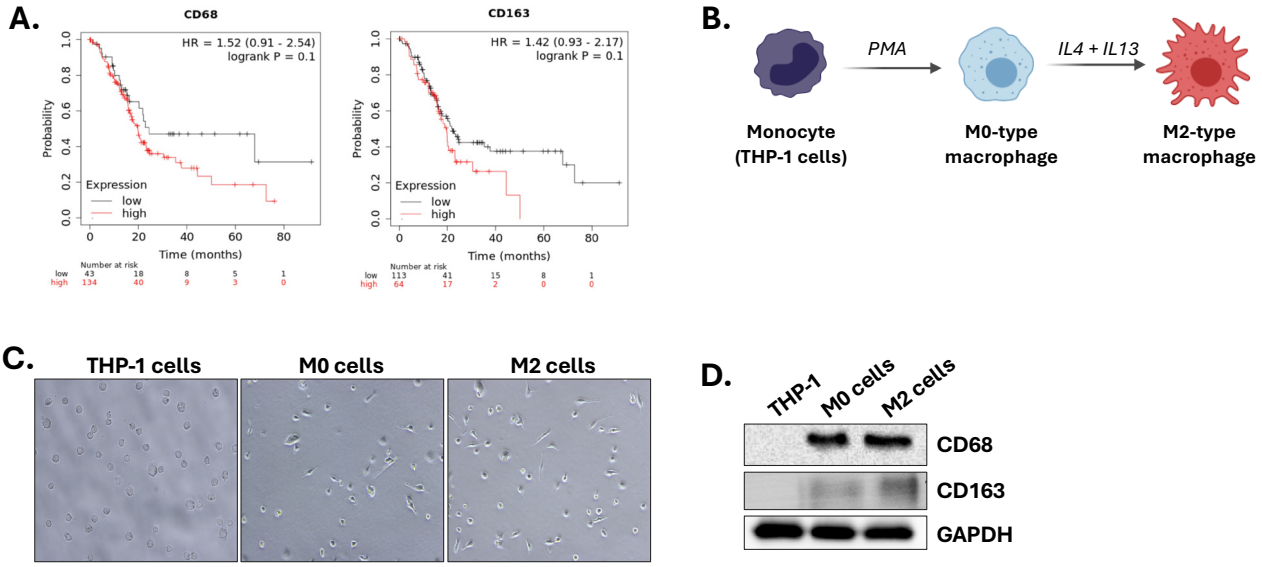

Figure 1: The survival analyses were performed in KM plotter using publicly available pancreatic ductal adenocarcinoma mRNA data that is available within the database. The presence of macrophages in tumors is associated with poor overall survival in PDAC patients. **(A)** High expression of CD68 and CD163 is correlated with poorer overall survival (OS) in PDAC patients as determined by Kaplan-Meier survival analysis (p= 0.1). The numbers of patients with low and high eEF2K expressions are presented at the bottom of the graph. Mo, months. **(B)** Macrophages used in the study were differentiated from THP-1 monocytic cell lines. The differentiated process were performed as illustrated. **(C)** The differentiation efficacy was first evaluated by morphological changes. **(D)** The changes in the expression of differentiation-related markers were assessed by Western blot.

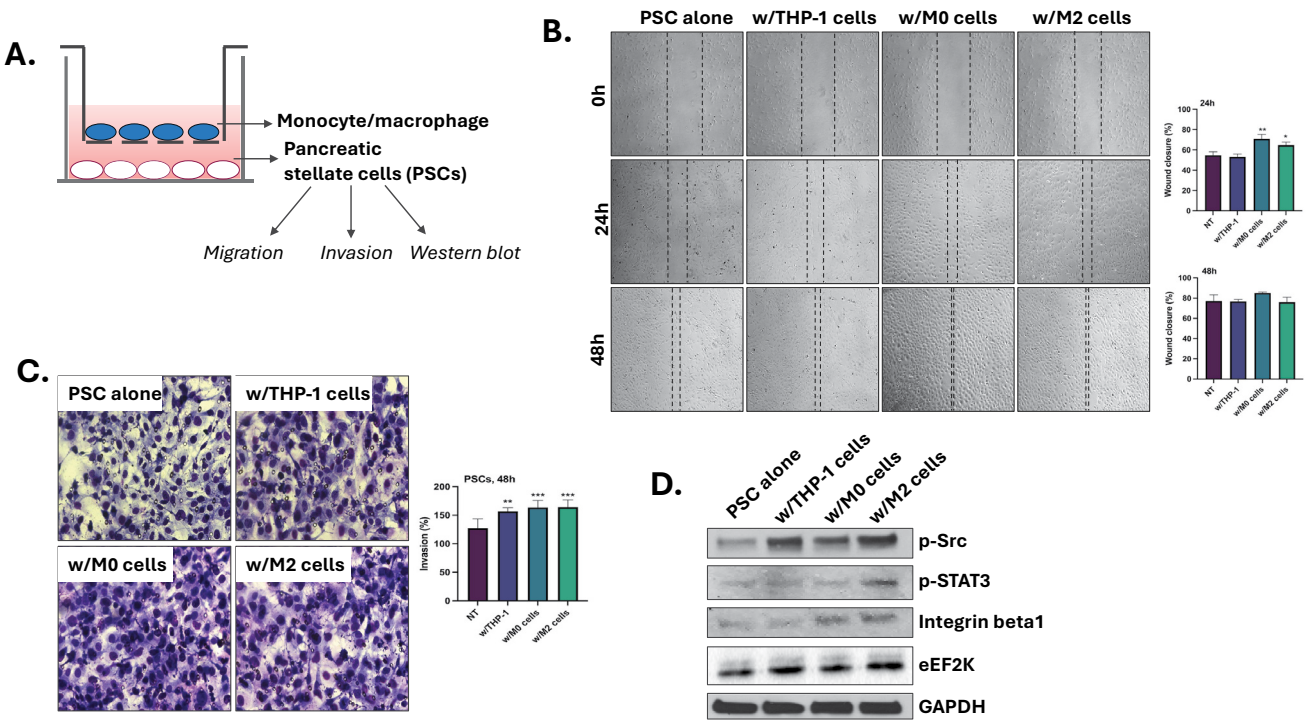

Figure 2: Macrophages increased the migration and invasion abilities and the expression of metastasis-related proteins of pancreatic stellate cells (PSCs). **(A)** PSCs were indirectly co-cultured with monocytes or macrophages for 48 hours as illustrated. **(B, C)** The effects of macrophages on cell migration and invasion were evaluated by wound healing assay and transwell invasion assay, respectively. (*p<0.05, **p<0.01, ***P<0.001, relative to PSC alone). **(D)** The changes in the expression of migration- and invasion-related proteins were assessed by Western blot.

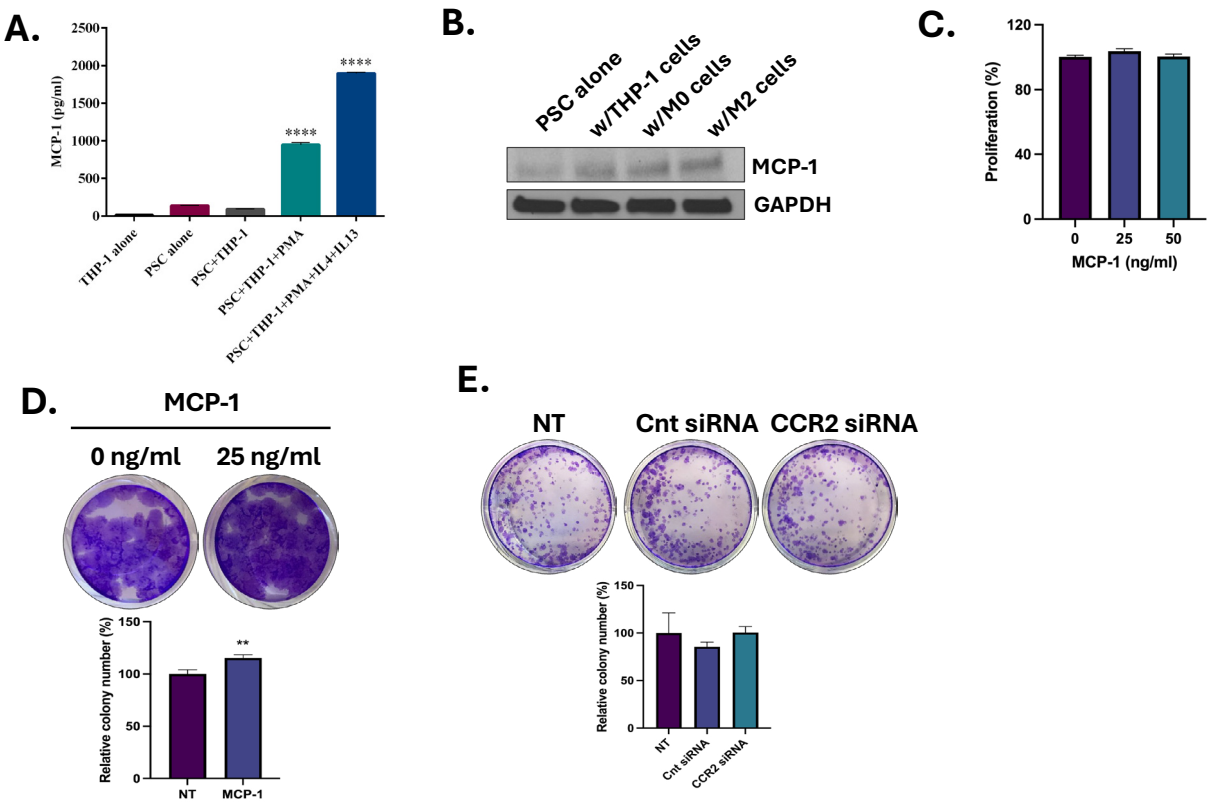

Figure 3: MCP-1 protein did not alter the proliferation and but slightly increased colony formation in PSC cells. (A) Increased levels of MCP-1 and eEF2K were detected in PSCs in the presence of macrophages. **(B)** Released MCP-1 levels in monocytes were measured by ELISA (****p<0.01, relative to PSC alone). **(C)** While MCP-1 treatment did not alter PSCs' proliferation, **(D)** it slightly induced colony-forming ability of cells. **(E)** Silencing of MCP-1 receptor, CCR2, did not change colony-forming ability of PSCs.

To investigate the interaction between PSCs and macrophages, we differentiated THP-1 monocytic cells into M0 mature macrophages or M2 pro-tumorigenic macrophages. The differentiation process is illustrated in **Fig. 1B.** The differentiation efficacy was first evaluated by morphological changes (**Fig. 1C**). Monocytes tend to grow in suspension, whereas when they differentiate into macrophages, they acquire the ability to attach to surfaces (**Fig. 1C and 1D**). The changes in the expression of differentiation-related markers were assessed by Western blot. The expression of the pan-macrophage marker, CD68, was detected in both M0- and M2-macrophages, while pro-tumorigenic macrophage marker, CD163, was expressed only in M2-macrophages (**Fig. 1D**).

3.2. Indirect co-culture of PSCs with monocytes/macrophages increased their migration and invasion abilities

To evaluate the effect of paracrine interactions between macrophages and PSCs on migration, invasion, and protein expression, indirect co-culture experiments were performed (**Fig. 2A**). Briefly, monocytes/macrophages were seeded into inserts (0.4 micron pore size), while PSC cells were seeded at the bottom of the wells, and the two cell types were co-cultured for 48 hours. Notably, 24 h of co-culture of PSCs significantly increased their migration ability (**Fig. 2B**). Besides, the presence of macrophages was shown to induce invasion of PSCs (**Fig. 2C**). Consistently, macrophages promoted the expression of p-Src, p-STAT-3, and Integrin-β1, which are related to migration and invasion abilities of cells. Furthermore, the expression of eukaryotic elongation factor 2 kinase (eEF2K), an oncogenic protein overexpressed in PCa, was also shown to elevate in co-culture conditions (**Fig. 2D**).

3.3. MCP-1 levels increased in the presence of monocytes/macrophages

Following 48 hours interaction between PSCs and monocytes/macrophages, released MCP-1 levels, which play a critical role in monocyte recruitment and macrophage differentiation, were measured via ELISA. As shown in the graph, while monocytes and PSCs in mono-culture conditions released limited levels of MCP-1, the presence of macrophages significantly increased released MCP-1 levels (**Fig. 3A**). The highest levels of MCP-1 release were detected in M2-pro-tumorigenic macrophage-PSC co-culture group (**Fig. 3A**). Consistently, MCP-1 protein expression was also found to be elevated when PSCs co-cultured with macrophages (**Fig. 3B**).

3.4. MCP-1 administration induced colony formation but not proliferation of PSCs

We then treated PSCs with recombinant MCP-1 protein to investigate changes in PSC proliferation and colony formation. MCP-1 treatment did not affect PSC proliferation but slightly increased colony formation (**Fig. 3C, D**). Moreover, targeting MCP-1 signaling by suppressing its receptor, CCR2, did not significantly reduce the colony-forming ability of the cells (**Fig. 3E**).

3.5. Gas6 expression increased in the presence of M2 macrophages

In addition to MCP-1, changes in the expression of another important chemokine, Gas6, which plays a role in monocyte-macrophage differentiation, were assessed. After 48 hours of co-culture, Gas6 expression was found to be elevated in the presence of macrophages, particularly M2 macrophages (**Fig. 4A**). Additionally, the expression of the active form of the Gas6 receptor, p-Axl, was also increased in macrophage-interacted groups (**Fig. 4A**).

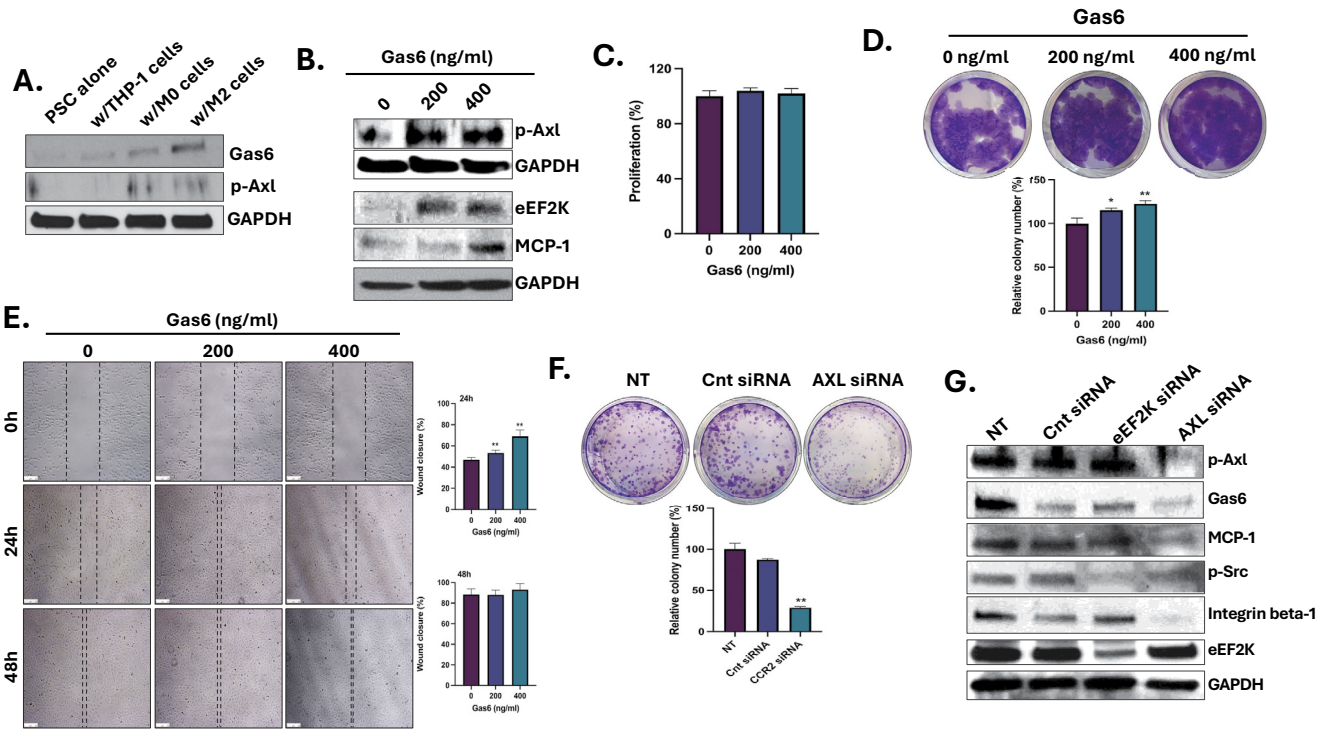

Figure 4: Increased Gas6 levels induced colony-formation and migration of PSCs and targeting Gas6/Axl signaling decreased colony-forming ability and the expression of aggressiveness-related proteins. (A) Gas6 protein and p-Axl were detected to be increased in the presence of macrophages. **(B)** Gas6 treatment induced the phosphorylation of its receptor and the expression of eEF2K and MCP-1 proteins. **(C-E)** While Gas6 exposure did not alter cell proliferation, caused an induction in colony formation and migration abilities of PSCs. **(F)** Targeting Gas6/Axl signaling by suppressing its receptor via siRNA caused a reduction in colony-forming ability of PSCs and **(G)** decreased the expression of p-Axl, Gas6, MCP-1, p-Src and Integrin-β1.

3.6. Gas6 treatment induced the expression of MCP-1 and promoted colony-formation and migration of the cells

We then applied recombinant Gas6 to PSCs to evaluate its role on PSCs colony formation, migration and protein expression. Following 30 minutes Gas6 exposure, the expression p-Axl was shown to increase (**Fig. 4B**). Additionally, eEF2K protein expression was increased in response to Gas6 treatment. Interestingly, 400 ng/ml of Gas6 dramatically induced MCP-1 protein expression, suggesting a potential crosstalk between these two proteins (**Fig. 4B**). Although Gas6 treatment did not significantly alter PSC proliferation, it induced colony formation and cell migration (**Fig. 4C-E**).

3.7. Targeting the Gas6/Axl axis decreased colony-formation and MCP-1 expression

Next, we silenced the Gas6 receptor, Axl, using siRNA technology. Axl silencing significantly reduced the colony-forming ability of PSCs (**Fig. 4F**). As expected, silencing of Axl decreased expression levels of Gas6 and p-Axl (**Fig.**

4G). Interestingly, MCP-1, p-Src, and Integrin-β1 were also reduced in Axl-silenced groups, while there were no changes in eEF2K expression (**Fig. 4G**).

Discussion

In this study, we showed that indirect interaction between PSCs and macrophages increases the migration and invasion abilities of PSCs. Notably, the Gas6 protein, primarily released by monocytes/macrophages, was shown to play a role in regulating communication between these two cell types. Targeting Gas6 receptor, Axl, resulted in a decrease in the expression levels of Gas6, MCP-1, p-Src, and Integrin-beta1, further supporting the central role of Gas6/Axl signaling in regulating processes related to cancer aggressiveness.

The presence of macrophages, especially M2 pro-tumorigenic macrophages, has been known to correlate with tumor growth, metastasis, and resistance to therapy (21, 22). Consistently, high expression levels of macrophage markers, CD68 and CD163, are associated with poorer overall survival in PDAC patients (23). Most studies have focused on the effect of TAMs on cancer cells; however, research on their role in PSCs, the most common cell type in PCa TME, remains limited. Therefore, we indirectly co-cultured PSCs with monocytes/macrophages to evaluate the effect of this interaction on the behaviors of PSCs. The results showed that macrophages enhanced the migration and invasion abilities of PSCs via paracrine signaling mechanisms.

TAM-derived factors such as cytokines, chemokines and exosomes have been shown to support tumor progression by promoting tumor proliferation, motility and invasion (24, 25). For instance, MCP-1, a chemokine involved in macrophage recruitment and differentiation, is known to promote tumor aggressiveness by regulating the interactions between tumor cells and macrophages (26). In addition, increased levels of MCP-1 in the serum of PDAC patients are associated with poor prognosis (27). Despite studies indicating its role in cancer-macrophage communication, research focusing on its role from the perspective of PSCs is limited. Our results showed that MCP-1 levels were increased as a result of paracrine interaction between PSCs and TAMs, and MCP-1 administration enhanced colony formation of PSCs, suggesting that MCP-1 may act as a mediator in the crosstalk between macrophages and PSCs.

In addition to MCP-1, we investigated the role of Gas6, another important chemokine involved in monocyte-macrophage differentiation and tumor aggressiveness. Gas6 contributes to tumor progression by promoting macrophage differentiation and cancer cell proliferation, migration and angiogenesis (28, 29). Our results showed that Gas6 expression was increased in the presence of M2 macrophages, and recombinant Gas6 treatment enhanced colony formation and cell migration. Furthermore, Gas6 administration further elevated MCP-1 levels, and targeting the Gas6 receptor, Axl, significantly reduced colony formation and MCP-1 expression in PSCs, suggesting a potential feedback loop between Gas6 and MCP-1. Currently, no study has demonstrated the crosstalk between Gas6 and MCP-1 in the cancer progression process. The only study indicating a potential interaction between Gas6 and MCP-1 showed that Gas6 expression was related to increased infiltration of inflammatory monocytes expressing CCR2 in venous thrombosis mouse models. Additionally, *in vitro* expression of both CCR2 and CCL2 was shown to depend on Gas6 expression in monocytes and endothelial cells (30). Here, we showed for the first time the role of Gas6 in macrophage-PSC interaction and potential interaction between Gas6 and MCP-1.

Conclusion

Our study showed the role of macrophage-derived factors, MCP-1 and Gas6, in promoting aggressive behaviors of PSCs. The findings specifically highlight the significance of Gas6 signaling in mediating macrophage-PSC interactions and suggest that targeting the Gas6/Axl axis could offer a new therapeutic strategy for future studies. Further research is needed to explore the potential of this pathway as a target for therapeutic intervention and to better understand the mechanisms underlying its effects on tumor progression.

Declarations

Acknowledgments

D.K thanks The Scientific and Technological Research Council of Turkey (TUBITAK) 2214A International Doctoral Research Fellowship Programme, Turkey (Project Number: 1059B141500214). This article is extracted from my doctorate dissertation entitled "Targeting Pancreatic Cancer and Tumor Microenvironment Through Eukaryotic Elongation Factor 2 Kinase (eEF2K) Inhibition", supervised by Egemen Dere (Ph.D. Dissertation, Uludag University, Bursa, Turkiye, 2017, Council of Higher Education Thesis Number: 470558).

Funding

N/A.

Conflicts of Interest

The authors declare no competing interests.

Ethics Approval

N/A

Availability of Data and Material

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material. Raw data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

D.K. wrote the manuscript and performed all experiments. D.K. and B.O. conceived and coordinated the study. E.D. and E.U. contributed to writing the manuscript. All authors analyzed the results and approved the final version of the manuscript.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1370292

Correlation of Perceived Social Support with Medication Adherence and Quality of Life in Individuals with Chronic Obstructive Pulmonary Disease

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Received: 04.10.2023
Accepted: 01.10.2024

ABSTRACT

Background/Purpose: It is known that declining social support increases the disease burden in individuals with chronic obstructive pulmonary disease. The association between perceived social support with medication adherence and quality of life in COPD patients is unclear. The aim of this study was to show the correlation of perceived social support with medication adherence and quality of life in individuals with chronic obstructive pulmonary disease.

Methods: A descriptive and correlational study was conducted. A Patient Information Form, the Multi-Dimensional Scale of Perceived Social Support, the St. George Respiratory Questionnaire and the Medication Adherence Report Scale were used to collect data. A total of 221 patients with COPD were included in the study. Descriptive statistics, the Mann–Whitney U test, Kruskal-Wallis tests, and Spearman's correlation analysis were used to analyze the data.

Results: Perceived social support was negatively correlated with the respiration score ($r=-0.23$, $p\leq0.01$), and positively with medication adherence ($r=0.17$, $p<0.05$). Perceived support from family and friends positively affects health-related quality of life ($p<0.05$). It was also found that perceived social support, respiration score and medication adherence mean scores varied according to many of the descriptive characteristics ($p<0.05$).

Conclusion: Identifying the sources of social support can promote developing strategies which enhance the coping resources.

Keywords: chronic obstructive pulmonary disease, medication adherence, nursing, perceived social support, quality of life, social support.

ÖZET

Amaç: Kronik obstrüktif akciğer hastalığı olan bireylerde azalan sosyal desteğin hastalık yükünü artırdığı bilinmektedir. KOAH hastalarında algılanan sosyal destek ile ilaç uyumu ve yaşam kalitesi arasındaki ilişki net değildir. Bu çalışmanın amacı, kronik obstrüktif akciğer hastalığı olan bireylerde algılanan sosyal desteğin ilaç uyumu ve yaşam kalitesi arasındaki ilişkiyi sunmaktır.

Yöntemler: Tanımlayıcı ve ilişki arayıcı bir çalışma yürütüldü. Verilerin toplanmasında "Hasta Bilgi Formu", "Çok Boyutlu Algılanan Sosyal Destek Ölçeği", "St. George Solunum Anketi" ve "İlaç Uyumunu Bildirim Ölçeği" kullanıldı. Çalışmaya toplam 221 KOAH hastası dahil edildi. Verilerin analizinde tanımlayıcı istatistikler, Mann-Whitney U testi, Kruskal-Wallis testleri ve Spearman korelasyon analizi kullanıldı.

Bulgular: Algılanan sosyal destek ile solunum skoru arasında negatif yönde ($r=-0.23$, $p\leq0.01$), ilaç uyumu ile pozitif yönde ilişki bulundu ($r=0.17$, $p<0.05$). Aile ve arkadaşlardan algılanan destek sağlıkla ilgili yaşam kalitesini olumlu yönde etkilediği saptandı ($p<0.05$). Ayrıca, algılanan sosyal destek, solunum skoru ve ilaç uyumu ortalama puanlarının tanımlayıcı özelliklerin birçoğuna göre değiştiği bulundu ($p<0.05$).

Sonuç: Sosyal destek kaynaklarının belirlenmesi, baş etme kaynaklarını artıran stratejilerin geliştirilmesini teşvik edebilir.

Anahtar Kelimeler: Kronik obstrüktif akciğer hastalığı, ilaç uyumu, hemşirelik, algılanan sosyal destek, yaşam kalitesi, sosyal destek.

COPD continues to be a worldwide health problem because of the steadily increasing burden of morbidity and mortality (1). In individuals who cannot cope with the physical, psychological and social effects of COPD, the symptom burden and severity of the disease increase, and have a negative effect on health-related quality of life (2). In addition, in individuals with COPD who have difficulty in adhering to medication and who continue to be exposed to risk factors, repeated attacks are seen as the stages of the disease advance (3). The quality of life of persons with COPD who cannot achieve symptom management (4) or who have difficulty in achieving medication adherence (5) gets progressively worse. Also, their confidence in fighting the disease is reduced, and they feel a greater need for social support (6).

In individuals with COPD, increased social support is important for a good level of medication adherence, self-care management (7), and for seeing fewer signs relating to depression, anxiety and stress (8). Also, social support which is perceived to be at a good level helps the improvement of a patient's functional capacities and the control of physical and psychological effects (2). A poor level of social relations in those with COPD can create a risk for the solution of problems relating to the disease (9). For this reason, in order to be able to implement approaches to recovery from the effects of COPD, the factors making it difficult to control the effects of the disease must be determined. As far as we know, there is no research in the literature simultaneously examining the correlation of social support with medication adherence and quality of life in individuals with COPD and the factors affecting it. Therefore, the aim of this study was to determine the correlation of perceived social support with medication adherence and quality of life in individuals with COPD.

Material and Method

Design and Participants

The research was conducted with a descriptive and correlational design, and was performed at the chest diseases outpatients' department of Ankara City Hospital, the second largest hospital in Ankara and Turkey. The program G*Power (v3.1.9.2) was used to determine the sample size. Taking account of direct effect sizes standardized with two correlation tests (correlation: point biserial model), and taking 95% confidence, 95% test power and an effect size of 0.30, a minimum sample size of 111 was determined. Patients were included in the research who had had a diagnosis of COPD for at least one year, who did not have a COPD exacerbation and/or a respiratory tract infection, and who were at stage1 (mild), stage 2 (moderate) or stage 3 (severe) according to the GOLD report. Those who were at stage 4 (very severe), those who had had a COPD diagnosis for less than one year, and those with an exacerbation and/or a respiratory tract infection were excluded from the study. The research was completed with 221 volunteer participants who met the inclusion criteria.

Data Collection and Instruments

The face-to-face interview technique was used to collect data between December 2021 and May 2022. The patients' sociodemographic and clinical characteristics were obtained from interviews conducted with the patients by the researchers, from patients' files, and from the hospital's electronic medical records system. Data collection instruments;

Patient Information Form: This form was developed by the researchers in accordance with the literature. On the form, there are a total of 21 questions, covering sociodemographic characteristics such as age, gender, education and work status, and COPD-related characteristics such as time since COPD diagnosis, smoking, treatment and accompanying diseases (2,4,6,9).

Multi-Dimensional Scale of Perceived Social Support (MSPSS): The scale consists of 12 items in total. MSPSS has three subscales with four items each to identify support from families, friends and other individuals. The possible score range of each subscale is 4–28 points, with a minimum possible total score of 12 points and a maximum of 84 points. A high score obtained from the scale indicates a high level of perceived social support (10). Eker et al. (2001) calculated the Cronbach's alpha for the MSPSS to be 0.89, and our Cronbach's alpha was 0.89.

St. George Respiratory Questionnaire (SGRQ): The SGRQ consists of 50 items that survey patients' recollection of their symptoms (symptom scores), the disturbance to patients' daily physical activity (activity scores) and psychosocial dysfunction (impact scores). The three sections of the test are scored separately and a total score is calculated, ranging from 0 to 100. A score of 0

indicates perfect health condition, while 100 shows the worst health condition (11). Polatlı et al. (2013) calculated the Cronbach's alpha for the SGRQ to be 0.88, and our Cronbach's alpha was 0.86.

Medication Adherence Report Scale (MARS): The scale consists of five items in total. The total test score is determined by summing the scores obtained from the items. The scores obtained from the scale range from 5 to 25. Higher total scores indicate better medication adherence and lower total scores indicate poor medication adherence (12). Temeloğlu Şen et al. (2019) calculated the Cronbach's alpha for the MARS to be 0.78, and our Cronbach's alpha was 0.96.

Statistical Analysis

SPSS IBM™ version 24.0 was used to perform all analyses. The Kolmogorov-Smirnov test was conducted to determine whether the data was normally distributed. Descriptive statistics, the Mann–Whitney U test and Kruskal-Wallis tests were used for the analysis of the data. The correlations between MSPSS, SGRQ and MARS were tested using Spearman correlation coefficient. Multiple linear regression analysis was used to examine the association of MSPSS and SGRQ. A p-value of less than 0.05 was considered significant.

Ethical Considerations

This research was conducted in conformity with ethical principles and the Helsinki Declaration. Before starting the study, approval from the Ethics Committee (decision number 14/14, dated 19 August 2021) and consent from each participant were obtained.

Results

The mean age of those participating in the research was 60.41±11.80 years, and their mean time since COPD diagnosis was 4.17±3.96 years.

Descriptive statistics for MSPSS, SGRQ and MARS total and subscale scores

Participants' total score means obtained from MSPSS, SGRQ and MARS were 51.87 (SD = 17.56), 31.47 (SD = 10.2) and 19.84 (SD = 5.53) respectively (Table 1).

Comparison of participants' MSPSS, SGRQ and MARS mean scores according to their descriptive characteristics

Table 1: Descriptive statistics for MSPSS, SGRQ and MARS total and subscale scores

Variable	Mean (SD)	Min-Max
MSPSS total	51.87 (17.56)	12.00-84.00
Family support	21.12 (7.22)	4.00-28.00
Friend support	16.60 (7.96)	4.00-28.00
Other person support	14.11 (8.30)	4.00-28.00
SGRQ total	31.47 (10.02)	10.00-57.00
Symptom score	7.54 (0.77)	2.00-8.00
Activity score	9.62 (3.95)	1.00-24.00
Impact score	13.92 (6.83)	1.00-27.00
MARS total	19.84 (5.53)	5.00-25.00

Abbreviations: MSPSS=Multi-Dimensional Scale of Perceived Social Support; SGRQ=St. George Respiratory Questionnaire; MARS=Medication Adherence Report Scale

Low MSPSS score means were obtained by participants who had another chronic disease in addition to COPD (p=0.00), lived alone (p=0.00), were single (p=0.03), had a primary or middle school education (p=0.00), did not work (p=0.00), had an economic income less than expenditure (p=0.02), were at a severe stage (p=0.00), had been hospitalized (p=0.00), had resorted to the emergency service (p=0.00), were receiving LTOT (p=0.00), or who were using a large number of medications (Table 2).

Table 2: Comparison of participants' mean MSPSS, SGRQ and MARS scores according to their descriptive characteristics

			MSPSS		SGRQ		MARS	
		n (%)	Mean (SD)	MWU*/KW** p	Mean (SD)	MWU*/KW** p	Mean (SD)	MWU*/ KW** p
Gender	Female	53 (24.0)	51.55 (15.80)	-0.179* 0.86	33.25 (10.54)	-1,421* 0.16	20.80 (5.05)	-0.750* 0.45
	Male	168 (76.0)	51.98 (18.12)		30.91 (9.31)		19.60 (5.66)	
Marital Status	Married	184 (83.3)	53.14 (17.55)	-2.245* **0.03**	30.82 (10.12)	-2.245* **0.03**	20.09 (5.55)	-1.870* 0.06
	Single	37 (16.7)	45.59 (16.40)		34.73 (8.91)		18.57 (5.30)	
Working	Yes	81 (36.7)	56.90 (17.63)	-3.199* **0.00**	27.83 (8.01)	-4.091* **0.00**	18.62 (6.38)	-1.972* **0.04**
	No	140 (63.3)	48.96 (16.90)		33.58 (10.47)		20.54 (4.85)	
Chronic disease accompanying COPD	Yes	126 (57.0)	48.02 (17.97)	-3.753* **0.00**	34.14 (9.82)	-4.668* **0.00**	19.70 (5.37)	-0.840* 0.40
	No	95 (43.0)	56.99 (15.66)		27.93 (9.19)		20.02(5.76)	
LTOT	Yes	58 (26.2)	45.05 (17.83)	-3.39* **0.00**	41.12 (6.33)	-8.574* **0.00**	20.29 (4.55)	-0.128* 0.90
	No	163 (73.8)	54.30 (16.86)		28.04 (8.77)		19.67 (5.84)	
Training on COPD in the last 1 year	Yes	87 (39.4)	50.10 (17.51)	-1.000* 0.32	35.32 (8.55)	-4.755* **0.00**	20.23 (4.67)	-0.038* 0.97
	No	134 (60.6)	53.02 (17.56)		28.97 (10.13)		19.58 (6.02)	
Persons lived with	Alone[a]	41 (18.6)	42.32 (17.36)	32.814** **0.00** a<b, a<c b<c, d<c	32.71 (9.63)	34.207** **0.00** c<a, c<b c<d, b<d	17.88 (5.61)	11.018** **0.01** a<b
	Spouse[b]	90 (40.7)	51.38 (16.50)		33.27 (9.81)		20.90 (5.07)	
	Spouse and children[c]	70 (31.7)	60.60 (16.37)		26.27 (8.69)		19.23 (6.01)	
	Children[d]	20 (9.0)	43.15 (11.27)		39.05 (7.90)		21.20 (4.31)	
Economic status	Income less than expenditure[a]	119 (53,8)	49.27 (17.26)	8.254** p= **0.02** a<c	30.53 (9.91)	2.391** 0.30	19.43 (5.88)	0.848** 0.65
	Income and expenditure equal[b]	92 (41.6)	54.27 (17.98)		32.78 (10.30)		20.27 (5.19)	
	Income more than expenditure[c]	10 (4.5)	60.80 (11.17)		30.60 (7.90)		20.70 (4.00)	
Education status	Primary school[a]	49 (22,2)	47.22 (18.81)	16.494** **0.00** a<d, b<d, a<c	33.61 (10.88)	12.376** **0.01** c<b, d<b	18.86 (6.84)	1.123** 0.77
	Middle school[b]	62 (28.1)	48.48 (19.36)		34.10 (10.48)		20.24 (4.45)	
	High school[c]	76 (34,4)	54.00 (15.37)		29.34 (9.01)		19.74 (5.66)	
	University[d]	34 (1.8)	60.00 (13.33)		28.35 (8.31)		20.74 (4.84)	
Smoking	Never smoked[a]	17 (7.7)	54.41 (13.83)	0.899** 0.64	29.71 (10.74)	15.696** **0.00** b>c	22.53 (3.26)	9.185** **0.01** a>c, b>c
	Quit smoking[b]	116 (52.5)	50.63 (17.43)		33.98 (9.32)		20.67 (4.62)	
	Currently smoke[c]	88 (39.8)	53.02 (18.39)		28.50 (9.98)		18.22 (6.49)	
Use of Antidepressants	Yes	14 (6.3)	45.07 (18.53)	-1.545* 0.12	36.64 (13.74)	-1.742** 0.08	16.14 (7.08)	-2.234* **0.03**
	No	207 (93.7)	52.33 (17.44)		31.12 (9.66)		20.09 (5.34)	
COPD duration	1 year[a]	54 (24.4)	53.52 (16.29)	5.166** 0.16	25.57 (7.47)	59.659** **0.00** a<b, a<c a<d, b<c	19.35 (6.20)	5.066** 0.17
	2-5 years[b]	111 (50.2)	53.30 (17.69)		30.15 (9.44)		19.82 (5.42)	
	6-15 years[c]	45 (20.4)	46.69 (17.32)		40.62 (7.40)		19.80 (4.78)	
	≥ 16 years[d]	11 (5.0)	50.64 (21.25)		36.27 (9.02)		22.55 (5.96)	
COPD Stage	Stage 1[a]	114 (51.6)	55.87 (16.74)	18.730** **0.00** b<a, c<a, c<b	27.25 (8.27)	58.249** **0.00** a<b, a<c b<c	19.11 (6.06)	3.180** 0.20
	Stage 2[b]	75 (33.9)	50.32 (17.77)		33.39 (10.04)		20.71 (4.49)	
	Stage 3[c]	32 (14.5)	41.28 (15.22)		42.00 (5.75)		20.41 (5.52)	
Hospitalization in the last one year because of exacerbation	No[a]	130 (58.8)	56.07 (16.85)	22.359** **0.00** b<a, c<a, c<b	26.59 (8.25)	74.684** **0.00** a<b, a<c	19.86 (5.95)	1.968** 0.37
	Once[b]	79 (35.7)	47.44 (17.13)		38.22 (8.10)		19.76 (4.58)	
	Two or more times[c]	12 (5.5)	35.58 (10.60)		39.92 (7.49)		20.08 (6.83)	
Visit to emergency service in the last one year because of exacerbation	No[a]	87 (39.4)	56.67 (17.88)	16.573** **0.00** b<a, c<a, c<b	25.51 (8.53)	55.334** **0.00** a<b, a<c	20,80 (5,82)	11.866** **0.00** b<a
	Once[b]	123 (55.7)	49.80 (16.78)		34.96 (9.02)		19,08 (5,10)	
	Two or more times[c]	11 (4.9)	37.09 (10.22)		39.64 (7.50)		20,64 (6,90)	
Total number of medications used	1-2[a]	103 (46.6)	56.55 (16.69)	28.851** **0.00** c<a, c<b	27.89 (8.32)	27.701** **0.00** a<b, a<c	19.63 (5.75)	1.834** 0.40
	3-5[b]	76 (34.4)	52.49 (15.75)		33.45 (10.14)		20.57 (5.02)	
	≥ 6[c]	42 (19.0)	39.29 (17.01)		36.67 (10.54)		19.02 (5.82)	

**MWU: Mann–Whitney U test value, **KW: Kruskal–Wallis test value, Significant difference at p<0,05; value in bold: significant;*
Abbreviations: MSPSS=Multi-Dimensional Scale of Perceived Social Support; SGRQ=St. George Respiratory Questionnaire; MARS=Medication Adherence Report Scale; LTOT= Long-term oxygen therapy,

SGRQ score means were low in participants who were married (p=0.03), lived with their spouse and children (p=0.00), were working (p=0.00), had a high school or university education (p=0.01), had quit smoking (p=0.00), had had a COPD diagnosis for one year (p=0.00), were not at a severe stage (p=0.00), did not have another chronic disease in addition to COPD (p=0.00), had not been hospitalized (p=0.00), had not resorted to the emergency service (p=0.00), were not receiving LTOT (p=0.00), who had received education on COPD (p=0.00), and who used few medications (p=0.00) (Table 2).

The SGRQ score means were high of participants who did not live alone (p=0.01), were not working (p=0.04), did not smoke (p=0.01), had not resorted to the emergency service (p=0.00), and did not use anti-depressants (p=0.03) (Table 2).

Correlation between age and mean MSPSS, SGRQ and MARS scores

A weak negative correlation was found between age and MSPSS (r=-0.23, p≤0.01), and a moderate positive correlation was found with SGRQ (r=0.47, p≤0.01).

Correlation between MSPSS, SGRQ and MARS

The correlation between MSPSS and SGRQ mean scores was weak and negative (r=-0.23, p≤0.01), and that between MSPSS and MARS was very weak and positive (r=0.17, p<0.05) (Table 3).

Table 3: Correlation between MSPSS, SGRQ and MARS (n=221)

Family support Friend support			**MSPSS**				**SGRQ**				**MARS**
			Other person support	**MSPSS**	**Symptom score**	**Activity score**	**Impact score**	**SGRQ**	**MARS**		
MSPSS	Family support	r	1	-	-	-	-	-	-	-	-
	Friend support	r	**0,28***	1	-	-	-	-	-	-	-
	Other person support	r	0,05	**0,56***	1	-	-	-	-	-	-
	MSPSS total	r	**0,52***	**0,85***	**0,77***	1	-	-	-	-	-
SGRQ	Symptom score	r	**-0,33***	**-0,23***	0,01	**-0,21***	1	-	-	-	-
	Activity score	r	**-0,20***	**-0,31***	-0,13	**-0,30***	**0,37***	1	-	-	-
	Impact score	r	**-0,31***	**-0,18***	0,04	**-0,18***	**0,53***	**0,67***	1	-	-
	SGRQ total	r	**-0,30***	**-0,23***	-0,03	**-0,23***	**0,50***	**0,80***	**0,92***	1	-
MARS	**MARS total**	r	**0,39***	0,10	-0,01	**0,17****	-0,07	0,00	-0,11	-0,08	1

*r: Spearman correlation ; *p≤0,01;**p<0,05*

The effect of the mean scores of MSPSS and its subdimensions on the mean scores of SGRQ and its subdimensions

It was found that as family and friend support increased, the symptom score (p=0.01; p=0.03), the activity score (p=0.03; p=0.01) and the SGRQ mean score (p=0.00; p=0.01) decreased. As family and friend support increased, the impact score (p=0.00; p=0.01) decreased, and as MSPSS increased, the impact score (p=0.03) also increased (Table 4).

Table 4. Effect of MSPSS and subdimensions mean scores on SGRQ and subdimension mean scores (n=221)

Dependent variables	Independent variables	B	t	p
Symptom score	Constant	8.08	46.47	**0.00***
	Family support	-0.03	-2.79	**0.01***
	Friend support	-0.03	-2.26	**0.03***
	MSPSS	0.01	1.51	0.13
	F=5.146, p= 0.00*, R=0.258, R^2=0.066			
Activity score	Constant	13.32	15.35	**0.00***
	Family support	-0.11	-2.20	**0.03***
	Friend support	-0.18	-2.65	**0.01***
	MSPSS	0.03	0.85	0.39
	F=9.105, p= 0.00*, R=0.334, R^2=0.112			
Impact score	Constant	19.76	13.13	**0.00***
	Family support	-0.37	-4.09	**0.00***
	Friend support	-0.32	-2.78	**0.01***
	MSPSS	0.14	2.20	**0.03***
	F=8.609, p= 0.00*, R=0.326, R^2=0.106			
SGRQ total	Constant	41.01	18.68	**0.00***
	Family support	-0.47	-3.62	**0.00***
	Friend support	-0.48	-2.83	**0.01***
	MSPSS	0.16	1.74	0.08
	F=9.423, p=0.00*, R=0.339, R^2=0.115			

*p: Multiple linear regression analysis, *p<0.05: Significance level; B= regression coefficient*

Discussion

It was found in the study that perceived social support in individuals with COPD was correlated with medication adherence and health-related quality of life. It was found that as family and friend support increased, quality of life also increased. The presence of comorbidities accompanying COPD (2), living alone (7) and being single (4) could negatively affect perceived social support. Also in this study, perceived social support was low in those who had another chronic disease other than COPD, those who live alone and those who were single. Zhao et al. (2020) found that the social support perceived by individuals with COPD was provided mostly by their families (13). The findings of the present study support the literature. Perception of inadequate social support can cause more negative feelings and inadequate self-care in those with COPD (8). For this reason, interventions should be developed to increase social support for those with comorbidities and those living alone. Turnier et al. (2021) found that COPD patients with a higher level of perception of social support were older and married, and had a good level of economic income (4). In the present study also, those who were single or whose economic income was not at a good level had a low level of perceived social support. However, it was found that as age increased, perceived social support and quality of life declined. Also, perceived social support was poor in those

who were hospitalized or who resorted to the emergency service. The severity of COPD can have an adverse effect on perceived social support (9). Having a higher level of social support is correlated with a better quality of life and a smaller symptom burden (4). The findings of the study support the literature.

Health-related quality of life is one of the factors defining an individual's health and well-being, and which is greatly affected by COPD (14). Merino et al. (2019) found that the quality of life of individuals with COPD was not at a good level (40.9± 25.0), and that the effect of their activity score on their quality of life (52.7 ±28.7) was greater (15). In the present study also, a high respiration score showed that quality of life was not at a good level. But in contrast, in other studies (15,16), the impact score was mostly negatively affected. In the impact score, difficulties experienced in the performance of in work, occupation and daily activities are queried. This difference may arise from the higher mean age of the patient populations on which the other studies were performed, or from the smaller number of those working. With increasing age, the frequency with which comorbidities are seen increases, and symptoms get worse (16,17). Hospitalization and the frequency of exacerbations are an indicator of quality of life at a low level (16). It was found in the present study also that those with comorbidities had difficulty in achieving control of the disease, and that their quality of life was not at a good level. Also, it was found that symptom burden increased with advancing age, and that therefore, restrictions were experienced in daily life activities. It is to be expected that the quality of life of individuals whose coping with the disease and its effects is inadequate will be poor, and that their need for health care services will increase.

Even though medication adherence is important for improving health-related quality of life in COPD, a lack of adherence to medication is often seen (16,17). Müllerov et al. (2016) found that individuals with COPD who resorted more to the emergency service, who were younger, who were still smoking and who had two or more comorbidities reported a low level of medication adherence (18). It was found in another study that the adherence to long term treatment was better in those who did not smoke than in those who did (19). The findings of the study support the literature. Lower medication adherence in individuals with COPD who continue to smoke compared to those who have quit is an expected situation. In contrast to these findings, there are studies which report no correlation between smoking and medication adherence (3,20,21). Moretti et al. (2017) found individuals with COPD whose adherence to prescribed drugs was higher were hospitalized less for acute exacerbations (22). In contrast, there was no difference in this study in medication adherence scores according to hospitalization. Similarly, Duarte-de-Araújo et al. (2018) did not find any significant correlation between medication adherence and number of exacerbations (20). Humenberger et al. (2018) found a higher level of medication adherence in those with very severe COPD (3). In the same study, no correlation was found between medication adherence and gender or age. In other studies, it has been reported that there was no significant correlation between age or gender and medication adherence in individuals with COPD (20,21). In the present study also, medication adherence levels showed no difference according to age or gender.

Boland et al. (2016) found that the health-related quality of life of individuals with COPD who adhered to medication was at a worse level than that of patients whose medication adherence was weak (5). In another study, no correlation was found between medication adherence and quality of life (16). In the present study also, no significant correlation was found between quality of life and adherence to medication. The reason for this may be that most participants were at a mild stage. Adherence to treatment is strongly correlated with patients' beliefs concerning the need felt for prescription medicines and the functional severity of the disease (20). Medication adherence at the beginning of treatment affects health related quality of life in a positive way by reducing symptoms of the disease and improving health condition. However, improvement in health related quality of life in the long term may trigger non-adherence to medication (23). Mollaoğlu and Yanmış (2018) found that as perceived social support increased, levels of adherence to medication also rose (24). The findings of the present study support the literature.

Limitations of the Study

One limitation of this study is selection bias because of the questionnaire and scales used in the collection of data. The research was conducted at a single center. The research results are limited by the responses given by the participants who met the research inclusion criteria. For this reason, the results of the research cannot be generalized.

Conclusion

In this study, it was found that the dimension of family support had the most influence on perceived social support scores, while the effect of the activity score was greater on quality of life. It was found that perceived social support declines with advancing age, and that quality of life is not at a good level. Perceived social support was negatively correlated with the respiration score, and positively with medication adherence. It was found that in individuals with COPD, health related quality of life increases as family and friend support increases. It is recommended that qualitative and quantitative studies be conducted evaluating the effect of perceived social support on medication adherence and quality of life. In those whose perceived social support is low, interventions should be developed to increase social support. Education can be given to those with COPD, care-giving family members and nurses on the importance of providing adequate social support and to create awareness of what they can do in this regard, in order to improve medication adherence and quality of life.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1411541

The Longitudinal Association Between Human Milk Composition and Nutritional Status of Exclusively Breastfeeding Mothers

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Received: 28.12.2023
Accepted: 03.09.2024

ABSTRACT

Purpose: The presented study investigated the human milk composition changes associated with the nutritional status of exclusively breastfeeding mothers.

Methods: A total of 59 volunteer mothers whose infants were followed at a well-child outpatient clinic were included in the study. During a six-month study period, anthropometric measurements and body composition of the mothers were evaluated at monthly visits, energy and macronutrients of breast milk were analyzed, and 24-hour food consumption records were taken every 15 days. The study conducted between June 2017 and September 2018 was completed by 15 mothers.

Results: A statistically significant downward trend for total protein (tau-b = -0.208; $p < 0.001$) and true protein (tau-b = -0.230; $p < 0.001$), and upward trend for total lactose (tau-b = 0.119; $p = 0.032$) was determined in human milk of the duration of first 6 months. A weak positive correlation was found between maternal body fat percentage and human milk lactose content, and between fat-free mass and true protein content in the first month of lactation. It was stated that there was a weak negative correlation between the percentage of protein and carbohydrate intake of the mothers in the 1st and 6th months and the energy, protein, and fat composition of human milk.

Conclusions: It was concluded that the macronutrient components of human milk had a trend in the first 6 months of lactation and the composition was affected by the mothers' fat mass and protein intake, especially in the first month.

Keywords: Body Composition, Body Mass Index, Human Milk, Macronutrient, Nutrient Intakes, Energy.

ÖZET

Amaç: Bu çalışmada, emziren annelerin beslenme durumu ile ilişkili anne sütü bileşimindeki değişiklikler araştırılmıştır.

Yöntemler: Bebekleri çocuk sağlığı izlem polikliniğinde takip edilen 59 gönüllü anne çalışmaya dahil edilmiştir. Altı aylık çalışma sürecinde, aylık ziyaretlerle annelerin antropometrik ölçümleri ve vücut kompozisyonları değerlendirilmiş, anne sütünün enerji ve makro besin öğeleri analiz edilmiş, her 15 günde bir 24 saatlik besin tüketim kaydı alınmıştır. Haziran 2017 - Eylül 2018 tarihleri arasında yürütülen çalışmayı 15 anne tamamlamıştır.

Bulgular: İlk altı ay boyunca anne sütünün toplam protein (tau-b = -0,208; p < 0,001) ve true protein (tau-b = -0,230; p < 0,001) için istatistiksel olarak anlamlı bir azalma eğilimi ve toplam laktoz için artış eğilimi (tau-b = 0,119); p = 0,032) saptanmıştır. Emzirmenin birinci ayında, annenin vücut yağ yüzdesi ile anne sütü laktoz bileşimi ve yağsız doku kütlesi ile true protein içeriği arasında pozitif yönlü zayıf bir ilişki saptanmıştır. Annelerin 1. ve 6. aylardaki protein ve karbonhidrat alım yüzdesi ile anne sütünün enerji, protein ve yağ bileşimi arasında negatif yönlü zayıf bir ilişki olduğu tespit edilmiştir.

Sonuçlar: Anne sütünün makro besin ögesi bileşemi emzirmenin ilk 6 ayında bir değişme eğilimi gösterdiği ve bileşimin özellikle ilk ayda annelerin yağ kütlesi ve protein alımından etkilendiği belirlenmiştir.

Anahtar Kelimeler: Vücut kompozisyonu, beden kütle indeksi, anne sütü, makrobesin, besin alımı, enerji.

Human milk (HM) is the uniquely balanced nutrition that contains macronutrients, micronutrients, hormones, antibodies, and bioactive molecules that are necessary for infants (1). The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) recommend that every newborn should exclusively breastfeed for the first 6 months of life, followed by HM with complementary foods for at least 2 years (2).

The composition of HM changes rapidly from the time of birth. Initially, it changes from colostrum to transitional milk and from transitional milk to mature milk (3). It is difficult to determine HM consumption because it is dynamic and changes for several reasons. Changes occur during lactation due to time of day or night or within a single feed due to duration of sucking the breast or due to the time of the pumping session. It also changes between populations. The nutritional status of the lactating mother may also affect energy density and nutrient content of the HM (4-5). Vitamins and trace elements vary in HM depending on the diet and body storages (6).

Obesity, which is increasing in Turkey as in the whole world, is especially common in the female population and affects both maternal and infant health (7-8). The literature emphasizes that higher maternal BMI is associated with higher protein concentrations in human milk (9-10). Also, higher human milk fat content has been reported in overweight and obese women compared to normal weight women (11). Additionally, early changes in milk composition have been detected in the milk of obese mothers, with increases in potentially obesity-promoting fatty acids and decreases in protective fatty acids (12). Bzikowska et al. (2018), found that carbohydrate composition in human milk is also not associated with maternal BMI or the body composition of breastfeeding women (11).

The effect of the mother's nutritional status on HM is not clear in the literature, especially studies with exclusive breastfeeding are limited. The aim of this study is to investigate the longitudinal association between body composition and BMI of the mother, on macronutrient composition of the HM.

Materials and Methods

Study Design and Participants

This study was conducted as a cross-sectional descriptive design between June 2017 and September 2018 in the well-child outpatient clinic of the university hospital, in Istanbul. Ethics committee approval was received from Marmara University School of Medicine, Clinical Research Ethics Committee in May 2017 (Ethics Committee Number: 09.2017.340).

Those who were included in the study were volunteer mothers who started to feed on postpartum day one and who were found to have no contraindication in body composition analysis when they came to the outpatient clinic for follow-up during the first 30 days after birth. Exclusion criteria were gestational age less than 37 weeks and more than 43 weeks, infants weighing less than 2.5 kg and more than 4.5 kg, mothers who smoked and/or consumed alcohol, mothers who experienced problems that delayed the start of breastfeeding, mothers with acute or chronic diseases at the time of data collection and mothers who did not breastfeed exclusively. Mothers who could not complete the study were excluded from the study.

The plan of the research prepared according to the Consolidated Standards for Reporting Studies (CONSORT) 2010 flow chart (13) is shown in Figure 1. At the baseline of the study, 70 mothers were interviewed, and 65 mothers were found eligible for the study. After excluding mothers who did not meet the criteria's, 59 volunteer mothers were enrolled. During the study period of 6 months, 44 mothers were lost at follow-up for various reasons, such as going to different clinics for follow-up, the absence of HM, initiation of formula and/or complementary feeding (Figure 1).

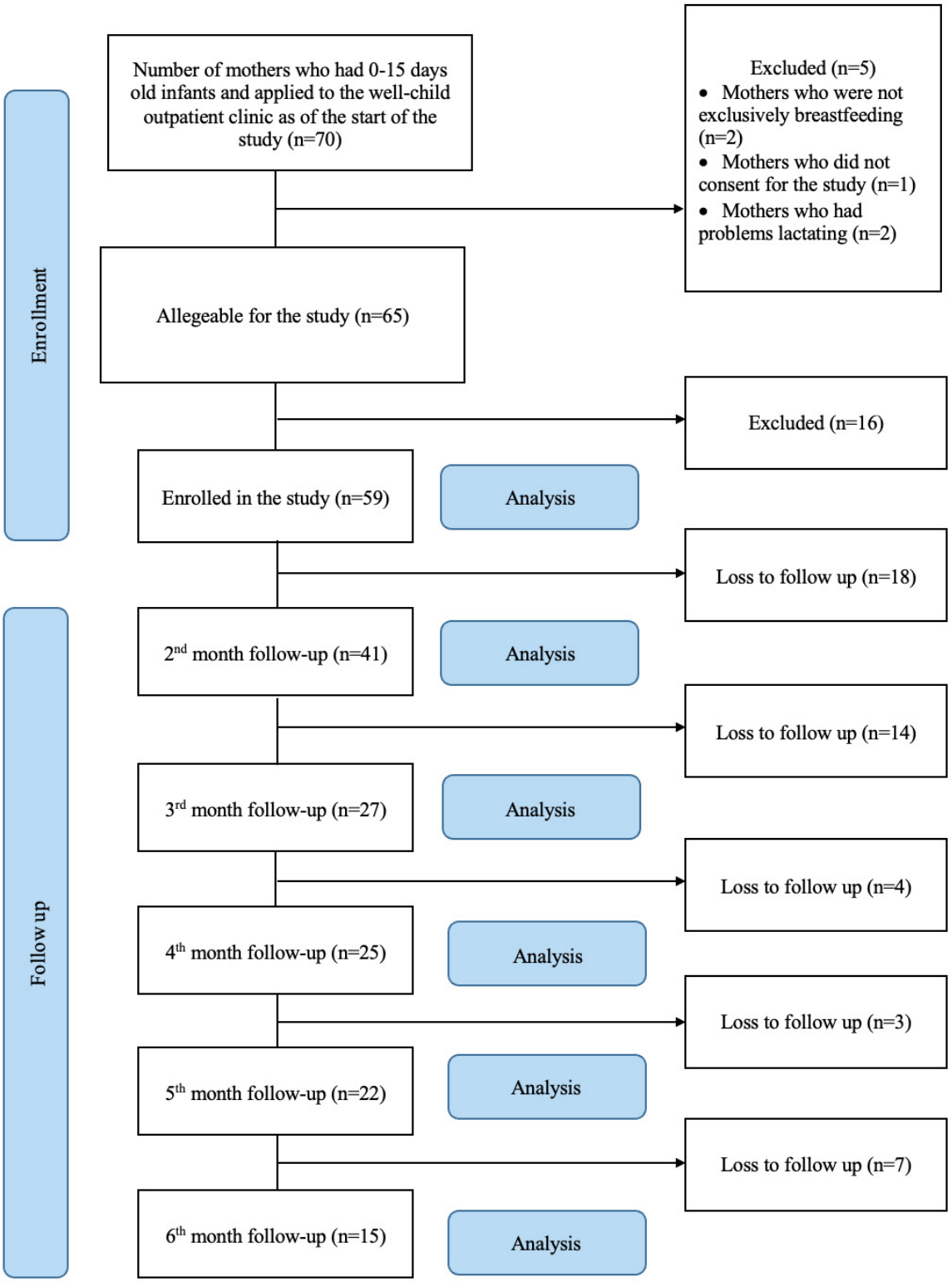

Figure 1: CONSORT 2010 Diagram

Data Collection

At the baseline, a questionnaire form that was constructed by the researchers was filled out in face-to-face interviews. The questionnaire consisted of questions about demographic characteristics, delivery method, weight gain during pregnancy and breastfeeding characteristics.

Collection and analysis of the human milk

Four mL of mature HM was obtained from mothers at the well-child outpatient clinic and the analysis was repeated 2 times for the reliability of the results and the mean value was used. Samples were collected monthly for 6 months, between 9 am and 12 am to minimize possible circadian influences on the milk composition. After the mother fed the infants from the right breast, the milk obtained by hand expression from the right breast was placed in Eppendorf tubes. The samples were analyzed with Miris® HMA TM (Human Milk Analyzer) within 2 hours after expression. Total protein, true protein, fat, lactose, and energy values were determined (14). The HMA provided a calculation of 'total protein' which refers to the protein content based on the total amount of nitrogen in a sample and 'true protein' regarding the correction for non-protein nitrogen compounds, and reflects only the content of actual protein, thus the "true" denotation. Miris HMA uses the factor 6.38 to convert N content to protein content. Additionally, HMA enabled the evaluation of fat and lactose concentrations in HM samples. The calculation of energy was based on the following conversion factors: 4.0, 9.25, 4.4 kcal per 100 mL for lactose, fat and protein, respectively (15).

Anthropometry and body composition parameters

The height (accuracy ± 0.1 cm) and body weight (accuracy ± 0.1 kg) of the mothers were measured according to the standards (16). Body mass index (BMI) was calculated according to WHO classification. Mothers were divided into three groups; normal weight if BMI was between 18.50-24.99 kg/m^2, overweight if BMI was between 25.00-29.99 kg/m^2 and obese if BMI was ≥ 30.00 kg/m^2 (17). Body composition analysis was performed by the bioelectrical impedance method using Inbody 270 device. Total fat percentage, fat mass and lean body mass (LBM) were determined. During the measurement, the mothers' feet were bare and dry, it was confirmed that the mother did not eat or drink at least 3 hours before measurement. This was repeated once a month for 6 months.

Food Consumption

Twenty-four-hour dietary recalls were obtained from the mothers who participated in the study every 15 days. Every month, when HM was collected the food consumptions were taken in face-to-face interviews, and at other times they were asked on the phone throughout the study period. Monthly two 24-hour dietary recalls were taken from each participant and monthly averages were calculated. The information obtained from the dietary recalls was recorded and evaluated by using BeBiS (Nutrition Information Systems) 8.2 nutrition program (18).

Physical activity level

The level of physical activity (PA) was assessed using the short version of the International Physical Activity Questionnaire - Short Form (IPAQ-SF) and it was applied to the mothers monthly for 6 months (19). The validity and reliability of IPAQ for Turkish society was conducted by Sağlam in 2010 (20). The Short Version of the IPAQ (7 questions) assesses physical activity in 4 areas, including leisure, home, work, and transport-related physical activity. Physical activity level is classified as inactive, minimally active, and highly active according to general scores. MET-scoring method, vigorous PA score is equal to vigorous weekly PA expenditure multiplied by 8 METs. Moderate weekly PA expenditure is multiplied by 4 METs and walking PA by 3.3 METs to calculate moderate and walking PA score, respectively. Total PA score is the sum of vigorous, moderate, and walking PA scores. Based on their total and/or vigorous PA score, the subjects were classified into three PA categories (PA class): low, moderate, and high (19).

Statistical Analysis

All statistical analyses were performed using the SPSS 20.0 package program. The Kolmogorov–Smirnov test was used to assess the normality of the distributions. Wilcoxon Signed Rank test was used to test for differences between mothers' characteristics and HM composition according to month of lactation. Kendall's tau-b correlation was applied to analyze the measure of the strength and direction of association that exists between HM composition and month of lactation. The correlation of mothers' characteristics and HM composition were performed using the Spearman's correlation test. The results were evaluated at a 95% confidence interval and a significance level of $p < 0.05$.

Results

A total of 59 mothers participated in the study, 36 mothers completed the evaluations in the third month and 15 mothers completed the evaluations in the sixth month (Figure 1). At the first evaluation, the median age of the mothers was 27.0 years. The percentage of mothers aged between 25-29 was 37.3%. It was found that 35.6% of the mothers were secondary school graduates and the frequency of mothers who graduated from primary and high school was equal (20.3%). It was determined that the majority of mothers (93.2%) were not working. It was stated that 27.1% of the mothers participating in the study had their first birth and 35.6% had their second birth.

Lactation month and HM composition correlation analysis showed that month of lactation was moderately negatively associated with total protein (Kendall's tau-b = -0.208) and true protein (Kendall's tau-b = -0.208) ($p < 0.001$), and positively weak associated with lactose (Kendall's tau-b = 0.119) ($p = 0.032$). It was determined that there was no significant association between energy and fat content of HM and lactation months (Figure 2).

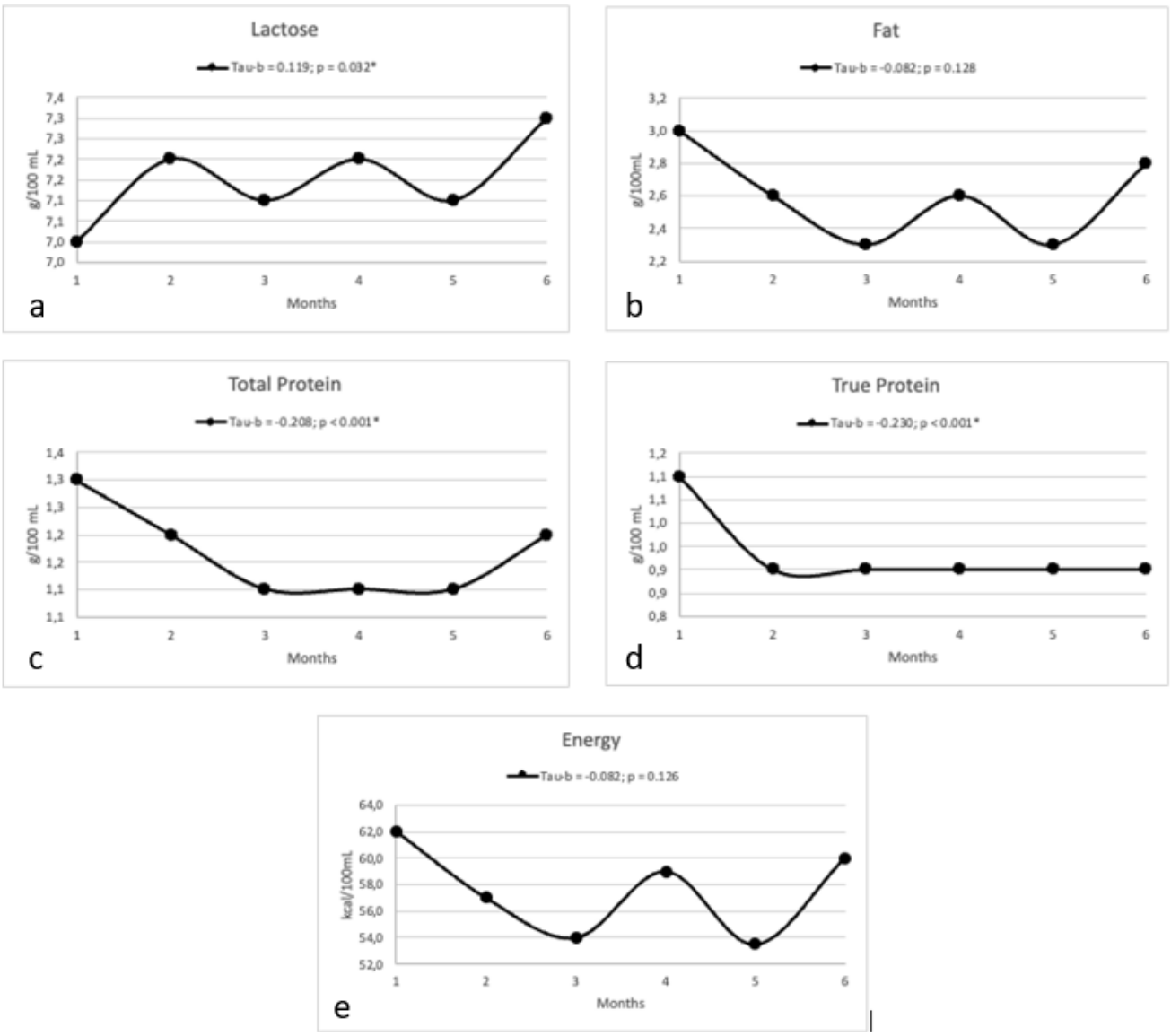

Figure 2: Composition of human milk trend in 0-6 months of lactation

Anthropometric measurements, energy and nutrient intakes, MET-scores, and the human milk composition during the six-month lactation period are presented in Table 1. Body fat percentage increased at the 3rd month compared to the 1st month (p = 0.004). Body weight, BMI, energy and macronutrient intakes and physical activity levels of the mothers did not change significantly during the first 6 months of lactation (p > 0.05).

The correlation between HM composition and mothers' anthropometric measurements, energy and nutrient intakes, and MET-scores are shown in Table 2. There was a weak positive correlation between body fat mass percentage and HM lactose content in addition to fat free mass and true protein content at the 1st month. There was also a weak negative correlation between maternal protein intake and the percentage of energy from protein and the energy and fat content of HM at the 1st month. A moderately negative correlation was found between the percentage of energy from lactose and true protein content of HM at the 6th month.

Table 1: Comparison of anthropometric measurements, energy and nutrient intakes and MET-scores of mothers according to lactation month

Characteristic	Month of lactation **Median (IQR 25th-75th quartiles)**						p1	p2
	1. month (n=59)	2. month (n=36)	3. month (n=26)	4. month (n=24)	5. month (n=21)	6. month (n=15)		
Anthropometric data and body composition measures								
Weight (kg)	74.0 (62.2 – 80.5)	74.2 (63.7 – 84.9)	75.5 (67.4 – 87.3)	77.6 (68.3 – 85.9)	78.3 (67.9 – 88.8)	84.7 (69.0 – 92.4)	0.751	0.950
Body mass index (kg/ m2)	27.1 (24.4 – 32.5)	28.3 (24.3 – 32.9)	30.1 (26.6 – 33.7)	29.2 (26.3 – 33.8)	32.4 (26.1 – 34.8)	32.4 (26.1 – 36.0)	0.628	0.975
Body fat mass (%)	35.3 (29.1 – 39.6)	36.9 (29.7 – 42.6)	39.9 (33.2 – 44.2)	38.9 (29.6 – 43.2)	40.1 (34.2 – 45.6)	40.3 (35.8 – 46.5)	**0.004**	0.272
Fat free mass (%)	25.9 (23.6 – 28.0)	24.8 (23.3 – 28.5)	24.8 (23.8 – 28.4)	24.9 (24.0 – 28.3)	27.6 (23.5 – 28.8)	27.8 (23.3 – 29.1)	**0.010**	0.443
Energy and macronutrient intake								
Energy (kcal)	1687.4 (1350.5 – 1920.0)	1526.8 (1292.8 – 1803.6)	1454.0 (1325.9 – 1835.7)	1436.2 (1156.2 – 1724.0)	1367.1 (1227.5 – 1725.0)	1389.3 (1162.7 – 1623.4)	0.585	0.233
Protein (g)	52.3 (45.1 – 69.6)	50.6 (42.1 – 61.4)	54.5 (47.1 – 65.9)	49.1 (41.5 – 61.7)	54.6 (37.1 – 63.1)	53.2 (41.1 – 62.1)	0.509	0.820
Protein (% kcal)	13.9 (11.3 – 15.4)	13.7 (11.6 – 15.5)	14.5 (12.1 – 16.7)	14.0 (12.1 – 16.1)	14.3 (11.5 – 15.7)	16.4 (13.9 – 17.3)	0.210	0.100
Fat (g)	65.5 (51.9 – 78.6)	61.3 (52.4 – 79.9)	58.6 (52.1 – 79.7)	65.5 (53.3 – 75.0)	59.9 (49.8 – 69.9)	55.2 (50.3 – 72.3)	0.741	0.609
Fat (% kcal)	36.2 (31.3 – 40.8)	37.6 (33.4 – 41.5)	38.6 (32.8 – 42.5)	39.6 (34.4 – 45.5)	39.5 (33.8 – 45.4)	39.4 (34.5 – 46.2)	0.539	0.427
Carbohydrates (g)	208.5 (163.0 – 256.2)	183.3 (141.9 – 218.6)	183.7 (129.8 – 204.7)	150.5 (120.2 – 201.8)	159.4 (134.7 – 227.7)	152.6 (125.8 – 188.0)	0.439	0.233
Carbohydrates (% kcal)	49.1 (43.8 – 53.3)	47.8 (42.8 – 52.8)	46.3 (39.4 – 52.5)	43.6 (40.2 – 51.4)	46.8 (42.6 – 50.3)	44.8 (36.6 – 49.9)	0.820	0.733
MET-score	0.0 (0.0 – 346.5)	0.0 (0.0 – 396.0)	198.0 (0.0 – 540.0)	0.0 (0.0 – 297.0)	0.0 (0.0 – 132.0)	0.0 (0.0 – 198.5)	0.324	0.183

1Difference between First and Third Month of Lactation
2 Difference between First and Sixth Month of Lactation
Wilcoxon signed rank test for paired samples.

Table 2:. Correlations between human milk composition and mothers' characteristics

	Month of lactation	Composition of Human Milk				
		Energy[1]	Total Protein[2]	True Protein[2]	Fat[2]	Lactose[2]
Anthropometric data and body composition measures		r*				
Weight (kg)	1	0.064	0.018	0.055	0.017	0.167
	3	-0.027	-0.226	-0.324	0.085	-0.186
	6	0.391	-0.039	-0.132	0.370	-0.354
Body mass index (kg/ m²)	1	0.013	-0.151	-0.091	-0.012	0.198
	3	0.009	-0.225	-0.259	-0.065	0.052
	6	0.454	-0.027	-0.118	0.407	-0.395
Body fat mass (%)	1	0.055	-0.219	-0.196	0.040	**0.281***
	3	0.019	-0.168	-0.193	-0.041	0.059
	6	0.497	0.094	-0.006	0.423	-0.153
Fat free mass (%)	1	0.033	0.254	**0.276***	-0.024	-0.066
	3	-0.062	-0.212	-0.329	0.172	-0.372
	6	-0.057	-0.207	-0.173	0.022	-0.373
Energy and macronutrient intake						
Energy (kcal)	1	0.055	-0.058	-0.025	0.020	0.040
	3	-0.139	-0.034	0.125	-0.252	0.213
	6	-0.215	0.022	-0.014	-0.210	0.070
Protein (g)	1	**-0.310***	0.058	0.092	**-0.325***	-0.050
	3	-0.010	-0.270	-0.271	0.122	-0.234
	6	-0.474	-0.196	-0.235	-0.470	0.227
Protein (% kcal)	1	**-0.274***	0.097	0.106	**-0.276***	-0.057
	3	-0.079	-0.107	-0.293	0.054	-0.201
	6	-0.314	-0.095	-0.067	-0.343	-0.084
Fat (g)	1	-0.030	-0.193	-0.169	-0.033	0.028
	3	-0.159	-0.199	-0.081	-0.138	0.034
	6	-0.176	0.299	0.233	-0.210	0.118
Fat (% kcal)	1	0.048	-0.180	-0.205	0.078	-0.045
	3	-0.136	-0.162	-0.231	0.032	-0.168
	6	-0.116	0.506	0.487	-0.160	-0.034
Carbohydrates (g)	1	0.018	0.027	0.057	-0.021	0.090
	3	0.030	0.048	0.186	-0.136	0.330
	6	-0.083	-0.184	-0.179	-0.061	0.045
Carbohydrates (% kcal)	1	0.068	0.179	0.190	0.029	0.040
	3	0.050	0.111	0.191	-0.134	0.360
	6	0.129	-0.427	**-0.554***	0.177	0.104
MET-score	1	-0.214	0.019	0.080	-0.221	0.004
	3	0.028	0.049	0.213	-0.054	-0.043
	6	-0.424	-0.322	-0.276	-0.421	0.545

1 Energy is presented as kilocalories (kcal) per 100 mL.
2 Macronutrients and dry matter are presented as grams per 100 mL.

Discussion

The present study indicated that there was a decrease in the protein content and an increase in the lactose content of the HM in the 6-month period. It was found that especially in the first month, body fat mass and protein intake affect the composition of human milk. However, no correlation was found between other macronutrient intakes of mothers and HM composition in any other months.

While many studies of HM composition have been conducted, components of HM are still being investigated. According to the studies evaluating the composition of HM; the average fat content does not differ greatly; it has been found to range from 3.2 to 3.6 g/dl between populations. Lactose and protein content of HM is less variable; mature milk contains between 6.3-8.1 g/dl lactose and 0.9-1.2 g/dl protein (4,21). In line with previous studies, HM macronutrient content did not change significantly according to the months. In this study, it was determined that the HM fat content was 2.7-3.3 g/dl, the lactose content was 6.9-7.2 g/dl, the protein content was 1.0-1.2 g.

Previous studies have shown that the protein content of HM decreases rapidly during the first month and then gradually towards the sixth month of lactation (22-23). Bzikowska-Jura et al. found a statistically significant downward trend for total protein (tau-b = −0.31) and true protein (tau-b = −0.30) concentration in HM in the duration of 6 months (18). In line with Bzikowska-Jura et al. this study stated that lactation month was moderately negatively associated with total protein and true protein, in addition a positive weak association with lactose was found (11). Although the literature and our study show that there are changes in HM over a 6-month period, there is not enough data to claim that this situation is the same for all populations.

When the literature is examined, it is seen that HM fat increases as BMI increases (24-28). Daniel et al. showed that for every 1 kg/m^2 increase in BMI, the HM fat content increases by 0.56 g/L (24). In another study, fat content in HM was higher at 6 months ($p = 0.002$) and protein content at 5 and 6 months of postpartum ($p < 0.03$) in overweight mothers compared to mothers with normal BMI (28). In the literature, it has been stated that there is a correlation between mothers' BMI and HM composition (24-29) and there are differences in HM composition according to BMI classification (28); in this study, unlike other studies, it was determined that there was no correlation between BMI and HM fat content.

Maternal BMI was positively associated with a higher protein level in HM (26-30). Daniel et al. found no significant association between maternal BMI and HM total protein (24), protein content in HM did not appear to differ between overweight and/or obese and normal weighted women (27). Similar to the studies of Daniel et al. (24) and Leghi et al. (27), there was no correlation found between BMI and the protein content of HM in this study.

Research shows that association of maternal BMI and HM lactose content is inconsistent. While Lenghi et al., found that higher BMI was associated with higher lactose concentrations at different stages of lactation (27), in other studies it was determined that BMI was negatively correlated with the lactose content of HM (26-31). On the contrary Daniel et al., did not find any relationship between BMI and HM lactose content (24). In a study conducted with 2632 mothers in Korea, it was found that the mothers' BMIs were negatively correlated with the lactose content of HM (26). In a meta-analysis, a total of 31 studies (5078 lactating women) were included in the qualitative synthesis and nine studies (872 lactating women) in the quantitative synthesis, BMI was associated with different lactose concentrations at different stages of lactation (27). In another study, women with high BMI had significantly lower HM lactose content at 4 and 6 months postpartum than those in the normal BMI range (28). In this study, similar to the study of Daniel et al. (24), it was determined that there was no correlation between BMI and the lactose content of HM.

In the literature, the results of the relationship between the body composition of the mother and the energy and macronutrient content of HM are contradictory. As for the fat content of HM, there are studies that demonstrate higher body fat mass is related with higher HM fat content (27,32) whereas, other studies found no correlation (1,31). Some studies found a correlation between body composition and lactose content of HM (27,31), other studies found no correlation (1,33). For the protein content of the HM; a study shows higher body fat percentage is related to higher HM protein content, it also demonstrates that this correlation weakens as the lactation month progresses (33), contrarily there are studies that did not find any correlation between body composition and HM protein content (1,31). In a meta-analysis, maternal obesity was associated with higher HM fat and lactose concentrations at different stages of lactation (27). In the presented study, there was no correlation found between the fat content of the HM and maternal body composition at any month. However, a weak positive correlation between body fat mass percentage and HM lactose content was found in addition to fat free mass and true protein content at 1st

month. In the early period of lactation, maternal body fat stores are used during pregnancy to support milk production. Therefore, the physiological effects of rapid fat mobilization make it difficult to establish a correlation between mothers' ideal weight and HM fat concentration in the first 3-4 months of lactation (29).

Maternal diet has been reported to affect the HM composition, with conflicting results (5, 11, 34-35). Yang et al. (2014) found that dietary intake had a less impact on HM fat content than maternal BMI (25). In a study, HM fat content seemed to have a weak positive correlation with maternal fat intake, although it was not statistically significant (1). Quinn et al. showed that the contents of fat and energy of HM increase with the duration of breastfeeding, however no relationship was found with maternal diet (31). The studies conducted by Iranpour et al. (2013) and Daud et al. (2013) demonstrated that maternal food intake during lactation did not modify the composition of HM (3,29). In another study, significant positive associations were found between protein, fat, carbohydrate and energy intake, and levels of macronutrients in HM, especially in protein content (30). Unlike other studies present study shows that maternal protein intake and the percentage of energy from protein has a weak negative correlation with the energy and fat content of HM at 1st month. A moderately negative correlation was found between the percentage of energy from lactose and true protein content of HM at 6th months.

This study has multiple strengths. First of all, the samples were obtained as hindmilk during the day, immediately after breastfeeding, with the same technique (by hand expressing) and always from the same breast (right), only mothers who exclusively breastfed were included. Secondly, advanced techniques and protocols were used to assess the milk collection, which allowed possible errors in HM composition to be minimized. Thirdly, it was a longitudinal study in which milk samples from 0-6 months were collected. Also, the participants from different socioeconomic levels were presented in the study and the body composition of the mothers was measured by researchers with advanced techniques.

Limitations of the present study include food consumption records were obtained with a recall method based on mothers' declaration and some were done with telephone interviews. This method does not reflect daily changes in diet and all dietary habits. Also, HM was collected and analyzed only once a month.

Conclusions

Knowing and alternating the body composition and maternal diet will affect HM content and this will be guiding in terms of planning education and counseling services to lactating women. The information obtained from this study will contribute to the development of strategies for mothers in the period of breastfeeding and improve the HM composition to ensure optimal feeding of infants.

Due to the small number of studies in this field and the inconsistency of the data, it is thought that the effect of the mothers' body mass index on the macronutrient content of HM should be evaluated in larger sample groups and randomized controlled studies.

Declarations

Funding

This study was supported by Marmara University Scientific Research Projects Commission (BAPKO) with SAG-A-120917-0496 number.

Conflicts of Interest

The authors declare no competing interests.

Ethics Approval

Ethics committee approval was received from Marmara University School of Medicine, Clinical Research Ethics Committee in May 2017 (Ethics Committee Number: 09.2017.340).

Availability of Data and Material

Data may be available from the principal investigator, Dr. Şule Aktaç, upon reasonable request.

Authors' Contributions

All authors critically reviewed the draft manuscript and approved the final version of the manuscript for publication.

Conceived and designed the analysis – ŞA

Collected the data – ŞA, SK, ZMÇ, AHİ and GS

Contributed data or analysis tools – ŞA, SK, ZMÇ, AHİ, GS, PB and FEG

Performed the analysis – ŞA, SK, ZMÇ, AHİ, GS

Wrote the paper - ŞA, SK, ZMÇ, AHİ, GS, PB and FEG

Acknowledgments

We would like to thank the participants and Marmara University Pendik Training and Research Hospital Well-child Polyclinic nurses for their dedication and hard work in collecting the samples. This study was supported by Marmara University Scientific Research Projects Commission (BAPKO) with SAG-A-120917-0496 number.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1482901

Evaluation of Microbiota Awareness Among the Healthcare Professionals in Kars Harakani State Hospital

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Received: 13.05.2024
Accepted: 09.09.2024

ABSTRACT

Purpose: This study aimed to evaluate microbiota awareness among the healthcare professionals in Kars Harakani State Hospital by their sex, educational status, marital status, and occupational groups.

Methods: This descriptive and cross-sectional study was conducted between 1-31 December 2023 with the participation of the healthcare professionals (n=329) working at Kars Harakani State Hospital. In the study, a questionnaire form inquiring about sociodemographic characteristics and the Microbiota Awareness Scale (MAS) were used. MAS consists of the subfactors of "general information", "product information", "chronic disease", and "probiotic and prebiotic".

Results: Product information, chronic disease, and probiotic and prebiotic subscale scores and MAS total scale scores of females were found to be higher than males. The general information mean score of those with graduate education levels was higher than those with associate degree levels. The product information score of the married participants was determined to be higher than the single participants. The general information mean score of physicians was higher compared to the mean scores of nurses and technicians, while the product information mean score of technicians was lower than the mean scores of physicians, nurses, and midwives. The chronic disease mean score of nurses was higher than that of physicians, and their probiotic and prebiotic mean score and MAS total scale mean score were higher compared to the mean scores of technicians.

Conclusion: Microbiota awareness levels among healthcare professionals vary according to their occupational groups.

Keywords: Microbiota awareness, prebiotic, probiotic, healthcare professionals

ÖZET

Amaç: Bu çalışma Kars Harakani Devlet Hastanesi sağlık çalışanlarının mikrobiyota farkındalıklarının cinsiyet, eğitim durumu, medeni durum ve meslek gruplarına göre değerlendirilmesi amacıyla yapılmıştır.

Yöntem: Tanımlayıcı kesitsel tipte olan bu çalışma 1-31 Aralık 2023 tarihleri arasında Kars Harakani Devlet Hastanesi sağlık çalışanları (n=329) ile yapılmıştır. Çalışmada sosyodemografik bilgileri içeren anket formuna ek olarak mikrobiyota farkındalık ölçeği (MFÖ) kullanılmıştır. MFÖ "genel bilgiler", "ürün bilgisi", "kronik hastalık" ve "probiyotik ve prebiyotik" alt faktörlerinden oluşmaktadır.

Bulgular: Kadınların ürün bilgisi, kronik hastalık, probiyotik ve prebiyotik ve MFÖ toplam puanları erkeklerden yüksektir. Eğitim durumu lisansüstü olanların genel bilgiler puanı, ön lisans olanlardan yüksektir. Evli olanların ürün bilgisi puanı bekâr olanlardan yüksektir. Doktorların genel bilgiler puanı, hemşire ve teknikerlerden yüksek; teknikerlerin ürün bilgisi puanı, doktor, hemşire ve ebelerden düşüktür. Hemşirelerin kronik hastalık puanı, doktorlardan; probiyotik ve prebiyotik puanı ve MFÖ toplam puanı teknikerlerden yüksektir.

Sonuç: Sağlık personeli içinde meslek gruplarına göre mikrobiyota farkındalık düzeyi farklılık göstermektedir.

Anahtar Kelimeler: Mikrobiyota farkındalığı, prebiyotik, probiyotik, sağlık çalışanları

The human body is colonized by trillions of microorganisms (1). The first data regarding the existence of these microorganisms were discovered by Antonie Van Leeuwenhoek and described as "animalcules" (2). Leeuwenhoek's article titled "A Letter on Protozoa" provides the preliminary definitions of protists and bacteria, and the data of the period are considered the precursor of todays' human microbiota studies (3).

In its general definition, the microbiota is the total sum of microorganisms (bacteria, fungi, archaea, viruses, and protozoans) living in different parts of the skin, mouth, excretory system, lungs, and gastrointestinal system in our body (4). Microbiota has been one of the most significant areas of research in recent years. Especially data on the intestinal microbiota shed light on the diagnosis and treatment of many diseases. Many studies have emphasized the relationship between the microbiota and various diseases such as obesity, diabetes, cardiovascular diseases, neurological diseases, cancer, etc., and a healthy microbiota is considered a powerful weapon to protect from such diseases (5,6). Two major studies in microbiota research, namely the European Metagenomics of the Human Intestinal Tract (MetaHIT) and the USA Human Microbiome Project (HMP), demonstrated that a healthy intestinal microbiota is closely related to the general health of the human body (1,7). Countless factors such as nutrition, prebiotics and probiotics intake, method of birth, stress, etc. are significant in the modulation of the microbiota (8-10).

The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines prebiotics as substances used selectively by microorganisms living in our intestines and beneficial for health. While the safe and adequate intake amount of prebiotics is not definite, it is especially important in terms of supporting health that microorganisms in the intestinal microbiota produce short-chain fatty acids by using these substrata (11). As for probiotics, ISAPP defines them as living microorganisms that have beneficial effects on the health and physiology of the host when they are taken in adequate amounts. Various functions of probiotics such as strengthening the immune system, preventing diarrhea, and protecting from many infections affect human health directly or indirectly (12).

Healthcare professionals assume the role of providing consultancy in addition to providing medical care and treatment services. Therefore, microbiota awareness of healthcare professionals can be accepted as a criterion for the consultancy service they will provide to patients. This study aimed to evaluate the microbiota awareness of healthcare professionals by their sex, educational status, marital status, and occupational groups.

Material and Methods

This study was conducted as a descriptive and cross-sectional study between 1-31 December 2023. All healthcare professionals who agreed to participate in the study read and signed the Informed Consent Form, and a copy was given to them.

Study Population and Sample

The study population consisted of 780 healthcare professionals working at Kars Harakani State Hospital with at least an associate degree. The minimum sample size was calculated as 258 with a 95% confidence interval and 5% margin of error (13). 295 voluntary healthcare professionals who met the inclusion criteria were included in the study.

Study Inclusion Criteria

- Beig a healthcare professional working at Kars Harakani State Hospital,
- Having a minimum of associate degree in education,
- Being between 20-65 years old,
- Not having a chronic disease diagnosed by physicians,
- Not using any medications, and
- Volunteering to participate in the study.

Data Collection Tools

The study data were collected by using the sociodemographic questionnaire form prepared by the researcher in line with literature review and the Microbiota Awareness Scale (MAS).

The sociodemographic questionnaire form includes questions about certain characteristics of the participants such as age, sex, educational status, marital status, and occupations.

MAS is a scale developed by Külcü and Önal (2022) to evaluate the microbiota awareness of individuals (14). The

first 16 items of MAS are 5-point Likert-type questions, and the last 4 items are open-ended questions, 20 items in total. For the Likert-type questions, the respondent is asked to choose among the options of "strongly disagree", "disagree", "undecided", "agree", and "strongly agree", which are scored as 1, 2, 3, 4, and 5, respectively. Questions 17 and 18 on the scale are knowledge questions with 5 options, and it is calculated out of *5 (number of correct answers marked / number of correct answers - number of incorrect answers marked / number of incorrect answers), and it is rounded to the closest digit among 1, 2, 3, 4, and 5. Items 19 and 20 on the scale are open-ended questions, and each correct response is given 1 point, 4 and above correct responses are scored as 5 points, and no correct response is scored as 1 point. The minimum and maximum scores to be obtained from the scale are 20 and 100 points. The scale has no cutoff point, and high scores obtained from the scale are interpreted as a high level of microbiota awareness. It has four subscales, which are general information (items 1, 2, 4, 5, 6, and 13), product information (items 17, 18, 19, and 20), chronic disease (items 8, 10, 12, 14, and 16), and probiotic and prebiotic (items 3, 7, 9, 11, and 15).

Ethical Approval and Institutional Permission for the Study

Ethical approval for the study was obtained from Agri Ibrahim Cecen University Scientific Research Ethics Committee with the decision dated 30.11.2023 and numbered 256, and institutional permission was taken from the Head Physician's Office of Kars Harakani State Hospital.

Statistical Analysis Methods Used

The data collected were analyzed by using the IBM Statistical Package for the Social Sciences (SPSS) 22® software, and the normal distribution assumption for quantitative variables was checked with the Kolmogorov-Smirnov test. Descriptive statistics were presented as median (25-75 percentile) for quantitative variables and as frequency (%) for categorical variables. In the comparison of independent groups, as the normal distribution assumption was not met, the Mann-Whitney U test and Kruskal-Wallis H test were used. The statistical significance level was accepted as $p<0.05$.

Results

The general characteristics of the participants are presented in Table 1. Of the 329 healthcare professionals with a mean age of 32 years (range 21-62 years), 72.6% were female and 27.4% were male. Of the participants, 24.6% had associate degrees, 52.0% had undergraduate degrees, and 23.4% had graduate degrees. 56.8% of the participants were married, and 43.2% were single. 15.5% of the participants were physicians, 33.4% were nurses, 15.8% were midwives, and 35.3% were technicians.

Table1: General characteristics of the participants

		n	%
Sex	Female	239	72.6
	Male	90	27.4
Age (years)		32.0 (26.0 – 38.0)	
Education Status	Associate degree	81	24.6
	Undergraduate degree	171	52.0
	Graduate degree	77	23.4
Marital Status	Married	187	56.8
	Single	142	43.2
Profession	Physician	51	15.5
	Nurse	110	33.4
	Midwife	52	15.8
	Technician	116	35.3

Descriptive statistics were expressed as frequency (n) and percentage (%) or median (25th-75th percentile).

The comparison of the participants' MAS scores by sex is presented in Table 2. Female participants' mean scores on product information, chronic disease, probiotic and prebiotic, and MAS total scale scores were statistically significantly higher than those of male participants ($p=0.012$; $p=0.006$; $p<0.001$; $p=0.002$).

Table 2: Comparison results of MAS scores according to sex

	Sex		
	Female	**Male**	**p***
General Information	26.0 (24.0 – 28.0)	27.0 (25.0 – 28.0)	0.219
Product Information	8.0 (5.0 – 10.0)	7.0 (5.0 – 9.0)	**0.012**
Chronic Disease	15.0 (17.0 – 19.0)	16.0 (12.8 – 18.0)	**0.006**
Probiotic and Prebiotic	20.0 (17.0 – 21.0)	17.0 (16.0 – 20.0)	**<0.001**
MAS Total	70.0 (65.0 – 75.0)	67.0 (61.0 – 73.3)	**0.002**

**:Mann-Whitney U test*
Descriptive statistics are expressed as median (25th-75th percentile).

The results of the comparison of the participants' MAS scores by educational status are presented in Table 3. The general information mean score of those with graduate degrees was statistically significantly higher than the mean score of those with associate degrees (p=0.025).

Table 3: Comparison results of MAS scores according to educational status

	Education Status			
	Associate Degree	**Undergraduate Degree**	**Graduate Degree**	**p***
General Information	26.0 (24.0 – 27.0)[a]	27.0 (24.0 – 28.0)[a,b]	27.0 (26.0 – 28.0)[b]	**0.025**
Product Information	7.0 (5.0 – 9.0)	8.0 (5.0 – 10.0)	8.0 (5.0 – 10.0)	0.140
Chronic Disease	17.0 (15.0 – 19.0)	16.0 (15.0 – 18.0)	17.0 (14.0 – 18.0)	0.536
Probiotic and Prebiotic	19.0 (16.0 – 21.0)	19.0 (16.0 – 21.0)	19.0 (17.0 – 20.5)	0.999
MAS Total	69.0 (63.0 – 72.0)	69.0 (63.0 – 75.0)	70.0 (65.5 – 76.5)	0.360

**:Kruskal-Wallis H test*
Similar letters in the same row indicate statistical similarity and different letters indicate dissimilarity.
Descriptive statistics are expressed as median (25th-75th percentile).

The results of the comparison of the participants' MAS scores by marital status are presented in Table 4. The product information mean score of the married participants was found to be statistically significantly higher compared to the mean score of the single participants (p=0.028).

Table 4: Comparison results of MAS scores according to marital status

	Marital Status		
	Married	**Single**	**p***
General Information	27.0 (24.0 – 28.0)	26.0 (25.0 – 28.0)	0.854
Product Information	8.0 (5.0 – 10.0)	7.0 (5.0 – 9.0)	**0.028**
Chronic Disease	17.0 (15.0 – 19.0)	16.0 (14.0 – 19.0)	0.919
Probiotic and Prebiotic	19.0 (17.0 – 21.0)	19.0 (17.0 – 21.0)	0.203
MAS Total	69.0 (64.0 – 75.0)	69.0 (63.8 – 74.0)	0.255

**:Mann-Whitney U test*
Descriptive statistics are expressed as median (25th-75th percentile).

The results of the comparison of the participants' MAS scores by occupational groups are presented in Table 5. The general information mean score of the physicians was significantly higher than that of the nurses and technicians (p<0.001). The product information mean score of the technicians was significantly lower than that of the physicians, nurses, and midwives (p<0.001). The chronic disease mean score of the nurses was significantly higher than that of the physicians (p=0.002). The probiotic and prebiotic mean scores of the nurses were significantly higher than those of the technicians (p=0.002). The MAS total scale mean score of the nurses was significantly higher than that of the technicians (p=0.001).

Table 5: Comparison results of MAS scores according to occupational groups

	Profession				
	Physician	**Nurse**	**Midwife**	**Technician**	**p***
General Information	27.0 (28.0-28.0)[a]	26.0 (24.0-28.0)[b]	27.0 (24.0-28.0)[a,b]	26.0 (24.3-27.8)[b]	**<0.001**
Product Information	8.0 (6.0-10.0)[a]	8.0 (6.0-11.0)[a]	8.0 (5.0-10.0)[a]	6.0 (5.0-8.8)[b]	**<0.001**
Chronic Disease	15.0 (13.0-17.0)[a]	17.0 (15.0-19.0)[b]	16.0 (14.0-18.0)[a,b]	16.0 (14.0-19.0)[a,b]	**0.002**
Probiotic and Prebiotic	18.0 (17.0-20.0)[a,b]	20.0 (17.8-21.0)[a]	19.0 (18.0-21.0)[a,b]	18.0 (16.0-21.0)[b]	**0.002**
MAS Total	69.0 (64.0-73.0)[a,b]	72.0 (67.0-76.0)[a]	69.0 (64.0-72.0)[a,b]	67.0 (61.0-73.0)[b]	**0.001**

**:Kruskal-Wallis H test*
Similar letters in the same row indicate statistical similarity and different letters indicate dissimilarity.
Descriptive statistics are expressed as median (25th-75th percentile).

Discussion

Healthcare professionals assume the responsibility of providing consultancy to their patients as well as medical treatment services. Therefore, their knowledge of the relationship between microbiota and health and their high level of microbiota awareness can be accepted as a criterion for the consultancy they will provide to their patients. This study aimed to evaluate the microbiota awareness of the healthcare professionals working at Kars Harakani State Hospital.

In the study, the product information, chronic disease, probiotic and prebiotic, and MAS total scale mean scores of the female participants were found to be higher than those of the male participants. In the study they conducted, Deniz Akan et al. (2020) determined that male healthcare professionals had higher levels of microbiota awareness, while Serinçay (2021) reported that the probiotic information level of the physicians receiving specialty education in medicine did not differ between males and females (15,16). In a study that was conducted on Nutrition and Dietetics students as healthcare professional candidates and in which the same scale was used, no difference was found between male and female students in terms of microbiota awareness (17). In a study including 1,066 healthcare professionals from 30 countries, no statistically significant difference was observed between female and male healthcare professionals in terms of probiotic information (18). In another study conducted on university students, the scale mean scores of the females were reported to be higher than those of the males (19). In the study conducted by Oliver et al. (2014), it was determined that females believed more in the benefits of probiotics and prebiotics for health than males did (20). In a similar study, it was demonstrated that females knew the concept of probiotics more compared to males and that females displayed a more positive attitude regarding the dissemination of information about the use of probiotics (21). These results similar to the results of the present study may have stemmed from the fact that women are more interested in nutrition and cuisine culture in society.

In the present study, the general information score of the individuals with graduate education level was found to be higher than that of the participants with associate degree education level. In their study, Deniz Akan et al. (2020) found that the microbiota information levels of those with graduate education level were higher (15). In another study, in which the relationship between educational levels and prebiotic and probiotic information was examined, it was determined that the participants with master's degrees scored statistically significantly higher compared to those with undergraduate education levels (22). In this context, it can be stated that different study areas in graduate education in health departments may have increased microbiota awareness.

In the present study, the product information score of the married participants was found to be higher than that of the single participants, but another study reported that single individuals knew more about the microbiota concept (15). In a study covering 1,265 Australian adults, marital status did not create a difference in terms of prebiotic and probiotic awareness (23).

In the present study, the general information mean score of the physicians was found to be higher than those of the nurses and technicians, while the product information mean score of the technicians was determined to be lower compared to those of the physicians, nurses, and midwives. Moreover, the chronic disease mean score of the nurses was higher than that of the physicians, and their probiotic and prebiotic mean score and MAS total scale mean score were higher than those of the technicians. In a study evaluating the microbiota information and awareness of midwives and nurses working in an obstetrics clinic, it was reported that 26.2% of the participating midwives and nurses never heard of the term microbiota, and 36.2% heard about it but did not exactly know what it was (24). In a study evaluating the information levels of physicians, nurses, and other healthcare professionals working at a university hospital about microbiota, it was observed that the physicians had a higher level of microbiota awareness compared to the nurses and other healthcare professionals (15). Another study found that although physicians generally knew about probiotics, it was seen that when they were presented with more specific information, they did not have adequate information (16). A study conducted on a comprehensive sample showed that more than 80% of the physicians and three-fourths of the nurses defined probiotics correctly (18). In a study including dietitians, pediatricians, and practicing physicians, the possibility of recommending probiotics-containing foods was found to be higher among the pediatricians and practicing physicians compared to the dietitians (25). In a study including dietitians, nurses, physicians, and pharmacists, it was found that the participants were more familiar with the definition of probiotics (88%) than the definition of prebiotics (22%), and it was interpreted that this situation may have been associated with the marketing and advertisement of supplements that contain probiotics (20). In the study they conducted in different countries of Europe, Pettoello-Mantovani et al. (2019) demonstrated that dietitians, pediatricians, and practicing physicians had a high level of consensus on the attitudes of healthcare professionals toward nutrition recommendations and probiotics (26).

Conclusion

Appropriate consultancy provided to patients by healthcare professionals is in direct proportion to their awareness levels. The present study showed that healthcare professionals had different levels of microbiota awareness but at an inadequate level in general.

The relatively small sample size and the inclusion of only one hospital's healthcare workers in the study are among the limitations of the study. However, it is important to evaluate the microbiota awareness levels of healthcare professionals with an appropriate measurement tool. In this context, this study is important in terms of being the first study to evaluate the microbiota awareness levels of healthcare workers using the MAS developed by Külcü and Önal (2022), the validity and reliability of which were accepted to be good.

Many studies in the literature show that the microbiota awareness levels of healthcare professionals are generally poor and that although their probiotic information levels are high, they are hesitant to recommend probiotics to their patients due to inadequate data about them.

In conclusion, it is necessary to train healthcare professionals on microbiota, probiotics, and prebiotics in a way that will contribute to their clinical practices and most importantly, with an evidence-based approach. Thus, their trust in the products they will recommend to their patients and the efficiency of the treatment provided to the patients will be increased.

Declarations

Funding

No financial support was received for this study.

Conflict of Interest/Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

Ethics committee permission dated 30.11.2023 and numbered 256 was obtained from Agri Ibrahim Cecen University Scientific Research Ethics Committee in order to carry out the study.

Availability of Data and Material

The data are original.

Authors' Contributions

Conceived and designed the analysis: H.S., H.T., E.E.Ç., M.K., B.Ç.; Collected the data: H.T., Contributed data or analysis tools: H.S., H.T., E.E.Ç., M.K., B.Ç.; Performed the analysis: H.S.; Wrote the paper: H.S., H.T., E.E.Ç., M.K., B.Ç.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1489968

Evaluation of Sexual Life According to Pregnancy Trimesters

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Received: 27.05.2024
Accepted: 02.09.2024

ABSTRACT

Aim: Physiological changes during pregnancy affect the couple's sexual life. Changes in sexual desire and arousal are inevitable with the strong effect of hormones. The aim of this study was to evaluate the sexual function levels of pregnant women according to trimester periods.

Materials and Methods: The study was conducted prospectively; Those who applied to the Gynecology and Obstetrics clinic in between November 2023 and December 2023; Women whose pregnancy was between 6 and 40 weeks were included. After obtaining informed consent from patients who met the inclusion and exclusion criteria, the 'Female Sexual Function Index-FSFI' questionnaire was administered face-to-face and age, parity, educational status, employment status and body mass index were calculated and recorded.

Results: A total of 198 pregnant women between 6-40 weeks of gestation who applied to the gynaecology and obstetrics outpatient clinic accepted to participate in the study. Of the pregnant women who participated in the study, 64 were in the first trimester, 64 were in the second trimester and 67 were in the third trimester. When the groups were compared, 93.75% of the first trimester pregnant women, 93.75% of the second trimester pregnant women and 98.5% of the third trimester pregnant women were diagnosed with sexual dysfunction and the rate of sexual dysfunction was significantly higher in the third trimester.

Conclusion: This study also showed that sexual function problems of women increase in the first and last trimesters of pregnancy; sexual desire and satisfaction with sexuality, arousal and orgasm decreases.

Keywords: pregnancy, sexual function, trimester

ÖZET

Amaç: Gebelik döneminde meydana gelen fizyolojik değişiklikler çiftin cinsel hayatını etkilemektedir. Hormonların güçlü etkisi ile de cinsel istek ve uyarılmada değişikliklerin olması kaçınılmazdır. Çalışmada gebelerin trimester dönemlerine göre cinsel fonksiyon düzeylerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya prospektif olarak; Kasım 2023 -Aralık 2023 tarihleri arasında Mengücekgazi Eğitim Araştırma hastanesi kadın hastalıkları ve doğum polikliniğine başvuran; 6-40 hafta arasında gebeliği bulunan kadınlar dâhil edildi. Dahil edilme ve dışlanma kriterlerini karşılayan hastalara onam alındıktan sonra 'Kadın Cinsel İşlev Ölçeği-FSFI' anketi yüz yüze olarak uygulandı ve yaş, parite, eğitim durumu, çalışma durumu, beden kitle indeksleri hesaplanıp kayıt altına alınarak bu verilerin trimesterler arasında farklılık gösterip göstermediği değerlendirildi.

Bulgular: Kadın hastalıkları ve doğum polikliniğine başvuran; 6-40 hafta arasında gebeliği bulunan 198 gebe çalışmaya katılmayı kabul etti. Çalışmaya katılan gebelerin 64'ü birinci trimester gebelik haftasındaki, 64'ü ikinci trimester gebelik haftasındaki ve 67 tanesi de üçüncü trimester gebelik haftası içerisindeki kadınlardan oluşmaktaydı. Birinci trimesterdaki gebelerin %93,75 , ikinci trimesterdaki gebelerin %93,75 ve üçüncü trimesterdaki gebelerin %98,5 cinsel fonksiyon bozukluğu tanısı alarak gruplar kıyaslandığında üçüncü trimesterda cinsel işlev bozukluğu görülme oranı anlamlı daha yüksek olarak görüldü.

Sonuç: Bu çalışma göstermiştir ki gebeliğin ilk ve son trimesterinde kadınların cinsel işlev sorunları artmakta; cinsel istek ve cinsellikten memnuniyet duyma, uyarılma ve orgazm olma durumları azalmaktadır.

Anahtar Kelimeler: gebelik, cinsel fonksiyon, trimester

Pregnancy is a process characterized by physiological and psychological changes and hormonal fluctuations. Rapidly rising estrogen and progesterone in the blood and the main hormone of pregnancy, Human Chorionic Gonodotropin (HCG), causes weight gain due to increased intravascular and extravascular fluid and changes in the digestive, respiratory and cardiovascular systems, especially in the first trimester [1]. In addition to changes in all systems, psychological changes such as fatigue, weakness, headache, insomnia and intolerance to odors also occur. Additionally, changes in the mammary gland may occasion breast tenderness and milk production during sexual arousal. Although it does not seem possible that ; these rapid and intense changes in thewoman during pregnancy does not affect the sexual life of the couple. [2]. Especially in the first trimester of pregnancy, increased blood flow in the vulvar and pelvic region increases sexual arousal in women. In the second trimester, adaptation to sexual life may become easier due to the psychological acceptance of pregnancy and the establishment of hormonal and physical balance.Changes in the sexual life of the couple will be inevitable with the meaning attributed to pregnancy in social life, cultural factors and the mission of motherhood.

Materials and Methods

The study prospectively included women with a pregnancy between 6-40 weeks who applied to the gynecology and obstetrics outpatient clinic of Mengücekgazi Training and Research Hospital between November 2023 and December 2023. Patients who were previously diagnosed with sexual dysfunction and who were prohibited from sexual intercourse due to risky pregnancy were excluded from the study. After obtaining consent from the patients who met the inclusion and exclusion criteria, the 'Female Sexual Function Questionnaire-FSFI' was administered face-to-face. The 19-question FSFI questionnaire scores the participants' sexual function status in the last four weeks on the sub-parameters of sexual desire, orgasm, arousal, satisfaction, lubrication and pain. The cut off value was taken as = 26.55, with the highest score being 36 and the lowest score being 2. Pregnant women with a score below 26.55 were considered to have sexual dysfunction. Age, parity, educational status, employment status, and body mass index were calculated and recorded, and the variability of these data between trimesters was compared. In determining the study group, the rule of MacCallum, Widaman, Zhang and Hong that the size of the sample group should be at least 5 times the number of items in the scale was taken into consideration and 198 pregnant women with 10 times the number of questions in the questionnaire were included in the study. The study was started after the approval decision dated 02.11.2023 and numbered 2023-19/13 was obtained from Erzincan Binali Yıldırım University Clinical Research Ethics Committee.

Statistical Analyses

SPSS 21.0 program was used for statistical analysis and ratios, and the distribution of variables was evaluated by Kolmogorov-Smirnov test and histograms. Mean, standard deviation (SD), frequency and percentage distribution were used for descriptive statistical methods and Kruskal Wallis H Test was used for comparison of dependent and independent variables. The cut-off value for significance was $p \leq 0.05$.

Results

Between November 2023 and December 2023, 198 pregnant women who applied to the Gynecology and Obstetrics polyclinic of Mengücekgazi Training and Research Hospital between 6-40 weeks of gestation were questioned and 198 pregnant women agreed to participate in the study. Of the pregnant women who participated in the study, 64 were in the first trimester of pregnancy, 64 were in the second trimester of pregnancy and 67 were in the third trimester of pregnancy. The ages of the patients were normally distributed and ranged between 19 and 42 years with a mean age was 28.84±5.2 years.

Demographic variables including age, gestational week, gravidity, parity, abortion and number of living children, education and employment status are shown in Table 1. The total number of pregnancies was between 1 and 8 (mean 2.32±1.2), parity between 0 and 5 (mean 1.01±0.9), and number of living children between 0 and 4 (mean 1.01±0.94). The number of abortions ranged between 0 and 5 (mean 0.318±0.65) (Table 1).

Table 1: Sociodemographic variables					
Data	Mean(±Ss.)(n=198)	1.Trimester(n=64)	2.Trimester(n=67)	3.Trimester(n=67)	p
Age	28,84±5,2	30,46 ±5,69	27,78±4,98	28,83±5,21	0,08
Pregnancy Week	22,06(±11,1)	9,67(±2,45.)	20,22(±3,82)	35,73(±2,45)	*0,00*
Gravide	2,32±1,2	2,44±1,17	1,99±1,17	2,55±1,42	*0,025*
Parity	1,01±0,9	1,11±0,88	0,78±0,10	1,13±1,08	0,055
Number of living children	1,01±0,94	1,11±0,88	0,78±0,10	1,13±1,08	0,49
Abortions	0,318±0,06	0,33±0,62	0,21±0,70	0,42±0,63	0,182
Education					*0,010*
Primary	28	15	4	9	
Secondary	40	11	16	13	
High school	71	26	27	18	
Associate degree	44	11	18	15	
University	15	1	2	12	
Working Status					0,537
Working	33	9	14	10	
Not working	165	55	53	57	

Pregnant women with a total FSFI score < 26.55 were considered to have sexual dysfunction, and the average score of the pregnant women participating in the study was calculated as 17.26±7.63. Only 9 patients' scores were above 26, and sexual dysfunction was observed in 95.9% of the participants (Table 2).

When the groups were compared, 93.75% of the pregnant women were diagnosed with sexual dysfunction in the first trimester, 93.75% in the second trimester, 98.5% in the third trimester, and the rate of sexual dysfunction in the third trimester was significantly higher.

Table 2: Rate of sexual dysfunction diagnosis according to trimester of pregnancy			
Pregnancy trimester	**FSFI Total score < 26,5**	**FSFI Total score >26,5**	**p**
1.Trimester n	60	4	
%	93,75	6,25	
2.Trimester n	60	4	0,14
%	93,75	6,25	
3.Trimester n	66	1	
%	98,5	1,5	
n total %	186 95,9	9 4,1	

Sexual function status of pregnant women in the first trimester was questioned; sexual desire scores ranged from 1.2 to 4.8 with a mean of 2.98±1.03. Sexual arousal scores ranged from 0.6 to 2.4 with a mean of 1.49±0.54, lubrication scores ranged from 0.00 to 6.00 with a mean of 3.41±1.61. Orgasm scores ranged from 0.00 to 4.00 with a mean of 2.46±1.15. Satisfaction scores ranged from 0.00 to 6.00 and the mean was 3.91±1.75. Pain discomfort scores ranged from 0.00 to 6.00 with a mean of 3.86±1.80. FSFI total scores ranged from 2.4 to 29.20 with a mean of 18.13±7.06 (Table 3).

In the second trimester, sexual desire scores ranged from 1 to 6, and the mean was 3.41±1.18. Sexual arousal scores range from 0.3 to 3.0 with a mean of 1.70±0.57, lubrication scores range from 0.00 to 6.00 with mean of 3.77±1.38 and orgasm scores range from 0.00 to 4. It varies between .00 and the mean is evaluated as 2.66±0.96. Satisfaction scores range from 0.00 to 6.00, with a mean of 4.1±1.51. Pain discomfort scores ranged from 0.00 to 6.00, with a mean of 3.79±1.46. FSFI total scores ranged from 3.0 to 30.0, with a mean of 19.54±6.07 (Table 3).

In the 3rd trimester pregnant group, sexual function status was questioned and sexual desire scores ranged between 1.2 and 5.4, with a mean of 3.06±1.14. Sexual arousal scores ranged from 0.3 to 3.0, with a mean of 1.29±0.65; Lubrication scores range from 0.00 to 6.00, with a mean of 3.34±1.77. Orgasm scores ranged between 0.00 and 4.00, and the mean was 2.00±1.45. Satisfaction scores range from 0.00 to 6.00, with a mean of 2.83±2.24. Pain discomfort scores ranged from 0.00 to 6.00, with a mean of 2.38±2.05. When FSFI total scores were calculated, the mean score was 17.26±7.65 and ranged between 1.5 and 30.0 (Table 3).

Table 3: Comparison of mean FSFI domains and total scores according to trimester of pregnancy

FSFI Domains	1.Trimester (n=64)	2.Trimester (n=64)	3.Trimester (n=67)	P		
				T1-T2	T1-T3	T2-T3
Desire	2,98±1,03	3,41±1,18	3,06±1,14	*0,081*	*0,95*	*0,004*
Arousal	1,49±0,54	1,70±0,57	1,29±0,65	*0,14*	*0,16*	*0,01*
Lubrication	3,41±1,61	3,77±1,38	3,34±1,77	*0,75*	*0,19*	*0,08*
Orgasm	2,46±1,15	2,66±0,96	2,00±1,45	*1,0*	*0,98*	*0,05*
Satisfaction	3,91±1,75	4,1±1,51	2,83±2,24	*1,0*	*0,04*	*0,01*
Pain	3,86±1,80	3,79±1,46	2,38±2,05	*1,0*	*0,001*	*0.01*
Total Score	18,13±7,06	19,54±6,07	17,26±7,65	*0,81*	*0,07*	*0,14*

Pregnancy trimesters were compared in terms of FSFI domains, there was no significant difference between first trimester and third trimester gestational weeks in terms of sexual desire; However, sexual desire was significantly higher in the second trimester pregnant group. The pregnancy trimesters were compared in terms of arousal, the arousal rate was significantly higher in the second trimester, while no significant difference was found between the first trimester and the other groups. Although the second trimester group scored the highest in terms of lubrication, there was no significant difference between the groups. While there was no significant difference between the first and second trimester pregnant groups in terms of orgasm and satisfaction; the scores obtained in the third trimester pregnant groups were significantly lower than the other groups. On the other hand, pain discomfort scores were close to each other in the first and second trimester pregnant groups, while they were significantly lower in the third trimester pregnant group.

There was no significant difference in FSFI total scores between groups, with women in the third trimester having the lowest mean scores (Table 3).

Discussion

Sexual function is an important part of physical and mental well-being and differences in sexual function during pregnancy have a significant impact on women's quality of life. On the other hand, it is also important for couples to maintain a healthy relationship[3].

Although the prevalence of sexual dysfunction during pregnancy varies according to the population studied; Studies have reported that sexual dysfunction can be seen at rates as high as 80% with various sub-parameters such as decreased libido and pain[4].

In a study conducted in Turkey in 2015, the prevalence of sexual dysfunction in pregnant women was up to 91%[5]. In a study by Bilge et al. examining the gestational periods, 46.1 % of the pregnant women who participated in the study were found to have low sexual function[6]. In the study in 2023, where sexual function was examined according to pregnancy periods, the rate of sexual dysfunction was determined to be 49.1 percent [7].

During pregnancy, there are also variations in sexual function according to the gestational periods. Studies have shown that the rate of sexual dysfunction is higher in the third trimester compared to other trimesters [6,8-10]. In this study conducted in accordance with the literature, the rate of sexual dysfunction was found to be higher in the third trimester.

Even though sexual dysfunction was found to be higher in the first trimester compared to the pre-pregnancy period due to conditions such as high rates of nausea and vomiting, increased sensitivity to odors including the odor of the partner, stress of having just learned about pregnancy, and breast tenderness; no significant difference was observed in this study compared to the second trimester, in accordance with similar studies[11-13].

Further each FSFI domains were examined, differences were observed according to the gestational periods. Sexual desire, arousal, orgasm and satisfaction sub-scores were significantly lower in the third trimester. In a study conducted in 2017, it was observed that the level of sexual satisfaction decreased during pregnancy [14]. In another similar study, it was observed that the level of sexual satisfaction in the first and third trimesters was lower than in the second trimester, similar to this study [6]. In a study conducted in Romania; while desire and arousal were found to remain constant throughout pregnancy; it was observed that orgasm increased in the second trimester, similar to this study, but was significantly lower in the third trimester. In the same study, satisfaction level was lower in the third trimester. While lubrication problems were observed to increase due to the effect of hormones in the same study; in this study, no significant difference was observed in terms of lubrication between pregnancy periods[7]. In the study conducted by Daud et al. in 2019, similar to this study, no significant difference was observed in terms of lubrication scores between trimesters; while desire, arousal, satisfaction and pain scores were significantly lower in the third trimester as in this study. According to Daud et al., there are several factors that cause a further decrease in sexual function status in the third trimester. Among the reasons are decreased libido levels, negative self-perception that the person is less attractive during pregnancy, being more tired, having concerns such as causing rupture of the amniotic membrane and causing the birth process to begin[4]. In addition to the increase in body weight during pregnancy; not finding the appropriate position in sexual intercourse and feeling pain during sexual intercourse or not feeling comfortable during sexual intercourse are also seen among other reasons[15-18]. On the other hand, according to the literature, a decrease in the desire for sexual intercourse can be seen in the spouses of pregnant women due to similar reasons such as the thought of harming the pregnant woman herself and, to a large extent, the fetus, or due to physical changes in pregnant women. On the other hand, according to many studies, the spouses of pregnant women find it appropriate to have sexual intercourse during pregnancy [16,17,19,20].

Along with the changing mood during pregnancy, the pregnancy process itself constitutes an alarming situation for women. In many studies, it has been shown that anxiety levels increase during pregnancy [6,18]. Misinformation about having sexual intercourse during pregnancy causes an increase in anxiety in pregnant women and a decrease in sexual activity. Since many factors, from the woman's birth style to the number of children, cause sexual health problems in women in the post-pregnancy period, sexual health problems should also be evaluated and followed up after pregnancy; Additionally, research shows that pregnant women want to get information about sexuality from professionals and that healthcare professionals should give women accurate information about sexuality[16,21,22,23].

Conclusion and Recommendations

One of the important factors affecting the quality of women's lives and relationships is having a healthy sexual life. During pregnancy, interest in sexual intercourse decreases in most women as pregnancy progresses. This study has also shown that women's sexual function problems increase in the first and last trimesters of pregnancy; sexual desire and sexual satisfaction, arousal and orgasm decrease.

In our country, as in other countries, sexuality is still seen as a taboo for women and continues to be important as a situation where accurate information should be accessed. It is important for healthcare professionals to question pregnant women about their sexual life and to provide necessary information before pregnancy, during pregnancy and after delivery in order to correct inaccurate information and beliefs and to prevent concerns that may arise in pregnant women and their partners.

Declarations

Funding

There are no financial supporters of the study.

Conflict of Interest

The authors have declared no conflict of interest.

Ethics Approval

After the approval numbered 2023-19/13 from the erzincan binali yıldırım university clinical research ethics committee, the study started.

Accessibility of data and materials (data transparency)

Authors agree to share data upon request.

Authors' Contributions

BKY and BNM performed the research, analyzed the data, and wrote the paper.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1501992

Turkish Validity and Reliability Study of the Digital Vaccine Literacy Scale

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Received: 16.06.2024
Accepted: 16.09.2024

ABSTRACT

Objectives: This study aimed to assess the validity and reliability of the Turkish version of the Digital Vaccine Literacy (DVL) scale.

Methods: This methodological study was conducted with 236 staff working at a foundation university hospital between September 2023 and April 2024. Data were collected using the Personal Information Form and DVL scale. The linguistic validity, content validity, exploratory factor analysis, and confirmatory factor analysis of the scale were conducted. Reliability was evaluated through item-total correlations, Cronbach's alpha coefficient, and test-retest reliability. Data were analyzed in SPSS 27.0 and AMOS 22.0 package programs.

Results: The study revealed 3 dimensions comprising 7 items, with factor loadings ranging from 0.612 to 0.851, explaining 78.63% of the total variance. The fit measures were acceptable ($\chi 2/df = 3.271$; RMSEA = 0.072; CFI = 0.912; NFI = 0.875; GFI = 0.874; TLI = 0.889; IFI = 0.876; $p < 0.001$) in confirmatory factor analysis. The overall Cronbach's alpha value of the scale was 0.730, while the sub-dimensions were 0.791, 0.891 and 0.781, respectively. The test-retest reliability correlation was positive, very strong and statistically significant ($r=0.962$, $p<0.001$).

Conclusions: It was found that the factor structure of the Turkish version of the DVL is the same as the factor structure of the original version, and it is a valid and reliable tool. Measurement of digital vaccine literacy will play a significant role in developing education strategies, accessing accurate information, preserving public health, supporting vaccine decision-making, and enhancing digital health skills.

Keywords: Digital, Vaccine, Literacy, Validation, Adaptation

ÖZET

Amaç: Bu çalışmanın amacı Dijital Aşı Okuryazarlığı (DAO) ölçeğinin Türkçe versiyonunun geçerlik ve güvenirliğini değerlendirmektir.

Yöntem: Bu metodolojik çalışma Eylül 2023 ve Nisan 2024 tarihleri arasında bir vakıf üniversitesi hastanesinde çalışan 236 personel ile gerçekleştirilmiştir. Veriler Kişisel Bilgi Formu ve DAO ölçeği kullanılarak toplanmıştır. Ölçeğin dil geçerliliği, kapsam geçerliliği, açımlayıcı faktör analizi ve doğrulayıcı faktör analizi yapılmıştır. Güvenirlik, madde-toplam korelasyonları, Cronbach alfa katsayısı ve test-tekrar test güvenirliği ile değerlendirilmiştir. Veriler SPSS 27.0 ve AMOS 22.0 paket programlarında analiz edilmiştir.

Bulgular: Çalışma, faktör yükleri 0,612 ile 0,851 arasında değişen ve toplam varyansın %78,63'ünü açıklayan 7 maddeden oluşan 3 boyut ortaya koymuştur. Doğrulayıcı faktör analizinde uyum ölçümleri kabul edilebilir düzeydedir ($\chi 2/df = 3.271$; RMSEA = 0.072; CFI = 0.912; NFI = 0.875; GFI = 0.874; TLI = 0.889; IFI = 0.876; $p < 0.001$). Ölçeğin genel Cronbach alfa değeri 0.730 iken, alt boyutlar sırasıyla 0.791, 0.891 ve 0.781'dir. Test-tekrar test güvenilirlik korelasyonu pozitif, çok güçlü ve istatistiksel olarak anlamlıdır ($r=0.962$, $p<0.001$).

Sonuç: DAO'nun Türkçe versiyonunun faktör yapısının orijinal versiyonun faktör yapısı ile aynı olduğu, geçerli ve güvenilir bir araç olduğu bulunmuştur. Dijital aşı okuryazarlığının ölçülmesi, eğitim stratejilerinin geliştirilmesinde, doğru bilgiye ulaşmada, halk sağlığının korunmasında, aşı kararlarının desteklenmesinde ve dijital sağlık becerilerinin geliştirilmesinde önemli bir rol oynayacaktır.

Anahtar Kelimeler: Dijital, Aşı, Okuryazarlık, Geçerlik, Uyarlama

Vaccines are a key ingredient in healthcare systems because of their proven track record in the prevention of a wide range of diseases. Their pertinent function is reducing the calamitous influence of outbreak epidemic diseases on humanity by immunizing the whole of society against pathogens. The first successful vaccine was developed by Edward Jenner in 1796 which panders smallpox (1). After that, vaccines for several diseases were developed, such as rabies, tuberculosis, pneumococcus, and ones against many childhood illnesses. In the recent past, COVID-19 showed that along with other measures, vaccines are key in preventing these diseases from spreading on large scales. The COVID-19 pandemic showed up that healthcare systems and societies in virtually all parts of the world have undergone significant upheavals. This pandemic has underlined the significance of vaccination that can be done on a mass level eventually and benefit to maintain public health. Only the timely development of the vaccine was a way to break the pandemic chain, and this work process was implemented by involving a large number of people and it was speeded up considerably (2).

With the COVID-19 crisis, vaccination has started to attract greater attention in the digital world, leading to an increase in online inquiries about vaccination (3). Information about vaccines is provided through various online platforms, including government official websites, forum sites, and social media. However, the reliability and accuracy of this information vary greatly. While official government websites are generally considered reliable, social media platforms often propagate misleading or unscientific content (4). Online communication can disseminate controversial information, resulting in uncertainty and doubt about vaccines (5). Information pollution on online platforms about the safety and accuracy of vaccines can make it difficult for people to make the right decisions and harm public health. This can lead to dangerous behaviors such as vaccine refusal and hinder the containment of the pandemic.

Misconceptions about the effectiveness of vaccines and lack of knowledge about their role in public health have led to a decrease in vaccination rates and an increase in vaccine hesitancy (6). In addition to these factors, incidents like the 1955 Cutter Incident and the more recent Dengvaxia controversy have also contributed to growing concerns about vaccine safety among the public. Many children contracted the disease and several deaths occurred due to the failure of Cutter Laboratories' polio vaccine to fully inactivate the virus (7). Similarly, the use of the Dengvaxia vaccine in the Philippines led to serious side effects, severely undermining public trust in vaccine safety (8). In Malaysia, a study found that vaccine hesitancy is a concern, with a minority of students not supporting vaccination due to safety issues (9). Therefore, models such as the Increasing Vaccination Model and the 5C Model are developed to understand the complex factors influencing vaccination decisions (10). These models indicate that the content of online information has the potential to determine the decision to vaccinate or not. Access to accurate information about the efficacy of vaccines, as well as understanding this information correctly, is of critical importance to enhance the success of vaccination efforts. Given the increasing reliance on digital platforms for health information, the fusion of Digital Health Literacy (DHL) with vaccine literacy becomes imperative, leading to the emergence of Digital Vaccine Literacy (DVL) as a pivotal component in empowering individuals to make informed choices regarding vaccination.

Health literacy refers to the extent to which a person can obtain, understand, and utilize fundamental health information and services, enabling them to engage in health-related choices (11). DHL necessitates a distinct set of skills, encompassing the capacity to search for, assess, analyze, incorporate, and utilize health information obtained from online platforms (12). Vaccine literacy, built upon the concept of health literacy, involves acquiring knowledge about vaccines and establishing a simple mechanism for their delivery and administration (13). Thus, the convergence of DHL and vaccine literacy gives rise to the concept of DVL. DVL influences both the motivation and the competence required to navigate online information to make well-informed decisions regarding vaccination theoretically.

In light of the above information, it is important to develop reliable tools for measuring knowledge and perceptions regarding vaccines. Such a scale can be used as a tool to assess the effectiveness of interventions designed to increase DVL and reduce vaccine hesitancy. Questionnaires commonly featured in the literature typically emphasize general vaccine literacy rather than specifically addressing online vaccine literacy (14). Therefore, in this study, we analyzed the Turkish reliability and validity of the scale

developed by Montagni et al. (2022) specifically to assess DVL. Assessing DVL in the Turkish community will allow for the identification of strengths and weaknesses in this area and facilitate the development of more effective education and information strategies. It is believed that the scale will assist public health experts, researchers, and policymakers in devising policies and interventions aimed at enhancing DVL. This can lead to the reduction of vaccine hesitancy and better informed communities.

Methods

Study Design

This study used a descriptive and methodological approach to adapt the DVL developed by Montagni et al. (2022) into Turkish and assess its validity and reliability. The study was conducted with staff working at a foundation university hospital. Research questions to be answered in the study;

(a) Is the DVL a valid measurement tool in the Turkish population?

(b) Is the DVL a reliable measurement tool in the Turkish population?

Linguistic Validity

The scale's linguistic validity was established through the translation-back translation technique. This process involved ensuring semantic equivalence by comparing the items of the original scale with those of the back-translated version. Two independent specialized translators translated the scale into Turkish, preserving the original content. A collaborative translation was then developed by evaluating these individual translations. Next, the translated scale underwent back-translation into English by an expert with a strong understanding of the culture in the scale's country of origin. Both the original and translated versions were evaluated for language equivalence before finalizing the scale for expert review.

Expert Reviews

In order to evaluate the items in the Turkish version of the scale for linguistic and cultural equivalence, researchers developed an Expert Review Form. This form was distributed via email to 10 experts with backgrounds in public health and methodological research. The Davis technique was employed to compute the content validity index (CVI) of the scale. In this technique, experts' opinions are rated on a scale from A to D, indicating the relevance of each item. The Item-Content Validity Index (I-CVI) value for each item is calculated by dividing the number of experts who selected ratings A and B by the total number of experts, while the Scale-Content Validity Index (S-CVI) is obtained by dividing the sum of I-CVIs for each item by the total number of experts. The acceptable threshold for I-CVI is set at 0.78, and for S-CVI it is set at 0.80 (15).

Pilot Test

Before implementing the scale in the main study sample, a pilot test involving 50 individuals was conducted to evaluate the clarity of the scale's questions. Participants in the pilot test were distinct from those included in the main study sample. Although adding the option "I don't know, I don't look for vaccine-related information" alongside the 4-point Likert scale is recommended, during the pilot study, it was concluded that it would be more accurate not to include this item. Individuals who do not search for vaccine-related information were identified with a question included in the Personal Information Form. Participants who selected the statement "I don't know, I don't look for vaccine-related information" were not included in the factor analysis. After the pilot tests, the final version of the scale was administered to the main study sample. In addition, the participants reported that they could not fully comprehend the 4-point Likert scale ranging from "1" (Disagree) to "4" (Agree), so it was deemed appropriate to change the scoring to "1: Strongly Disagree, 2: Disagree, 3: Agree, 4: Strongly Agree".

Sample and Settings

The population of the research consists of staff working at a foundation university hospital. The sample size for the study was determined based on the number of items in the scale. It is recommended to have a sample size of at least five times the number of scale items or a minimum of 100 participants for scale development and adaptation studies (16). However, increasing the sample size enhances the appropriateness of factor analysis and improves reliability. Consequently, the study was conducted with 236 individuals who volunteered to participate. Due to the limited sample size in our study, exploratory factor

analysis (EFA) and confirmatory factor analysis (CFA) were conducted on the same sample (17).

Data Collection and Instruments

The data were collected using an online survey administered to participants after providing an explanation about the study's purpose. Throughout the data collection phase, both the Personal Information Form and the DVL scale were utilized. The Personal Information Form comprises 9 questions designed to gather information about participants' gender, age, marital status, education level, department, presence of chronic illness, history of previous infectious diseases, vaccines received, and vaccine-related information search. The DVL scale, developed by Montagni et al. (2022), consists of 3 dimensions and 7 items. The scale assesses the understanding, reliability, and application of online vaccine-related information (18). Responses to the items are rated on a 4-point Likert scale, ranging from "1" (Disagree) to "4" (Agree). The total score from the scale ranges from 7 to 28. A higher score indicates an increased level of digital vaccine literacy. The Cronbach's alpha coefficient for the scale is 0.71.

Statistical Analysis

Data analysis was conducted using the Statistical Product and Service Solutions (SPSS) version 27.0 and the Analysis of Moment Structures (AMOS) version 22.0 software packages. The normality of the data was assessed using histogram graphs and z-scores of skewness and kurtosis values. Descriptive statistics, including frequencies, percentages, means, and standard deviations, were used to present the findings. The Kaiser-Meyer-Olkin (KMO) measure and Bartlett's test of sphericity were employed to evaluate sample adequacy and item suitability for factor analysis. A KMO value above 0.50 was considered acceptable for factor analysis (19). EFA was utilized to examine item-factor relationships, while CFA was employed to assess the underlying structure of the scale. Principal Component Analysis (PCA) was employed as the factor extraction method in EFA. The reliability of the scale was evaluated using Cronbach's alpha coefficient, item-total correlation, test-retest reliability, Hotelling's T-squared test, Tukey's Additivity test, average variance explained (AVE) and composite reliability (CR) values. Test-retest reliability was assessed by administering the scale to 50 participants who completed the DVL scale again after a 15-day interval. Internal consistency reliability was considered satisfactory if Cronbach's alpha exceeded 0.70, and items with a factor loading of ≥ 0.30 were deemed acceptable (20). A significance level of $p < 0.05$ was applied in all statistical analyses.

Results

The process leading to the final version of the DVL scale is given below in three steps.

Characteristics of the Participants

A total of 236 participants, 137 women and 99 men, participated in the study. Of these, 136 were single and 100 were married. When their educational status was analyzed, the majority of the participants were high school graduates (n=72, 30.5%). The average age of the participants was 37.10 ± 9.68 years. Out of 236 staff, 103 are healthcare workers (43.6%), 49 are academic personnel (20.8%), 40 are administrative personnel (16.9%), and 44 are technical and support services personnel (18.6%). Among 236 participants, 97 reported having a chronic disease, while 139 reported not having a chronic disease. Also, 157 people had previously had an infectious disease, while 79 had not. The most commonly identified chronic conditions are hypertension (n=26), COPD/asthma (n=14), and diabetes (n=11), respectively. The most commonly identified infectious diseases are COVID-19 (n=105), influenza (n=72), and pneumonia (n=15), respectively.

Among the 222 staff vaccinated outside the routine vaccination program, the most common vaccines administered were COVID-19 (n=192), tetanus (n=102), influenza (n=37), rabies (n=23), HPV (n=11), meningitis (n=5), pneumococcus (n=4) and rotavirus (n=4). When evaluating where participants accessed vaccine-related information, it was found that 108 individuals obtained information from the internet, 105 from official websites of government institutions, 45 from television, 39 from social media, 19 from newspapers/magazines, and 17 from forum websites. The number of individuals who did not look for vaccine-related information was 32 (Table 1).

Table 1: Demographic Information of the Participants		
Variable	**n**	**%**
Gender		
Male	99	41.9
Female	137	58.1
Marital status		
Single	136	57.6
Married	100	42.4
Educational level		
High School	72	30.5
Associate Degree	48	20.3
Bachelor's Degree	53	22.5
Master's Degree	37	15.7
Doctorate	26	11.0
Profession		
Healthcare personnel	103	43.6
Academic personnel	49	20.8
Administrative personnel	40	16.9
Technical and support services personnel	44	18.6
Presence of chronic illness		
I don't know	38	17.1
Hypertension	26	11.7
Diabetes	11	5.0
Cholesterol	8	3.6
COPD/Asthma	14	6.3
Arthritis	8	3.6
I have no chronic illness.	139	62.6
Presence of infectious disease		
I don't know	16	5.4
Covid-19	105	35.4
Influenza	72	24.2
Pneumonia	15	5.1
Tuberculosis	3	1.0
Hepatitis	7	2.4
I have not had any infectious disease.	79	26.6
Vaccinations received outside the routine immunization schedule		
Influenza	37	9.4
Covid-19	192	49.0
Tetanus	102	26.0
Rabies	23	5.9
HPV	11	2.8
Meningitis	5	1.3
Pneumococcus	4	1.0
Rotavirus	4	1.0
I have never been vaccinated.	14	3.6
Place where vaccine-related information is accessed		
Television	45	12.3
Newspaper/Magazine	19	5.2
Internet	108	29.6
Social media	39	10.7
Forum sites	17	4.7
Official websites of government agencies	105	28.8
I am not looking for information about the vaccine.	32	8.8

COPD: Chronic Obstructive Pulmonary Disease, HPV: Human Papillomavirus.

Validity Analysis of the DVL

To verify the content validity of the DVL, expert reviews were sought. The Davis technique was employed to assess expert opinions, and the CVI was computed. Based on feedback from 10 experts, the I-CVI was 1.0, and S-CVI was 0.92. This outcome indicates that experts unanimously considered the scale to be suitable, highlighting the high level of content validity of the Turkish version of DVL.

In order to assess the structural validity of the scale, both EFA and CFA were conducted. To obtain a more accurate result, participants who did not look for vaccine-related information were not included in the EFA and CFA. Prior to conducting factor analysis, the suitability of the dataset and sample size adequacy was evaluated using the KMO measure and Bartlett's test of sphericity. The KMO value obtained was 0.637, and Bartlett's test of sphericity yielded a significant result ($\chi2=618.720$; $p<0.001$), indicating that the data were suitable for factor analysis. In conducting the EFA, the PCA method was employed for factor extraction. EFA analysis revealed a three-factor structure consisting of 7 items with factor loadings ranging from 0.612 to 0.851 and explaining 78.63% of the total variance (Table 2). Subsequently, CFA was conducted (Figure 1). Looking at the goodness of fit indices of DVL, RMSEA was 0.072 and $\chi2/df$ was 3.271, indicating that the model showed an acceptable fit. Other fit indices according to CFA results were as follows: AGFI: 0.865, GFI = 0.874, NFI = 0.875, CFI = 0.912, TLI = 0.889, and IFI = 0.876 (Table 3). No high values were observed among items within the same factors. Therefore, it was not necessary to introduce a covariance link between the items or to repeat the CFA.

Table 2: Factors and Factor Loadings of the DVL

Items	Factors			Eigenvalues	% of variance	% Cumalative
	F1	F2	F3			
m1	0.852			2.758	39.39	39.39
m2	0.710					
m3		0.825		1.513	21.61	61.01
m4		0.795				
m5			0.811	1.234	17.62	78.63
m6			0.743			
m7			0.612			

F1: Understanding and trust official information, F2: Understanding and trust information in social media; F3: Appraisal of vaccine information online in terms of evaluation of the information and its application for decision making.

Table 3: Fit Index of the DVL

Fit Index	Excellent Fit	Acceptable Fit	DVL
/df	$0 \leq \chi^2/df \leq 3$	$3 \leq \chi^2/df \leq 5$	3,271
RMSEA	0,00 0,05	0,05	0,072
SRMR	0,00 0,05	0,05	0,056
CFI	0,95 ≤ CFI	0,85 ≤ CFI	0,912
GFI	0,90 ≤ GFI	0,85 ≤ GFI	0,874
AGFI	0,90 ≤ AGFI	0,85 ≤ AGFI	0,865
IFI	0,90 1,00	0,80	0,876
TLI	0,90 ≤ TLI	0,80 ≤ TLI	0,889
NFI	0,90 ≤ NFI	0,80 ≤ NFI	0,875

Reliability Analysis of the DVL

The item-total correlation values were examined, and it was determined that there were no items below 0.30. When each sub-dimension was evaluated within itself, it was found that the item-total correlation coefficients of the "F1 (understanding and trust official information)" sub-dimension of the scale were between 0.450-0.475, the item-total correlation coefficients of the "F2 (understanding and trust information in social media)" sub-dimension were between 0.511-0.566, and the item-total correlation coefficients of the "F3 (appraisal of vaccine information online in terms of evaluation of the information and its application for decision making)" sub-dimension were between 0.357-0.443. All items on the scale exhibited item-total correlations ranging from 0.357 to 0.566, surpassing the threshold. For the Turkish version of DVL, the Cronbach's alpha value for F1 sub-dimension was 0.791, for F2 sub-dimension was 0.891, for F3 sub-dimension was 0.781, and the total Cronbach's alpha value for the DVL scale was calculated as 0.730 (Table 4).

Table 4: Reliability Values of the DVL

Scale	Number of items	Item-total correlation	$\bar{X} \pm SD$	Skewness Kurtosis	Cronbach's alpha
DVL	7	0.357 - 0.566	2.81 ± 0.42	,031 / ,075	0.730
F1	2	0.450 – 0.475	2.18 ± 0.70	-,074 / -,691	0.791
F2	2	0.511 – 0.566	3.03 ± 0.69	-,643 / ,951	0.891
F3	3	0.357 – 0.443	3.08 ± 0.45	-,416 / -,129	0.781

F1: Understanding and trust official information, F2: Understanding and trust information in social media; F3: Appraisal of vaccine information online in terms of evaluation of the information and its application for decision making.

The response bias of DVL was analyzed with Hotelling's T-squared test. As a result of this test, it was determined that there was no response bias in the scales with an F statistic of 117.125 (Hotelling $T^2 = 718.027$; $p < 0.001$). In addition, Tukey's test of additivity was conducted to obtain a total score from the scale. The results showed that the scale was summable and the traits measured showed sufficient diversity ($p < 0.001$). When the AVE of the measurement model was evaluated, it was found that F1 was 0.615, F2 was 0.656, and F3 was 0.528, and when the CR was evaluated, it was found that F1 was 0.760, F2 was 0.792, and F3 was 0.768. Finally, a re-test was administered to 50 individuals after 15 days. Upon retesting the questionnaires, the test-retest reliability for the scale exceeded 0.70. A very strong, positive, and statistically significant correlation ($r=0.962$, $p<0.001$) was observed between the two measurements, indicating time invariance for the scale.

Discussion

This study aimed to assess the validity and reliability of the Turkish version of the DVL. This study included 236 participants from various professions, including healthcare personnel, academic personnel, administrative personnel, and technical and support services personnel. The results of the study showed that the Turkish version of the DVL has good validity and reliability.

The content validity of a measurement tool should be verified to ensure that it is indeed a true reflection of the concept that was targeted for measurement. Validity of the content was ensured by using the experts who were consulted to make an assessment for the Turkish version of the scale. The CVI of all items in the scale was greater than 0.80, showing that the scale items were comprehensible and the scale had adequate content validity (21). Before conducting the EFA and CFA, the suitability of the sample for factor analysis was checked via the KMO coefficient and Bartlett's sphericity test. The range of KMO values falls between 0 and 1, and KMO values ≥.50 are deemed as appropriate (22). The analysis results indicate that the KMO measure is 0.637 and Bartlett's test of sphericity is significant, which confirms the suitability of the sample for factor analysis.

The findings of EFA suggest that the factor structure of the Turkish version of the DVL aligns with that of the original version. The analysis revealed 3 dimensions comprising seven items, with factor loadings ranging from 0.612 to 0.852. Factor loading values greater than 0.30 indicate the considerable influence of the scale items on the overall construct (23). It is particularly the case with multi-dimensional scales that the explanation of more than 40% of the variance is taken as a good performance. A larger explained variance indicates a higher construct validity (24). In our study, the variance explained was more than

50% and reached the value of 78.63% which signified strong construct validity. The goodness-of-fit index results obtained from CFA show an acceptable fit for the Turkish version of the DVL (25).

The item-total correlation coefficients for the scale items range from .362 to .648, all indicating positive correlations. With values above 0.30 and being positive, these correlations suggest that the items in the instrument exhibit consistent behaviours and contribute to the scale's acceptable internal consistency (26). Hence, all items measure DVL in the same direction and are linked to the total score. Cronbach's alpha coefficient was found to be 0.791 for F1, 0.891 for F2, 781 for F3, and 0.730 for the overall score. The fact that Cronbach's alpha coefficient was above 0.70 for both the subscale and the overall score indicates that the scale has satisfactory reliability (27). In addition, regarding the test-retest method, a 15–21 day interval is typically recommended between administration (28). A correlation coefficient (r) of at least 0.70 is desirable for test-retest reliability, with higher values indicating increased reliability (29). In our study, the test-retest reliability coefficient correlation of 0.962 showed that the internal consistency reliability of the scale was at an acceptable level.

In our study, we also utilized the Hotelling T^2 test to identify a response bias. For there to be no response bias, the statistical result obtained from the test must be significant (30). The results showed that the scale had no response bias, and the responses' distribution was homogeneous (Hotelling $T^2 = 718.027$, $p < 0.001$). The Tukey Additivity test which is used to verify whether the two-factor interactions are additive has been conducted and revealed that the factors are indeed additive ($p < 0.05$).

Finally, when the AVE of the measurement model was evaluated, it was found to be 0.615, 0.656, and 0.528 for F1, F2, and F3, respectively, and 0.760, 0.792, and 0.768 for CR. Our results show that the AVE value is above the threshold value of 0.50 and the CR value is above the threshold value of 0.70 (25). Consequently, when all reliability and validity criteria are evaluated, it can be said that the Turkish version of DVL is a valid and reliable scale.

Limitation

The main limitation of the study is that EFA and CFA were conducted on the same sample. In addition, the generalizability of the findings to other populations is limited since the study was conducted on staff working in a foundation university hospital. To improve the development of the scale, future research should verify its validity and reliability with a larger sample size.

Conclusions

This study revealed that the Turkish version of the DVL is a valid and reliable instrument for assessing digital vaccine literacy. Factor analysis results show that the Turkish version has a factor structure consistent with the original version. Moreover, the internal consistency and test-retest reliability of the scale support the reliability of its use. The use of the Turkish version of the DVL may allow healthcare providers and public health professionals in Turkey to develop more effective strategies to identify and improve the level of digital vaccine literacy in the community. In this context, the use of the scale could be an important step towards the protection and promotion of public health, as well as an important contribution towards achieving social equity in digital health communication and access to information.

Declarations

Funding

This study had no external funding.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval

Approval was secured via email from the creators of the scale to conduct a validity and reliability study in Turkish. Following this, ethical clearance was obtained from the Bezmialem Vakıf University Ethics Committee (dated March 22, 2023, reference number 101249), and permission to conduct the study was granted by the hospital where the research was conducted (dated March 1, 2023, reference number 98706). Participants were informed about the study, and both written and verbal consent were obtained.

Availability of Data and Material

Data are available upon request from the corresponding author.

Authors' Contributions

ADK: Conceptualization, Methodology, Data curation, Formal Analysis, Investigation, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **ÖE:** Conceptualization, Methodology, Project administration, Supervision, Writing - Original Draft, Writing – review & editing.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1495245

Risk Factors for Colonization of Vancomycin-Resistant Enterococci in Patients in the Intensive Care Unit: A single-center Retrospective Study

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Received: 03.06.2024
Accepted: 26.09.2024

ABSTRACT

Background: Patients colonised with vancomycin-resistant enterococci (VRE) remain a problem worldwide, especially in intensive care units (ICU), necessitating the identification of associated risk factors. The aim of this single-centre retrospective study was to determine the risk factors for VRE colonisation in patients admitted to medical and surgical ICUs.

Methods: We analyzed data from 190 patients admitted to the ICUs between January 2020 and December 2022. Demographic information, clinical characteristics, laboratory results, antimicrobial usage, and comorbidities were obtained from digital patient records. Rectal swabs were collected weekly within 48 hours of ICU admission to detect VRE colonization.

Results: Out of 190 patients, 54 were colonized with VRE. Significant independent risk factors for VRE colonization included higher APACHE II scores on ICU admission (OR: 1.26, 95% CI: 1.03-1.55, p=0.024), longer hospital stay (OR: 1.25, 95% CI: 1.14-1.36, p<0.001), non-abdominal surgery (OR: 22.85, 95% CI: 6.90-75.72, p<0.001), and use of teicoplanin in the past three months (OR: 14.47, 95% CI: 4.55-46.03, p<0.001). VRE-colonized patients had lower mean C-reactive protein and albumin levels than non-VRE patients.

Conclusion: Higher APACHE II scores, prolonged hospital stays, non-abdominal surgeries, and recent teicoplanin use are significant risk factors for VRE colonization in ICU patients.

Keywords: Vancomycin-resistant enterococci, intensive care unit, colonization, risk factors

ÖZET

Amaç: Vankomisine dirençli enterokoklarla (VRE) kolonize olan hastalar, özellikle yoğun bakım ünitelerinde (YBÜ) olmak üzere dünya çapında bir sorun olmaya devam etmekte ve bu durum da VRE kolonizasyonu ile ilişkili risk faktörlerinin tanımlanması ihtiyacığını gündeme getirmektedir. Retrospektif olarak gerçekleştirdiğimiz bu tek merkezli çalışmanın amacı medikal ve cerrahi YBÜ'lere kabul edilen hastalarda meydana gelen VRE kolonizasyonu için risk faktörlerini tespit etmektir.

Yöntemler: Ocak 2020 ve Aralık 2022 tarihleri arasında YBÜ'lere kabul edilen 190 hastanın verileri analiz edilmiştir. Demografik bilgiler, klinik özellikler, laboratuvar sonuçları, antimikrobiyal kullanımı ve komorbiditeler elektronik tıbbi kayıtlardan elde edilmiştir. VRE kolonizasyonunu tespit etmek için YBÜ'ye kabulden sonraki 48 saat içinde başlanmak kaydıyla haftalık olarak rektal sürüntü örnekleri toplanmıştır.

Bulgular: Çalışma döneminde YBÜ'de takip edilen 190 hastanın 54'ü VRE ile kolonize olmuştur. VRE kolonizasyonu için anlamlı bağımsız risk faktörleri arasında YBÜ'ye kabulde daha yüksek APACHE II skorları (OR: 1.26, %95 GA: 1.03-1.55, p=0.024), uzamış hastanede kalış süresi (OR: 1. 25, %95 GA: 1.14-1.36, p<0.001), non-abdominal cerrahi operasyon geçirmek (OR: 22.85, %95 GA: 6.90-75.72, p<0.001) ve son üç ayda teikoplanin kullanımı (OR: 14.47, %95 GA: 4.55-46.03, p<0.001) bulunmuştur. Ayrıca VRE kolonize hastaların ortalama C-reaktif protein ve albümin düzeyleri VRE kolonize olmayan hastalara göre daha düşüktü.

Sonuç: Yüksek APACHE II skorları, hastanede kalış süresinin uzaması, abdomen dışı cerrahi operasyon geçirmek ve son üç ayda teikoplanin kullanımı, YBÜ hastalarında VRE kolonizasyonu için önemli risk faktörleridir.

Anahtar Kelimeler: Vankomisine dirençli enterokoklar, yoğun bakım ünitesi, kolonizasyon, risk faktörü

Vancomycin-resistant enterococci (VRE) are increasingly prevalent nosocomial pathogens, especially among severely ill patients in the intensive care unit (ICU) (1). The global increase in VRE presence in hospitals has led to the need for examining the factors linked to VRE colonization (2). The transmission dynamics of VRE in the hospital environment and the factors contributing to its spread remain complex (3). Colonization with VRE is essential for transmitting these multidrug-resistant organisms in healthcare (4). Identification of risk factors for VRE colonization is imperative to guide the implementation of effective infection control measures. Advanced age, comorbid conditions, antimicrobial exposure and healthcare contact have been recognized as contributing factors to VRE colonization in previous studies (5-7). Factors contributing to VRE colonization in ICU patients include extended ICU stays, previous renal replacement therapy, and the use of penicillin and third-generation cephalosporins in medical and surgical wards, use of carbapenems in intensive care units, enteral tube feeding, metabolic diseases, male gender, and a Charlson comorbidity index <3, emphasizing the need for infection control strategies, reduced ICU stay, and prudent antibiotic use (8–10). VRE colonization among critically ill patients in the ICU is a rising worry because of its link to higher rates of illness, death, and healthcare expenses (8). The aim of this single-centre retrospective study was to determine the risk factors for VRE colonisation in patients admitted to medical and surgical ICUs in our institution.

Materials and Methods

This retrospective study, carried out at a single center, examined patients admitted to the medical and surgical ICUs at our hospital from January 2020 to December 2022. Patient data for the study were collected from the digital patient records of those admitted to the ICUs within the specified timeframe. Demographic information, clinical characteristics, laboratory results, antimicrobial usage, comorbidities, and other relevant variables were extracted from the digital patient records. The study included patients who were 18 years or older and had been admitted to the medical and surgical ICUs during the specified period. Patients with incomplete medical records or missing data relevant to the study variables were excluded. During the study, rectal swabs were taken within 48 hours of admission to the ICU to detect existing VRE colonisation. Samples from patients staying in the ICU for over 48 hours were collected weekly until a positive VRE culture was detected, the patient left the ICU, or they passed away. *Enterococci* were considered to have been acquired in the ICU if detected in a patient in the unit for more than 48 hours. If a patient's result is negative for VRE according to the first swap taken within the 24 hours in ICU and on weekly rectal swaps taken three times consecutively, then the patient was accepted as negative for VRE (11). Prior antibiotic use was defined as administering antimicrobials three months before ICU admission. Prior ICU hospitalization was defined as an inpatient admission to the ICU for any reason three months before the current ICU admission. The key outcome evaluated was the colonization of VRE among ICU patients during their hospital stay.

Statistical Analysis

The participants' demographic and clinical details were delineated through descriptive analysis. We verified the normality of the variables with the Shapiro-Wilk assessments. Continuous data were presented as average ± standard variation or as a range from minimum to maximum values. We employed either Mann-Whitney U evaluations or t-examinations to contrast continuous data across groups. Categorical data regarding counts and proportions were detailed; group comparisons were made using either Pearson's chi-square or Fisher's precise chi-square assessments. To determine potential mortality risk factors, we implemented univariate logistic regression methods. Factors with a p-value below 0.10 in the univariate analysis were assessed using multivariate logistic regression to identify significant mortality-associated risks. The SPSS software version 28.0 facilitated all statistical investigations, setting the significance bar at $p < 0.05$

Results

In this retrospective study, we analyzed data from 190 patients admitted to the medical and surgical ICUs to determine the risk factors linked to VRE colonization. Out of these, 54 patients were colonized with VRE, while 136 were not. The mean age of VRE-colonized patients was 53.57 ± 20.37 years, compared to 51.25 ± 20.27 years in non-VRE-colonized patients (p=0.490) (Table 1). The two groups had a similar distribution of sexes., with females comprising 46.3% of the VRE group and 54.4% of the non-VRE group (p=0.396).

The APACHE II score on ICU admission was significantly higher in the VRE group (19.46 ± 2.87) compared to the non-VRE group (17.88 ± 3.53, p=0.007). A similar proportion of patients in both groups had been hospitalized within the three months preceding the study (46.3% vs. 41.9%, p=0.698) (Table 1).

Table 1: Comparison by univariate analysis of the demographic and clinical features of colonisation with VRE in intensive care unit patients

Variables	VRE colonization (n=54)	non-VRE colonization (n=136)	*P* Value
Age, years, mean ± SD	53.57 ± 20.37	51.25 ± 20.27	0.490
Sex, famale, n (%)	25.0 (46.30%)	74.0 (54.41%)	0.396
APACHE II score on ICU admission, mean ± SD	19.46 ± 2.87	17.88 ± 3.53	**0.007**
Previous hospitalization within 3 months, n (%)	25.0 (46.30%)	57.0 (41.91%)	0.698
Non-abdominal surgery, n (%)	29.0 (53.70%)	12.0 (8.82%)	**<0.001**
Abdominal surgery, n (%)	12.0 (22.22%)	14.0 (10.29%)	0.054
Charlson Comorbidity Index, mean ± SD	3.61 ± 1.38	3.33 ± 1.57	0.227
Diabetes mellitus, n (%)	15.0 (27.78%)	28.0 (20.59%)	0.381
Hypertension, n (%)	7.0 (12.96%)	28.0 (20.59%)	0.310
Chronic obstructive lung diaseses, n (%)	16.0 (29.63%)	25.0 (18.38%)	0.132
Coronary artery disease, n (%)	16.0 (29.63%)	24.0 (17.65%)	0.103
Chronic renal disease, n (%)	12.0 (22.22%)	13.0 (9.56%)	**0.037**
Cerebrovascular disease, n (%)	13.0 (24.07%)	18.0 (13.24%)	0.108
Malignancy, n (%)	7.0 (12.96%)	11.0 (8.09%)	0.447
Chronic steroid or immunosuppression therapy, n (%)	7.0 (12.96%)	18.0 (13.24%)	1.000
Pressure ulcers, n (%)	15.0 (27.78%)	45.0 (33.09%)	0.591
Mechanical ventilation, n (%)	26.0 (48.15%)	49.0 (36.03%)	0.169
Total parenteral nutrition, n (%)	16.0 (29.63%)	58.0 (42.65%)	0.135
Blood transfusion, n (%)	11.0 (20.37%)	26.0 (19.12%)	1.000
Urinary catheter, n (%)	52.0 (96.30%)	133.0 (97.79%)	0.624
Central-line catheter, n (%)	20.0 (37.04%)	51.0 (37.50%)	1.000
Nasogastric tube, n (%)	22.0 (40.74%)	54.0 (39.71%)	1.000
Drainage tubes, n (%)	8.0 (14.81%)	13.0 (9.56%)	0.432
White blood cells (G/L), mean ± SD	8.68 ± 1.53	8.79 ± 1.52	0.662
Neutrophil-to-lymphocyte ratio, mean ± SD	1.71 ± 0.45	1.71 ± 0.50	0.831
C-reactive protein (mg/L), mean ± SD	4.49 ± 1.18	4.93 ± 1.26	0.031
Platelets, (mm^3), mean ± SD	144.91 ± 24.66	144.41 ± 25.11	0.926
Albumin, (g/L),mean ± SD	3.85 ± 0.27	3.95 ± 0.29	**0.027**
Use of meropenem in past 3 months, n (%)	20.0 (37.04%)	37.0 (27.21%)	0.247
Use of vancomycin in past 3 months, n (%)	10.0 (18.52%)	32.0 (23.53%)	0.578
Use of teicoplanin in past 3 months, n (%)	25.0 (46.30%)	14.0 (10.29%)	**<0.001**
Use of metronidazol in past 3 months, n (%)	6.0 (11.11%)	21.0 (15.44%)	0.589
Use of tigecycline in past 3 months, n (%)	14.0 (25.93%)	29.0 (21.32%)	0.623
Use of linezolid in past 3 months, n (%)	4.0 (7.41%)	23.0 (16.91%)	0.109
Use of quinolone in past 3 months, n (%)	33.0 (61.11%)	65.0 (47.79%)	0.135
Use of third or fourth generation cephalosporins in past 3 months, n (%)	31.0 (57.41%)	56.0 (41.18%)	0.062
Use of beta-lactam/lactamase inhibitors in past 3 months, n (%)	18.0 (33.33%)	43.0 (31.62%)	0.955
Length of hospital stay, (day) mean ± SD	21.59 ± 5.37	15.12 ± 6.29	**<0.001**
Length of stay in ICU, (day) mean ± SD	15.06 ± 2.15	16.88 ± 6.17	0.092

The groups did not show a significant difference in the Charlson Comorbidity Index (3.61 ± 1.38 vs. 3.33 ± 1.57, p=0.227) (Table 1). Specific comorbidities, including diabetes mellitus, hypertension, chronic obstructive lung disease, coronary artery disease, chronic renal disease, cerebrovascular disease, malignancy, and chronic steroid or immunosuppression therapy, did not show significant differences except for chronic renal disease, which was more prevalent in the VRE group (22.2% vs. 9.6%, p=0.037) (Table 1).

A significantly higher number of VRE-colonized patients underwent non-abdominal surgery (53.7%) compared to non-VRE patients (8.8%, p<0.001). Abdominal surgery was performed in 22.2% of the VRE group and 10.3% of the non-VRE group (p=0.054) (Table 1). Pressure ulcers, mechanical ventilation, total parenteral nutrition, blood transfusion, urinary catheter, central-line catheter, nasogastric tube, and drainage tubes usage did not significantly differ between the groups (Table 1).

Laboratory findings indicated that the mean C-reactive protein level was significantly lower in the VRE group (4.49 ± 1.18 mg/L) compared to the non-VRE group (4.93 ± 1.26 mg/L, p=0.031). The albumin level was also significantly lower in the VRE group (3.85 ± 0.27 g/L) compared to the non-VRE group (3.95 ± 0.29 g/L, p=0.027) (Table 1).

Use of teicoplanin in the past three months was significantly higher in the VRE group (46.3%) compared to the non-VRE group (10.3%, p<0.001) (Table 1). There was no significant difference in the usage of other antibiotics, including meropenem, vancomycin, metronidazole, tigecycline, linezolid, quinolone, third or fourth generation cephalosporins, and beta-lactam/lactamase inhibitors (Table 1).

The mean length of hospital stay was significantly longer in the VRE group (21.59 ± 5.37 days) compared to the non-VRE group (15.12 ± 6.29 days, p<0.001). However, the length of ICU stay did not differ significantly between the groups (15.06 ± 2.15 days vs. 16.88 ± 6.17 days, p=0.092) (Table 1).

Multivariate logistic regression analysis identified four independent risk factors for VRE colonization in ICU patients: APACHE II score on ICU admission (OR: 1.26, 95% CI: 1.03-1.55, p=0.024), length of hospital stay (OR: 1.25, 95% CI: 1.14-1.36, p<0.001), non-abdominal surgery (OR: 22.85, 95% CI: 6.90-75.72, p<0.001), and use of teicoplanin in the past three months (OR: 14.47, 95% CI: 4.55-46.03, p<0.001) (Table 2).

Table 2: Multivariate analysis of risk factors for colonisation with VRE in intensive care unit patients

Variables	OR (Odds Ratio)	95% CI (Confidence Interval)	*P* Value
APACHE II score on ICU admission	1.26	1.03, 1.55	**0.024**
Length of hospital stay, (day)	1.25	1.14, 1.36	**<0.001**
Non-abdominal surgery	22.85	6.90, 75.72	**<0.001**
Use of teicoplanin in past 3 months	14.47	4.55, 46.03	**<0.001**

Discussions

In our study, we identified several significant risk factors for VRE colonization in ICU patients, including higher APACHE II scores on ICU admission, longer hospital stays, non-abdominal surgery, and the use of teicoplanin in the past three months, which provide critical insights for improving infection control strategies in healthcare settings.

We observed that higher APACHE II scores on ICU admission were significantly associated with an increased risk of VRE colonization. This finding aligns with previous studies suggesting that severe illness and higher severity scores are correlated with greater susceptibility to VRE colonization (12). Critically ill patients with higher APACHE II scores are more likely to have underlying comorbidities, require invasive procedures, and receive broader-spectrum antibiotics, all of which contribute to the risk of VRE colonization.

Our analysis highlighted the significant impact of prior antibiotic use on VRE colonization risk. The recent use of teicoplanin, a glycopeptide antibiotic, emerged as a strong independent risk factor for VRE colonization in our study. This finding is consistent with previous reports highlighting the association between glycopeptide antibiotic exposure and VRE colonization (13,14).

Teicoplanin, like vancomycin, exerts selective pressure on the intestinal microbiome, favoring the proliferation and persistence of VRE. The use of antibiotics such as piperacillin/tazobactam, meropenem, and vancomycin was particularly associated with higher risks of VRE colonization (15,16). In a similar study conducted in patients in the neonatal intensive care unit in Turkey, exposure to vancomycin was found to be a risk factor for VRE colonization (17). Our results underscore the importance of judicious use of glycopeptide antibiotics and the implementation of antimicrobial stewardship programs to mitigate the risk of VRE colonization.

We found that the length of hospital stay significantly influenced VRE colonisation. Prolonged hospitalisations provide more opportunities for exposure to hospital-acquired pathogens, including VRE. This is consistent with previous studies reporting higher VRE colonisation rates with prolonged length of hospital stay (5,18). In a similar study conducted in patients in intensive care units in Turkey, it was found that prolonged hospitalization was a risk factor for colonization (19). Longer hospitalization increases the exposure to potential VRE reservoirs, such as contaminated surfaces, healthcare workers, and other colonized patients, thereby enhancing the risk of transmission. Therefore, minimizing hospital stay durations should be a key component of infection control measures.

Our study also revealed a strong association between non-abdominal surgery and VRE colonization. This suggests that invasive procedures can increase the risk due to heightened exposure to antibiotics and healthcare environments. Previous studies have primarily focused on the role of gastrointestinal procedures or abdominal surgeries in VRE colonization (20,21). Our results suggest that non-abdominal surgical interventions may also contribute to the risk of VRE colonization, potentially due to factors such as surgical site infections, disruption of mucosal barriers, or increased antibiotic exposure.

It is noteworthy that chronic renal disease was more prevalent among VRE-colonized patients in our univariate analysis, although in the multivariate model, it did not appear as an independent risk factor. This finding aligns with previous studies reporting an association between chronic kidney disease and VRE colonization, potentially due to frequent healthcare exposures, invasive procedures, and altered immune function (22,23).

Interestingly, in our study, we did not find a significant relationship with VRE colonization and several factors previously reported as risk factors, such as advanced age, specific comorbidities (excluding chronic renal disease), the use of invasive devices, or exposure to specific antibiotics other than teicoplanin (24,25). These discrepancies may be attributed to differences in study populations, local epidemiology, and infection control practices.

We have a number of strengths in our study, such as a sample size that is relatively large and a comprehensive evaluation of potential risk factors. On the other hand, since the study was carried out in a single center, the applicability of the results to other healthcare environments may be limited.

In conclusion, this retrospective study identified higher APACHE II scores on ICU admission, longer hospital stays, non-abdominal surgeries, and recent use of teicoplanin as independent risk factors for VRE colonization among ICU patients. These findings highlight the importance of implementing targeted infection control measures, promoting antimicrobial stewardship, and minimizing modifiable risk factors to prevent the spread of VRE in the ICU setting. Future prospective, multicenter studies are warranted to validate and expand upon these findings.

Declarations

Ethical Approval

The study was granted ethical approval by the University of Health Sciences Bursa Yuksek İhtisas Training and Research Hospital Ethics Committee (Approval No. 2011-KAEK-25, Dated: 2023/08/14)

Author Contributions

Concept: C.S, Literature Review: C.S, Design : C.S, Data acquisition: C.S, Analysis and interpretation: C.S, Writing manuscript: C.S, Critical revision of manuscript: C.S

Conflict of Interest

The authors have no conflicts of interest to declare.

Financial Disclosure

Authors declared no financial support.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1336571

Indications, Surgical Techniques and Visual Outcomes of Pediatric Keratoplasty

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Received: 02.08.2023
Accepted: 28.01.2024

ABSTRACT

Purpose: In our study, we aimed to present our nine-year pediatric keratoplasty (KP) experience in a tertiary hospital with indications, surgical techniques and visual results.

Methods: Pediatric patients who underwent KP surgery between 2012 and 2021 in our department were retrospectively analyzed. Patients' gender, age at transplantation, indications, surgery technique, combined surgeries, best corrected visual acuity (BCVA), intraocular pressure (IOP), spherical equivalent (SE) values, postoperative complications and follow-up times were evaluated. Surgical success was considered as an IOP <22 mmHg with or without additional surgery, improvement or preservation of visual acuity.

Results: 72 eyes of 63 patients were included in the study. Twenty (31.7%) of the patients were female and 43 (68.3%) were male. There were keratoconus in 46 (63.9%) eyes, corneal scarring in 21 (29.2%) eyes, corneal dystrophy in 4 (5.6%) eyes, and corneal abscess in 1 (1.4%) eye. The mean age of transplantation was 14.03(4-17) years, and the follow-up period was 47.8(6-124) months. Recurrent KP surgery was performed in 1 (1.4%) patient due to graft failure. Preoperative BCVA was 1.13±0.64 logMaR, and postoperative BCVA was 0.45±0.63 logMaR ($p<0.01$). There were 65 (90%) eyes with a final BCVA of 20/200 or better, and 46 (64%) eyes with a final BCVA of 20/40 or better. Postoperative mean SE was 1.87±3.87 diopters. In 10 patients, higher IOP was detected in the postoperative controls, and trabeculectomy was performed in 2 patients.

Conclusion: After long-term follow-up of our patients, we achieved a vision of 20/200 or better in 63%. Although pre- and post-operative management is quite difficult in pediatric KP cases, long-term visual results can be satisfactory in correctly selected cases.

Keywords: Pediatric corneal transplantation, Penetrating keratoplasty, Deep Anterior Lamellar Keratoplasty

ÖZET

Amaç: Çalışmamızda üçüncü basamak bir hastanede dokuz yıllık pediatrik keratoplasti (KP) deneyimimizi, endikasyonları, cerrahi teknikleri ve görsel sonuçları ile sunmayı amaçladık.

Yöntemler: Kliniğimizde 2012-2021 tarihleri arasında KP cerrahisi yapılan pediatrik olgular retrospektif olarak incelendi. Hastaların cinsiyet, nakil olduklarındaki yaş, endikasyonları, cerrahi teknik, kombine cerrahiler, en iyi düzeltilmiş görme keskinliği (EİDGK), göz içi basıncı (GİB), sferik ekivalan (SE) değerleri, postoperatif komplikasyonlar ve takip süreleri değerlendirildi. Ek cerrahi yapılmaksızın ilaçlı veya ilaçsız GİB'in <22 mmHg olması, görme keskinliğinin iyileştirilmesi ya da korunması cerrahi başarı olarak kabul edildi.

Bulgular: Çalışmaya 63 hastanın 72 gözü alındı. Hastaların 20'si (%31,7) kadın, 43'ü (%68,3) erkekti. Kırk altı (%63,9) gözde keratokonus, 21 (%29,2) gözde korneal skar, 4 (%5,6) gözde korneal distrofi ve 1 (%1,4) gözde korneal abse mevcuttu. Ortalama nakil yaşı 14,03(4-17) yıl, takip süresi 47,8(6-124) aydı. Greft yetmezliğine bağlı 1 (%1,4) hastaya rekürren KP cerrahisi uygulandı. Preoperatif EİDGK 1,13±0,64 logMaR, postoperatif EİDGK 0,45±0,63 logMaR'dı($p<0,01$). Nihai EİDGK düzeyi 20/200 ve üzerinde olan 65 (%90), 20/40 ve üzerinde olan ise 46(%64) göz mevcuttu. Postoperatif ortalama SE 1,87±3,87 diyoptriydi. 10 hastada cerrahi sonrası kontrollerde GİB yüksekliği tespit edildi ve 2 hastaya trabekülektomi uygulandı.

Sonuç: Hastalarımızın uzun dönem takipleri sonrasında %63'ünde 20/200 ve üzeri bir görme elde ettik. Pediatrik KP olgularında pre ve post-operatif yönetim oldukça zor olmakla birlikte doğru seçilmiş olgularda uzun dönem görsel sonuçlar yüz güldürücü olabilmektedir.

Anahtar Kelimeler: Pediatrik kornea nakli, Penetran keratoplasti, Derin Anterior Lamellar Keratoplasti

Pediatric keratoplasty has started to be applied in children with visual loss due to bilateral corneal pathology in the 1970s (1). Pediatric keratoplasty has become more common nowadays with the widespread use of keratoplasty, advances in surgical technique, graft rejection, awareness of risk factors affecting visual prognosis and taking necessary precautions against them. Despite all these positive developments, it is observed that more graft rejection and worse visual results are obtained in children compared to adults (2). There are many debates about the indications and management of pediatric keratoplasty although the anatomical success in pediatric keratoplasty has increased over the years (3).

Pediatric corneal opacities are classified in 3 groups as congenital, traumatic and non-traumatic acquired (4). In the literature, it has been reported that pediatric keratoplasty indications are 14-64% congenital, 19-80% non-traumatic acquired and 6-29% traumatic causes (5-10). In addition, the rate of pediatric keratoplasty indications varies according to the regions. While congenital opacities are the most common cause in North America, anterior segment developmental anomalies are prominent in Asia and sequelae of corneal scar or infectious keratitis are prominent in Africa (5, 7,11,12).

Pediatric age group differs in preoperative, intraoperative and postoperative applications from adults. Difficulties in preoperative patient evaluation and detailed examination, especially in the pre-speech period, may affect the timing of surgery (13). It has been reported in previous studies that it may have complicating effects on keratoplasty surgery various differences in pediatric ophthalmic anatomy like that thin cornea, narrow anterior chamber, weakness in scleral rigidity, high vitreous pressure (2, 12). It has many difficulties of the postoperative follow-up process in children. That difficulties are infection, graft rejection due to the high immunity, early loosening of the sutures, problems in the follow-up and correction of refractive errors and the risk of amblyopia (13, 14).

Despite all these differences and difficulties, by the agency of developing technology increase the frequency of pediatric keratoplasty day by day. In this study, we aimed to share nine-year our tertiary hospital experience about pediatric keratoplasty with indications, surgical techniques and visual results.

Methods

In our study, the data of pediatric patients who operated keratoplasty in Akdeniz University Hospital Ophthalmology department between January 2012 and January 2021 were evaluated retrospectively. Our study which was conducted in accordance with the principles of the Declaration of Helsinki was approved by local ethics committee of Akdeniz University Faculty of Medicine (KAEK - 822 / 30.11.2021).

Seventy-two eyes of 63 patients whose data could be accessed and followed up for at least 6 months postoperatively were included in the study. Detailed anamnesis, gender, age, surgical indications, best corrected visual acuity (BCVA), intraocular pressure, spherical equivalent (SE) values, anterior and posterior segment examination data were recorded. The technique applied during surgery, combined surgeries if any, postoperative complications and follow-up times were recorded. All surgeries were performed by the same physician (M.U.) under general anesthesia.

Surgical success was considered as an under 22 mmHg IOP with or without medication and improvement or preservation of visual acuity in the follow-up without additional surgery.

Statistical Analysis

Statistical analyzes were performed using SPSS for Windows 22.0 (Statistical Product and Service Solutions, Inc., Chicago, IL, USA). The normality assumption was checked with Kolmogorov-Smirnov test. Descriptive statistical analysis methods (mean, standard deviation) were used in the evaluation of the data. Comparisons between groups were made using the independent simple t-test on independent samples. A value of $P < 0.05$ was considered significant.

Results

Demographic characteristics of 63 patients in the study are summarized at Table 1. Preoperative diagnoses of 54 (75%) penetrating keratoplasty (PKP) and 18 (25%) deep anterior lamellar keratoplasty (DALK) surgery are summarized at Table 2. Before 72 keratoplasty, 63 (87.5%) eyes were phakic, 5 (6.9%) eyes were pseudophakic and 4 (5.6%) eyes were aphakic. The distribution of surgical techniques applied by years is shown in Figure 1. The mean follow-up time after surgery was 47.8 (range, 6-124) months.

Table 1: Demographic characteristics of the patients		
		n (%)
Gender	Male	43 (68.3%)
	Female	20 (31.7%)
Laterality	Right	41 (56.2%)
	Left	32 (43.8%)
Age (mean, year)		14.03
Age (range, year)	4-12	21 (30%)
	13-17	51 (70%)
Keratoplasty type	PKP	54 (75%)
	DALK	18 (25%)
PKP: Penetrating Keratoplasty, DALK: Deep Anterior Lamellar Keratoplasty		

Table 2: Preoperative diagnoses			
		PKP	**DALK**
Diagnosis	**n (%)**	**n (%)**	**n (%)**
Keratoconus	46 (63.9%)	31(57.4%)	15(83.3%)
Corneal Scar	21 (29.2%)	19(35.2%)	2(11.1%)
Corneal Dystrophy	4 (5.5%)	3 (5.6%)	1 (5.6%)
Corneal Abscess	1 (1.4%)	1(1.9%)	0(%0)
Total	72(100%)	54(100%)	18(100%)
PKP: Penetrating Keratoplasty, DALK: Deep Anterior Lamellar Keratoplasty			

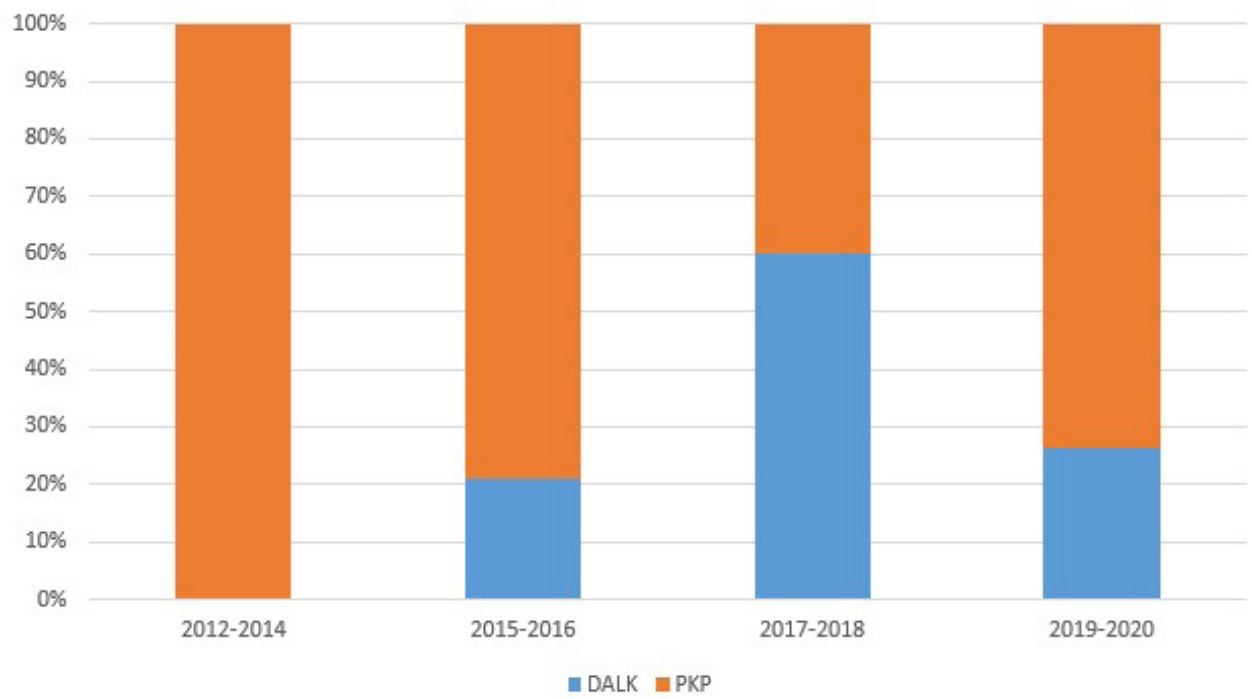

Figure 1: Distribution of pediatric keratoplasty technique by years

The mean BCVA before PKP was 1.19 ± 0.66 (range, 3.1 - 0.4) logMaR and after PKP was 0.46 ± 0.69 (range, 3.1 - 0) logMaR ($p < 0.01$). The mean BCVA before DALK was 0.95 ± 0.52 (range, 1.8 - 0.1) logMaR and after DALK was 0.40 ± 0.34 (range, 1.2 – 0.05) logMaR ($p < 0.01$). The mean BCVA before all surgeries was 1.13 ± 0.64 (range, 3.1 - 0.1) logMaR and after all treatments was 0.45 ± 0.63 (range, 3.1 - 0) logMaR ($p < 0.01$). Final BCVA was detected over 20/200 in 65 (90%) eyes and over 20/40 in 46 (64%) eyes after treatment.

The keratometric measurements which could not be evaluated preoperatively reliable could not be taken also in postoperative follow-up 21 eyes due to reasons such as graft loss, band keratopathy, and secondary glaucoma. With the mean keratometry and refraction values obtained in 51 (70.8%) eyes that could be measured, the postoperative mean SE was -1.87 ± 3.89 diopters.

Intraocular pressure elevation was detected in 10 eyes at postoperative controls and 8 eyes were brought under control after discontinuation of steroid treatment. Trabeculectomy was performed in 2 patients with high intraocular pressure. In 1 patient who developed graft failure in early controls; recurrent penetrating keratoplasty (re-PKP) was performed in 2 of 3 patients who developed late graft rejection, the mean time of re-PKP was 34.7 months. It was observed that the grafts of all 3 patients who underwent re-PKP were transparent in the follow-ups. No cataract or endophthalmitis development was observed in any of the patients postoperatively.

Discussion

Pediatric keratoplasty indications differ in developing and developed countries. While the most common indications in developed countries are keratoconus and corneal opacities, infectious keratitis and traumas take the first place in developing countries (10, 15-17). In our study, we see that the most common indication is keratoconus with a rate of 69.3% and second indication is trauma with a rate of 29.2%.

When we examined the studies related to graft survival rates in the literature, we saw that it varied a lot depending on the number of patients, follow-up time and the applied surgical method. Graft survival rates of at least 1 year after pediatric keratoplasty have been reported to be in the range of 35-82% (9, 15, 18-20). In our study, we found our graft survival rate to be 94.4%. When compared with previous studies, we detected that our survival rate was high. We think that this high rate may be due to the average age of over 10, the most common indication being keratoconus and DALK surgery was preferred in appropriate cases. In the literature, it has been reported that the rate of graft rejection increases as the age of previous keratoplasty application decreases (21).

Visual outcomes after pediatric keratoplasty are not always proportional to graft survival rates, especially in eyes with congenital opacities. Despite the presence of a transparent graft, low visual acuity has been attributed to the development of amblyopia, usually after visual stimulus deprivation (19). In studies evaluating visual acuities after pediatric keratoplasty, the rate of having 20/200 or better vision was reported as 33-80% (9, 22, 23). In our study, we achieved a final BCVA at 90% rate of 20/200 or better. We think that this high rate may be relative with the high preoperative visual acuity of keratoconus patients or the operated of relatively older children. In other study similar to our study, it was reported that better visual results were obtained in keratoplasty performed at the age of 10 and above (23, 24).

Concomitant ocular morbidity, especially such as presence of glaucoma, may also adversely affect final visual acuity. In our study, there was no patient with a preoperative diagnosis of glaucoma. Intraocular pressure elevation was observed in 10 eyes in the postoperative period and trabeculectomy surgery was performed in only 2 eyes (2.8%) because of treatment-resistant glaucoma. Studies have reported that the presence of glaucoma may have negative effects on graft life and visual prognosis (18). It has also been reported that glaucoma surgeries performed after keratoplasty do not have a negative effect on graft transparency (18). Graft rejection has not observed in our two patients who underwent trabeculectomy surgery.

In addition, it has been reported in the literature that 10-50% of infectious keratitis and 2-7% of cataracts may develop in the postoperative period (12). In our study, no postoperative infectious keratitis and/or cataract development was observed.

Limitations of our study are its retrospective design, limited number of patients, and variable postoperative follow-up times. These limitations are also present in previous studies. Pediatric keratoplasty is carried out less frequently when compared to adults. Therefore, we think that the information provided by this single-centered long-term study is valuable.

Conclusion

In conclusion, the frequency of pediatric keratoplasty has been increasing over the last years. Although the surgical indication varies according to the regions, the most common indications in our hospital are keratoconus and corneal scars. Although penetrating keratoplasty is performed more frequently, DALK can be performed in suitable cases. Visual success rates are higher in keratoplasty performed after the amblyopic period.

Declerations

The abstract of this article was presented as an oral presentation at the Turkish Ophthalmology Association (TOA) 55th National Congress. (3-7 Kasım 2021, Antalya, Türkiye)

Funding

The authors received no funding for the research, authorship and/or publication of this article from any government or private institution.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical Approval

This study was approved by the Ethics Committee of the Akdeniz University Faculty of Medicine (KAEK - 822 / 30.11.2021). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Availability of data and material

All data and material are available on request from the authors. The data that support the findings of this study are available from the corresponding author, [L.Y.], upon reasonable request.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1539955

Comparison of CA-125 and HE4 in ovarian cancer recurrence detection

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Received: 28.08.2024
Accepted: 02.09.2024

ABSTRACT

Purpose: This study aims to comprehensively evaluate CA-125 and HE4 as predictors of ovarian cancer (OC) recurrence in the same patient population.

Methods: We systematically searched the WOS, PubMed, and Scopus databases on May 8, 2024, for studies investigating both tumor markers CA-125 and HE4 in the same patient population of ovarian cancer recurrence. We calculated pooled values of AUC, sensitivity, specificity, and univariate or multivariate hazard ratios (HR) for both tumor markers in serum using a random effects model and StataMP 17.0 software.

Results: Thirteen articles comprising 1026 patients satisfied the inclusion criteria. Liquid-biopsy-based HE4 and CA-125 measurements were both proven to have high predictive value for detecting OC recurrence with comparable AUC values (AUC_{HE4}:0.78, 95% CI=0.73-0.83; AUC_{CA125}:0.80, 95% CI=0.73-0.88). While sensitivity of HE4 tests was higher than their specificity ($Sensitivity_{HE4}$=80.7%; 95% CI=73-88.4; I^2=77.05%; p<0.001; $Specificity_{HE4}$=77.8%; 95% CI=68.9-86.6; I^2=83.88%; p<0.001) in detecting OC recurrence, specificity was comparably higher for CA-125 analyses ($Sensitivity_{CA-125}$=71.4%; 95% CI=60.2-82.7; I^2=85,67%; p<0.001; $Specificity_{CA-125}$=94.5%; 95% CI=91.9-97.1; I^2=10.64%; p=0.34). Pooled HR values indicate that increased values of HE4 and CA125 increase the risk for worse progression-free survival by 3.1 (95% CI=1.3–5.0, I^2=0.00 %, p=0.38) and 2.4-fold (95% CI=1.3–3.5, I^2=0.00 %, p=0.93) respectively. HE4 indicates worse overall survival (HR=6.9, CI=0.8–12.6, I^2=0.00 %, p=0.7).

Conclusions: We suggest that HE4 is valuable as a recurrence tracker, with its higher sensitivity, while CA-125 can be used as a validator due to its higher specificity. Further prospective studies analyzing both biomarkers together are required for complete validation.

Keywords: ovarian cancer, recurrence, HE4, CA-125

ÖZET

Amaç: Bu çalışmanın amacı, over kanseri (OK) rekürrensinin izleminde, CA-125 ve HE4'ü aynı hasta popülasyonunda kapsamlı şekilde değerlendirmektir.

Yöntemler: OK rekürrensinin tespitinde CA-125 ve HE4 tümör belirteçlerinin etkinliğini araştıran çalışmalar, 8 Mayıs 2024'te WOS, PubMed ve Scopus veri tabanlarında sistematik olarak arandı. Serumdaki her iki tümör belirteci için AUC, duyarlılık, özgüllük ve tek değişkenli veya çok değişkenli tehlike oranlarının (HR) bileşik değerleri, StataMP 17.0 yazılımı kullanarak, rastgele etkiler modeli ile hesaplandı.

Bulgular: 1026 hastayı kapsayan on üç makale, dahil etme kriterlerini karşıladı. Sıvı biyopsi bazlı HE4 ve CA-125 ölçümlerinin, birbirine yakın bileşik AUC değerleri ile, OK rekürrensini yüksek prediktif etkinlik ile tespit ettiği gösterilmiştir (AUC_{HE4}:0.78, 95% CI=0.73-0.83; AUC_{CA125}:0.80, 95% CI=0.73-0.88). HE4 testlerinin OC rekürrensini saptamadaki duyarlılığı, özgüllüğünden daha yüksek iken ($Sensitivite_{HE4}$=80.7%; 95% CI=73-88.4; I^2=77.05%; p<0.001; $Spesifite_{HE4}$=77.8%; 95% CI=68.9-86.6; I^2=83.88%; p<0.001), CA-125 analizlerinde özgüllük karşılaştırmalı olarak daha yüksektir ($Sensitivite_{CA-125}$=71.4%; 95% CI=60.2-82.7; I^2=85,67%; p<0.001; $Spesifite_{CA-125}$=94.5%; 95% CI=91.9-97.1; I^2=10.64%; p=0.34). Bileşik HR değerleri; HE4 ve CA125 değerlerindeki artışın, daha kötü progresyona sahip sağkalım riskini sırasıyla 3,1 (95% CI=1,3–5,0, I^2=0,00 %, p=0,38) ve 2,4 kat (95% CI=1,3–3,5, I^2=0,00 %, p=0,93) artırdığını göstermektedir. HE4 yüksekliği, daha kötü genel sağkalımı göstermektedir (HR=6,9, CI=0,8–12,6, I^2=0,00 %, p=0,7).

Sonuçlar: Bu çalışmanın sonucunda elde edilen veriler ışığında; daha yüksek duyarlılığa sahip HE4'ün, OK rekürrensinin taranmasında etkinliğinin daha yüksek olduğu; özgüllük değeri daha yüksek olan CA-125'in ise rekürrensin doğrulanmasında sekonder biyobelirteç olarak daha etkin kullanılabileceği önerilmektedir. Her iki tümör biyobelirtecini birlikte analiz eden yeni prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: over kanseri, rekürrens, HE4, CA-125

Globally, ovarian cancer (OC) ranks as the eighth most common malignancy in women (1) and has the highest mortality rate among all gynecological neoplasms (2). The overall 5-year survival rate is below 40% (3). The standard initial treatment regimen consists of extensive cytoreductive surgery, systemic chemotherapy incorporating taxanes and platinum agents, and subsequent individualized maintenance therapies (4). The absence of robust predictive biomarkers, limited understanding of tumor biology, and the development of chemotherapy resistance exacerbate the poor prognosis as well as the high rates of recurrence (5). Therefore, implementing enhanced follow-up is crucial for the early detection of ovarian cancer recurrence.

CA-125 and HE4, which are diagnostic biomarkers that have successfully been used for the differentiation of benign and malignant OC cases, are currently being investigated for their prognostic roles in identifying disease recurrence. CA-125 is a biomarker bound by a monoclonal antibody generated using an ovarian cell line and its concentration in serum is widely used as a valuable tool for OC detection and surveillance (6,7). CA-125 levels at the time of disease relapse have been shown to predict overall survival regardless of treatment approach (8). The well-documented limitations of CA-125, including its poor sensitivity for early-stage disease, persistence as minimal residual disease, and elevation in various benign conditions, significantly hinder its clinical utility (9). HE4, which was initially identified in epididymal epithelium as a potential protease inhibitor involved in sperm maturation, is later observed to be abnormally elevated in OC tissue compared to healthy ovarian tissue. While HE4 demonstrates better prognostic value by predicting disease recurrence earlier than that of CA-125 (10–12), additional factors such as age, smoking, and renal disease were also shown to increase HE4 levels (13). Despite FDA approval of the combined use of HE4 and CA-125 in post-treatment monitoring, their efficacy in detecting recurrent disease remains understudied (14–18). Furthermore, there is substantial variation in the utilization of HE4 as a diagnostic and prognostic marker across European countries and worldwide (15).

This meta-analysis aims to evaluate the prognostic potential and recurrence-predictive value of serum HE4 and CA-125 by pooling the available data in the literature that is published until May 8, 2024.

Materials and Methods

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement to identify, select, appraise, and synthesize the studies included in this meta-analysis (19). Web of Science, PubMed, and Scopus databases were systematically searched up to May 8, 2024, for studies reporting the prognostic values of both CA-125 and HE4 tumor markers in detecting ovarian cancer recurrence. No date restriction was applied. The MeSH terms and additional keywords used for each database were: ("ovarian cancer" OR "ovarian carcinoma" OR "ovarian tumor" OR "ovarian tumour" OR "ovarian neoplasms" OR "ovarian malignancy") AND ("recurrence" OR "relapse") AND ("HE4" OR "human epididymis protein 4" OR "HE-4") AND ("CA125" OR "CA-125").

Screening and selection of studies

Documents shortlisted by initial keyword search were downloaded as BibTex documents from Web of Science, PubMed, and Scopus databases individually, and BibTex files were uploaded to the Mendeley 2.99.0 (Elsevier Ltd.) reference manager. Article duplications were initially removed by Mendeley's automatic duplication tracker. The remaining articles were then aligned by the document name, and additional duplications were removed manually.

The final article list for the initial screening phase was transferred from Mendeley to an Excel spreadsheet. Both authors (ŞO and CCS) independently reviewed the abstract of each article on this list according to PECOS criteria listed in (Supplementary Table 1). Descriptive information including article title, publication type/year/journal, author name, study type, tumor marker information, and information about the detection of recurrence were extracted from each abstract, entered in individual Excel sheets named "Initial Screening Results (ISR)" separately by ŞO and CCS, and used for the initial elimination process. Book chapters, case reports, conference proceedings, comments, dissertations, editorials, guidelines, meeting abstracts, meta-analyses, reviews, and technical reports were excluded. Original articles in English that investigated both biomarkers CA-125 and HE4 in the serum of patients with histologically confirmed recurrent ovarian carcinoma were included in the study. Articles lacking patient data (cell culture studies, studies performed on model organisms), studies examining cancers other

than ovarian cancer, studies that did not address recurrent cases, and those that did not evaluate both tumor markers consecutively in the same patient population were excluded from the study. The study population was restricted to studies that exclusively use recurrent OC patients as the study group, and non-recurrent OC patients as controls. Two investigators crosschecked each other's ISR sheet; discrepancies regarding article selection were resolved by discussion; and documents to be included in the detailed evaluation were shortlisted as a "Detailed Screening (DS) list".

Data extraction

During the secondary selection and data extraction process, the full-text contents of each article that was shortlisted in the DS list and their supplementary materials were further examined. Comprehensive data from the eligible studies were extracted as detailed in Table 1. Respective data from the human studies examining both tumor markers, CA-125 and HE4, in ovarian cancer recurrence which are compatible with the PECOS criteria (Supplementary Table 1) were extracted as Eligible Data (ED) by both authors (ŞO and CCS) separately. Data extraction sheets created by each author were cross-checked by the other investigator. Disagreements were reconciled through collaborative review, and the consolidated data was subjected to statistical analysis. Quality assessment of the included studies was performed according to quality appraisal guidelines (20).

Supplementary Table 1: PECOS criteria for inclusion and exclusion of studies

Criteria	Inclusion Criteria	Exclusion Criteria
Participants	Studies that involve - Female ovarian cancer patients whose recurrence is tracked following cancer treatment - Treatment regimes that are clinically valid for ovarian cancer treatment such as "surgery only", "surgery + chemotherapy", "NACT + surgery", "NACT + surgery + chemotherapy", etc.	- Patients with other types of cancer - Studies that do not examine ovarian cancer patients - Studies that do not examine humans
Exposure	Studies in which - CA-125 and HE4 are measured from patients' sera. - Measurements are performed from sera that are collected during the follow-up period	- Studies that do not involve measurement of CA-125 and HE4 from patients' sera. - Studies only involving HE4 and CA-125 measurements from the serum samples that are collected before the treatment, instead of the follow-up period.
Comparison	Studies in which - The recurrence prediction efficiencies of the following biomarkers are compared: HE4, CA125, and HE4 + CA125 combination	- Studies comparing the recurrence prediction efficiencies of markers other than HE4 and CA-125. - Studies comparing the efficiency of HE4 and CA-125 for cancer diagnosis or post-surgery success, but do not compare the efficiency of these markers in the detection of recurrence during the follow-up period.
Outcome	Studies in which - AUC (Area Under the Curve value for ROC analysis), - Sensitivity and specificity values - HR (Hazard Ratio) values are provided for - Detection of recurrence - Disease Free Survival (DFS) - Progression Free Survival (PFS) - Overall Survival (OS) with sufficient statistical details enabling meta-analysis	Studies that do not - Provide data regarding recurrence statistics, - Provide AUC, Sensitivity / Specificity, and HR values for - Provide 95% CI values if AUC and HR are analyzed - Provide 95% CI values for sensitivity and specificity OR positive predictive and negative predictive values OR number of patients with/without recurrence having low/high values for HE+ and CA-125.
Study Design	- Case-control - Prospective Cohort - Retrospective Cohort	- Review, editorial notes, book chapters - Studies that examine the biomarkers only on model organisms or cell culture, but provide no human patient data - Case Reports, technical reports - Conference proceedings, meeting abstracts, comments, dissertations, editorials - Guidelines

Statistical evaluation

StataMP 17.0 software (Stata Corp LLC, College Station, TX, USA) was used for statistical analyses. The AUC values of both tumor markers were analyzed individually and in combination to predict OC recurrence. Sensitivity and specificity were calculated for each tumor marker separately and in combination. Unadjusted hazard ratios (UHRs) presented as univariate HRs in the original studies, and adjusted hazard ratios (AHRs) reported as multivariate HRs were analyzed separately. Forest plots including the respective confidence intervals were generated to visualize pooled UHR or AHR estimates for PFS and OS, in addition to AUC, sensitivity, and specificity values. The homogeneity and heterogeneity of the pooled studies were assessed using the Q ($p<0.05$ indicates heterogeneity, $p>0.05$ indicates homogeneity) and I^2 statistics ($I^2<25$ % indicating unimportant heterogeneity; 25 %< $I^2<50$ % indicating moderate heterogeneity; 50 %< $I^2<75$ % indicating substantial heterogeneity; $I^2>75$ % indicating considerable heterogeneity), respectively (21). While the Regression-based Egger test was used for small-study effects, the random-effects model (DerSimonian – Laird estimation) was chosen for pools with remarkable heterogeneity. Publication bias was investigated using Begg's funnel plots and Egger's linear regression test.

Supplementary Table 2: Evaluation of the quality of the eligible articles included in the meta-analysis.

Article Ref	Name of First Author	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Confounding Measurement and Account	Analysis
(22)	Chen L.	YES	YES	YES	YES	PARTLY	PARTLY
(26)	Gong Z	YES	YES	YES	YES	PARTLY	YES
(27)	Han JJ	PARTLY	YES	PARTLY	PARTLY	PARTLY	YES
(28)	Innao P	YES	YES	PARTLY	YES	PARTLY	YES
(29)	Kotowicz BU	YES	YES	YES	YES	PARTLY	YES
(30)	Li R	PARTLY	YES	PARTLY	YES	PARTLY	YES
(5)	Nassir M	YES	YES	YES	YES	YES	YES
(31)	Rong Y	YES	YES	YES	YES	PARTLY	YES
(32)	Salminen L	YES	YES	YES	PARTLY	YES	YES
(33)	Shen ZY	YES	PARTLY	YES	YES	PARTLY	YES
(23)	Steffensen KD	YES	YES	YES	YES	PARTLY	YES
(24)	Sun J	YES	YES	YES	YES	PARTLY	YES
(25)	Uno M	YES	YES	YES	YES	YES	PARTLY

Results

An initial keyword search in the Web of Science, PubMed, and Scopus databases yielded 102 articles accepted by publishers as of May 8, 2024 (Figure 1). In the first screening step, the abstracts (and full-text documents if accurate elimination was compromised by lack of sufficient information in the abstract) of these articles were thoroughly reviewed and 49 articles were shortlisted for in-depth full-text screening. Only the studies where both CA-125 and HE4 were analyzed in recurrent OC cases were included in the final analysis. The flowchart depicted in Figure 1 provides a detailed overview of the selection process. At the end of the detailed full-text screening, 13 articles comprising 1026 patients were eligible for this meta-analysis, which reported the results for both CA-125 and HE4 measurements in patients with recurrence provided that these studies included the required statistical data. The risk assessment for bias performed according to quality appraisal guidelines (20) is shown in Supplementary Table 2. Key details from each article, such as study design, tumor marker information, sample characteristics, and patient demographics, were compiled and presented in Table 1 (5,22–33).

Table 1: Article Information, Study Characteristics

Study Details										
Article No	Ref	Year of publication	Name of First Author	Country of study	Study Type	Treatment Regime	Follow-Up Duration	Sample Size	Sample Type	Method for HE4 & CA125 Measurement
1	(22)	2018	Chen L	China	Cross-sectional	Surgery + Platin-based chemotherapy	4 years	103	Serum	ELISA
2	(26)	2022	Gong Z	China	Cross-sectional	N/A	1-3 years	73	Serum	ELISA (HE4) ECLIA (CA125)
3	(27)	2011	Han JJ	USA	Prospective Cohort	Surgery + platinum/ taxane adjuvant chemotherapy	Recruitment: From 2000-2005 Follow Up: Until 2009 (max 5 years)	23	Plasma	ELISA (HE4) N/A (CA125)
4	(28)	2016	Innao P	Thailand	Prospective Cohort	Surgery + platinum/ paclitaxel adjuvant chemotherapy	Recruitment: From June 2014 - March 2016 Follow-Up: For 22 months	47	N/A	N/A
5	(29)	2022	Kotowicz BU	Poland	Cross-sectional	(Group I) surgical treatment + standard systemic treatment (Group II) NACT + surgery	2.5 year	64	Serum	ECLIA - COBAS e601
6	(30)	2022	Li R	China	Cross-sectional	(Group I) NACT + surgery (Group II) Surgery + carboplatin + paclitaxel	Recruitment: From 2016 and 2019 Follow Up: To March 2022	159	Serum	N/A
7	(5)	2016	Nassir M	Europe-Multicenter	Retrospective Cohort	radical cytoreductive surgery + platinum-based chemotherapy	Until the day of the first recurrence	62	Serum	EIA (HE4) Luminex (CA125)
8	(31)	2021	Rong Y	China	Cross-sectional	Staging surgery or optimal cytoreductive surgery + Platinum-based combined chemotherapy	Recruitment: From July 2012 to December 2018 Follow-Up: To the end of 2019 (median follow-up: 35 months)	89	Serum	ECLIA
9	(32)	2020	Salminen L	Finland	Prospective Cohort	(Group I) Surgery + Chemotherapy (Group II) NACT + Surgery + Adjuvant Chemotherapy	Recruitment: Between 2009-2019 Follow-up: from 1.5 months to 10.2 years, median 2.5 years	143	Serum	EIA (HE4) ECLIA or EIA (CA125)
10	(33)	2019	Shen ZY	China	Cross-sectional	Surgery + Chemo (paclitaxel-cisplatin)	Recruitment: From July 2014 - Dec 2019 Follow Up: Every 3 months (Exact duration N/A in the text)	58	Serum	EIA (HE4) CLIA (CA125)
11	(23)	2016	Steffensen KD	Denmark	Prospective Cohort	radical cytoreductive surgery + carboplatin + paclitaxel	26-86 month	88	Serum	EIA
12	(24)	2020	Sun J	China	Cross-sectional	Surgery + Chemotherapy	Recruitment: From January 2014 - December 2016 Follow Up: 6-60 month	69	Serum	ECLIA
13	(25)	2023	Uno M	Japan	Cross-sectional	(Group I) NACT + Surgery (Group II) Surgery + carboplatin + paclitaxel	20.8 months (5.6-.43.9 months)	48	Serum	CMIA - ARCHITECT

ELISA: *Enzyme-Linked Immunosorbent Assay;* ***EIA:*** *Enzymatic Immuno Assay;* ***ECLIA:*** *Electrochemiluminescence;* ***CLIA:*** *Chemiluminescent immunoassay;* ***CMIA:*** *Chemiluminescent Microparticle Capture Immunoassay;* ***NACT:*** *Neoadjuvant Chemotherapy,* ***N/A:*** *Not available*

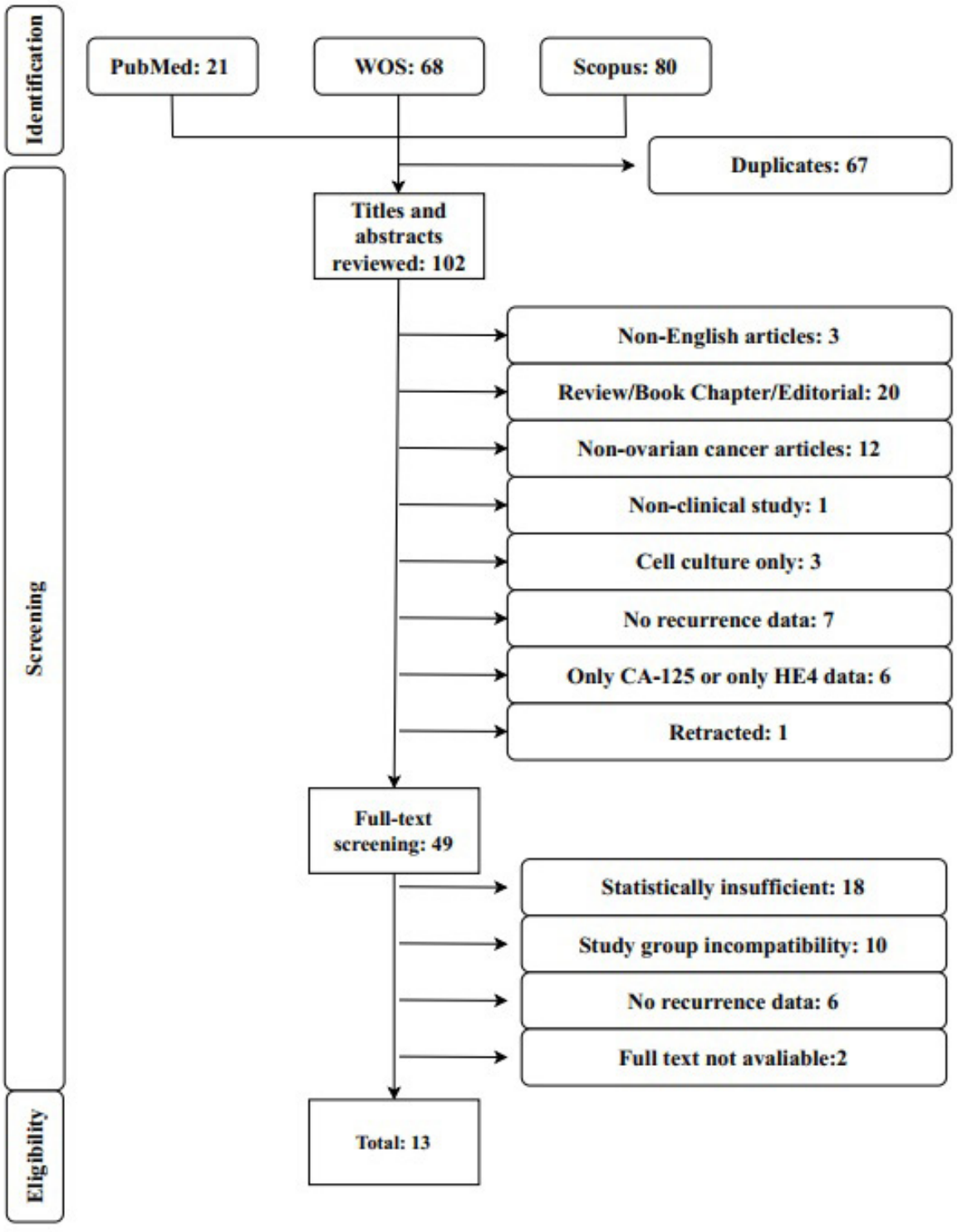


Figure 1: Flowchart of included articles.

Supplementary Table 3: AUC Data

Name of First Author	Year of publication	Sampling Time/ Recurrence Time	Biomarker	CutOff	Analysis Criteria	AUC	SE of AUC	Total Nb of Patients	# of patients with recurrence	# of patients without recurrence
Gong Z	2022		HE4	157.004 pmol/L	predicting poor prognosis	0.77	0.057	73	33	40
Gong Z	2022		CA125	175.243 kU/L	predicting poor prognosis	0.764	0.057	73	33	40
Kotowicz BU	2022	(rec6)*	HE4 (6 months)	N/A	predicting poor prognosis	0.785	0.063	64	24	40
Kotowicz BU	2022	(rec6)*	CA125 (6 month)	N/A	predicting poor prognosis	0.913	0.042	64	24	40
Kotowicz BU	2022	(rec12)*	HE4 (12 months)	N/A	predicting poor prognosis	0.739	0.063	64	31	33
Kotowicz BU	2022	(rec12)*	CA125 (12 month)	N/A	predicting poor prognosis	0.844	0.050	64	31	33
Li R	2022	PTFM	HE4	64.14 pmol/L	detecting recurrence	0.87	0.028	159	85	74
Li R	2022	PTFM	CA125	24.3 U/mL	detecting recurrence	0.94	0.019	159	85	74
Nassir M	2016	(rec12)*	HE4 (recurrence in 12 months)	49.5 pmol/L	diagnosis of recurrence in responders after 1st line chemotherapy	0.81	0.065	62	19	43
Nassir M	2016	(rec12)*	CA125 (recurrence in 12 months)	20 U/mL	diagnosis of recurrence in responders after 1st line chemotherapy	0.884	0.053	62	19	43
Nassir M	2016	(rec12)*	HE4 & CA125 (recurrence in 12 months)	49.5 pmol/L + 20 U/mL	diagnosis of recurrence in responders after 1st line chemotherapy	0.93	0.042	62	19	43
Rong Y	2021	(m6 rec6)*	HE4 (analyte measurement in 6th cycle)	70 pmol/L	diagnosis of recurrence in 6 months	0.73	0.076	89	16	73
Rong Y	2021	(m6 rec6)*	CA125 (analyte measurement in 6th cycle)	35 U/mL	diagnosis of recurrence in 6 months	0.705	0.078	89	16	73
Rong Y	2021	(m3/1 rec6)*	3rd cycle of HE4 &1st cycle of CA125	70 pmol/L + 35 U/mL	diagnosis of recurrence in 6 months	0.723	0.077	89	16	73
Rong Y	2021	(m6 rec24)*	HE4 (analyte measurement in 6th cycle)	70 pmol/L	DFS in 2 years	0.666	0.063	89	30	59
Rong Y	2021	(m6 rec24)*	CA125 (analyte measurement in 6th cycle)	35 U/mL	DFS in 2 years	0.6	0.065	89	30	59
Rong Y	2021	(m3/1 rec24)*	3rd cycle of HE4 &1st cycle of CA125	70 pmol/L + 35 U/mL	DFS in 2 years	0.625	0.064	89	30	59
Shen ZY	2019	PTFM	HE4	105 pmol/L	diagnosis of recurrence	0.737	0.067	58	26	32
Shen ZY	2019	PTFM	CA125	35 U/mL	diagnosis of recurrence	0.825	0.057	58	26	32
Steffensen KD	2016	(m6)*	HE4 (analyte measurement after 1st line treatment)	41 pmol/L	diagnosis of recurrence	0.6976	0.056	88	55	33
Steffensen KD	2016	(m6)*	CA125 (analyte measurement after 1st line treatment)	1 U/mL	diagnosis of recurrence	0.6079	0.061	88	55	33
Steffensen KD	2016	(m6)*	HE4 & CA125 (analyte measurement after 1st line treatment)	41 pmol/L + 1 U/mL	diagnosis of recurrence	0.7395	0.052	88	55	33
Sun J	2020	PTFM	HE4	184 pmol/mL	diagnosis of recurrence	0.858	0.046	69	54	15
Sun J	2020	PTFM	CA125	57.5 U/L	diagnosis of recurrence	0.847	0.048	69	54	15

AUC: *Area Under the Curve;* ***SE:*** *Standard Error;* ***PTFM:*** *Post Treatment Follow-Up Analyte Measurement;* ***T1:*** *Treatment regime 1;* ***T2:*** *Treatment regime 2;* ***m3/1:*** *HE4 is analyzed from the serum sample collected at 3rd month of the treatment, CA-125 is analyzed from the serum sample collected at 1st month of the treatment;* ***m6:*** *respective biomarkers that are analyzed from the serum sample collected at 6th month of the treatment;* ***rec6:*** *detection of recurrence at the 6th month of the follow-up;* ***rec12:*** *detection of recurrence at the 12th month of the follow-up;* ***rec24:*** *detection of recurrence at the 24th month of the follow-up;* ***DFS:*** *Disease-Free Survival*

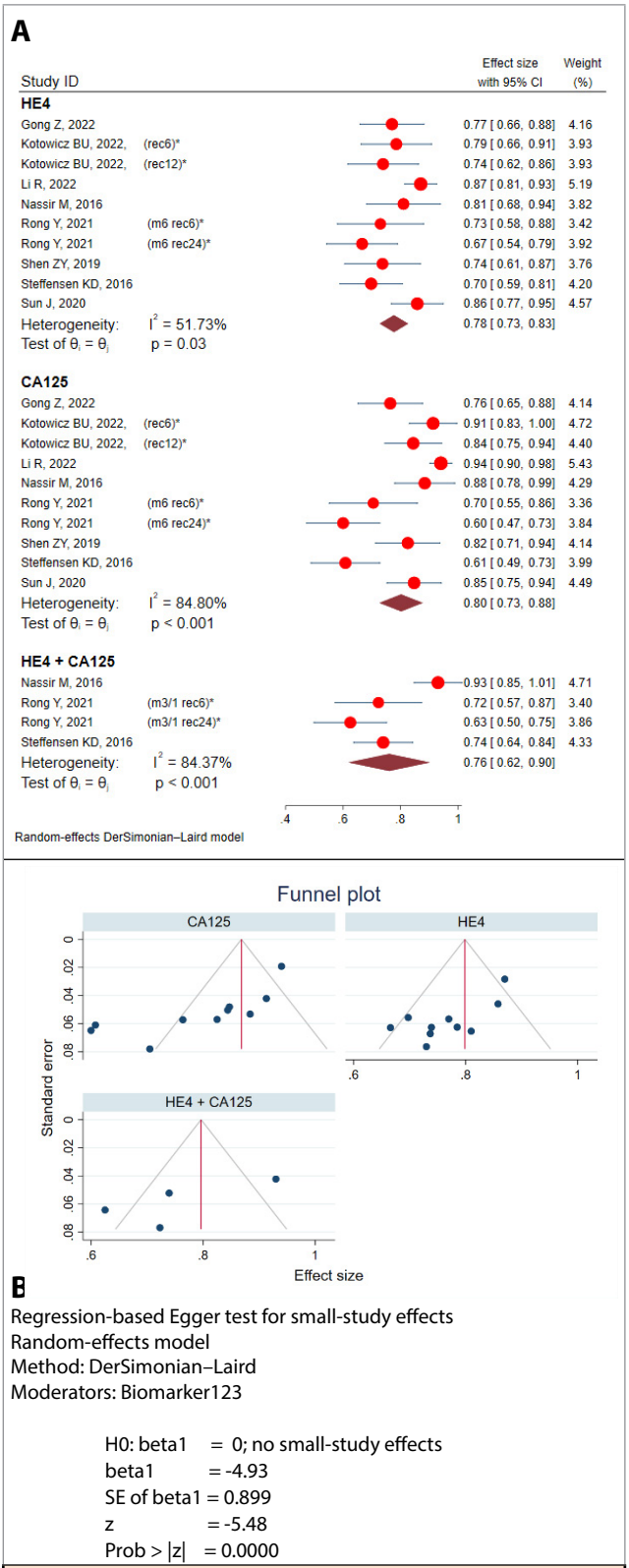
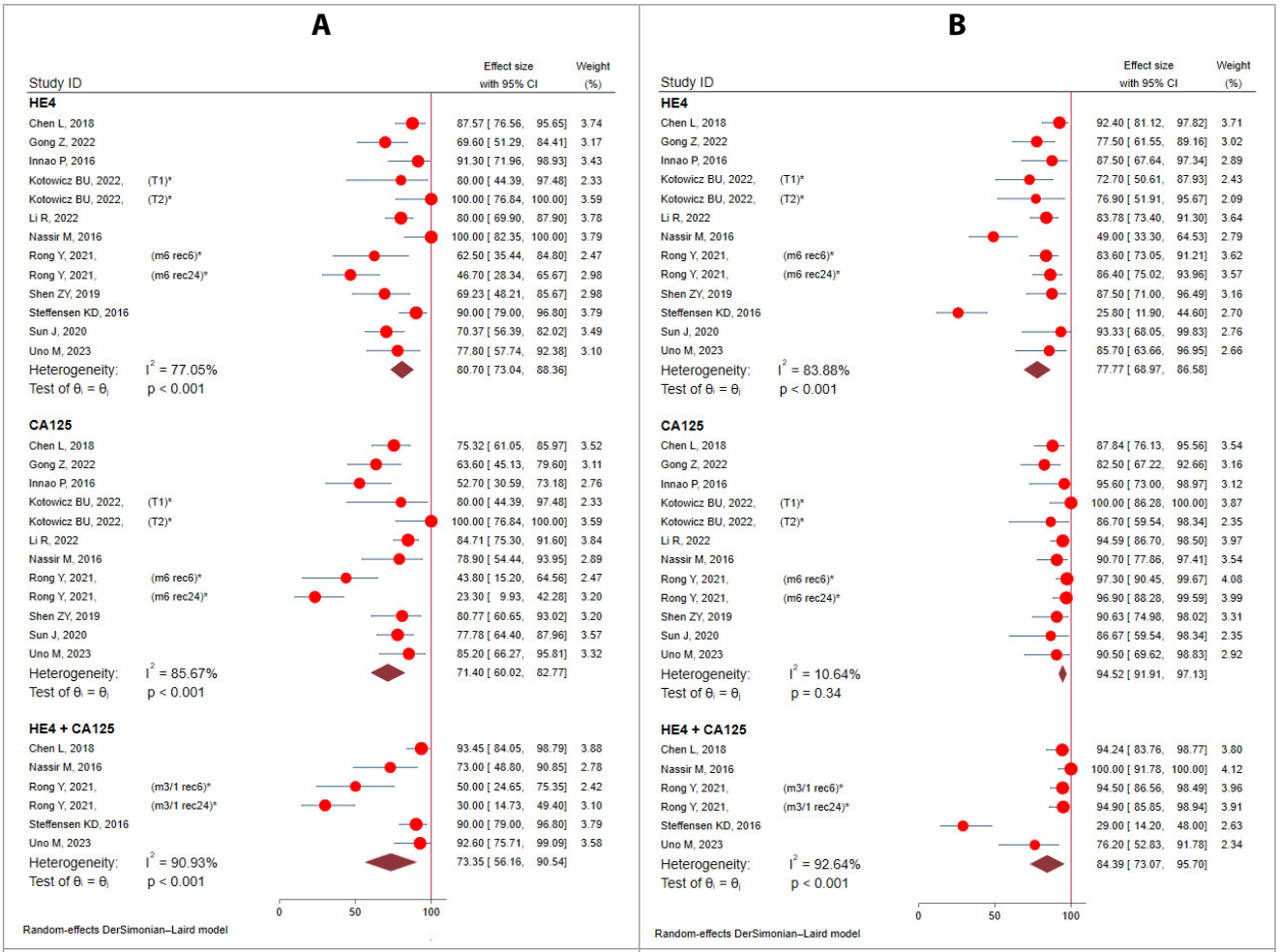


Figure 2: The association of HE4 and CA-125 with recurrence detection of ovarian cancer patients. Pooled AUC values of serum HE4, CA-125, and their combination regarding recurrence detection of ovarian cancer are seen as Forest graphs (**A**) and Funnel graphs together with the Egger-test scores (**B**).

While the potential of serum tumor markers CA-125 and HE4 for detecting the recurrence of OC was analyzed through ROC analysis in most of the eligible studies, only eight studies documented statistically sufficient AUC data (5,23,24,26,29–31,33); presented in detail in Supplementary Table 3. Three of these studies assessed AUC across different recurrence intervals (recurrence in 6 months, 12 months, or 24 months) or patient subgroups (5,29,31). Pooled AUC analysis of CA-125 and HE4 indicated comparable efficacy in detecting OC recurrence, with relatively higher heterogeneity index for CA-125 (AUC_{HE4}=0.78; 95% CI=0.73–0.83; I^2=51.73%; p=0.03; AUC_{CA-125}=0.80; 95% CI=0.73–0.88; I^2=84.80%; p<0.001 Figure 2). The performance of the two biomarkers together as a combined prognostic tool was analyzed only in three of these articles, one of which evaluated the combination in two different recurrence intervals (5,23,31). The high level of heterogeneity among the studies precludes a conclusion that the combination outperforms individual markers ($AUC_{HE4+CA-125}$=0.76; 95% CI=0.62–0.90; I^2=84.37%; p<0.001) (Figure 2).

Eleven of the eligible studies evaluated the sensitivity and specificity of serum tumor markers CA-125 and HE4 in predicting OC recurrence (5,22–26,28–31,33), comprehensive data is presented in Supplementary Table 4. Two of these studies assessed sensitivity and specificity across different recurrence intervals or patient subgroups (29,31). Pooled analysis performed here revealed an increased risk of recurrence in OC patients with higher serum HE4 ($Sensitivity_{HE4}$=80.7; 95% CI=73-88.4; I^2=77.05%; p<0.001; $Specificity_{HE4}$=77.8; 95% CI=68.9-86.6; I^2=83.88%; p<0.001), and higher serum CA-125 levels ($Sensitivity_{CA-125}$=71.4; 95% CI=60.2-82.7; I^2=85,67%; p<0.001; $Specificity_{CA-125}$=94.5; 95% CI=91.9-97.1; I^2=10.64%; p=0.34). Except for $Specificity_{CA-125}$, high heterogeneity was observed for all parameters due to the small sample size of the study pool, as shown in the funnel plot and indicated by the Egger test results. The usage of both tumor markers as a combination was evaluated only in five studies, one of which assessed two distinct recurrence intervals. The pooled analysis of the combination revealed sensitivity and specificity values comparable to each of the tumor markers measured individually ($Sensitivity_{HE4+CA-125}$=73.35; 95% CI=56.16-90.54; I^2=90.93%; p<0.001; $Specificity_{HE4+CA-125}$=84.39; 95% CI=73.07-95.70; I^2=92.64%; p<0.001) (Figure 3).



Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian–Laird
H0: beta1 = 0; no small-study effects
beta1 = -4.04
SE of beta1 = 0.912
z = -4.43
Prob > |z| = 0.0000

Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian–Laird
H0: beta1 = 0; no small-study effects
beta1 = -3.83
SE of beta1 = 0.714
z = -5.37
Prob > |z| = 0.0000

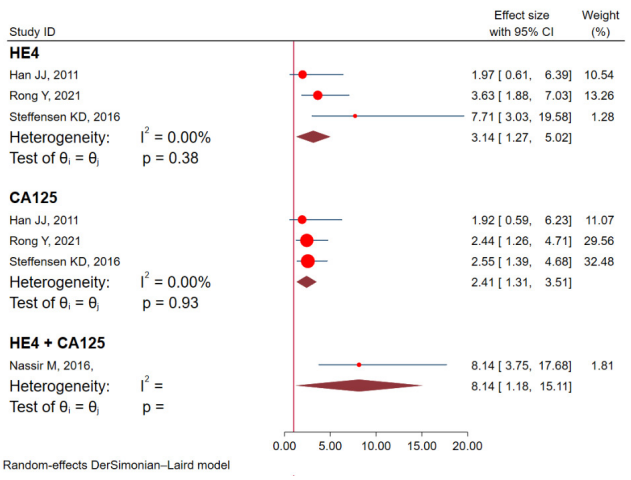
Figure 3: Sensitivity and Specificity of HE4 and CA-125 biomarkers for detection of recurrence in ovarian cancer patients. Pooled Sensitivity (**A** and **C**) and Specificity (**B** and **D**) values of serum HE4, CA-125, and their combination regarding recurrence detection of ovarian cancer are seen as Forest graphs (**A** and **B**) and Funnel graphs together with the Egger-test scores (**C** and **D**).

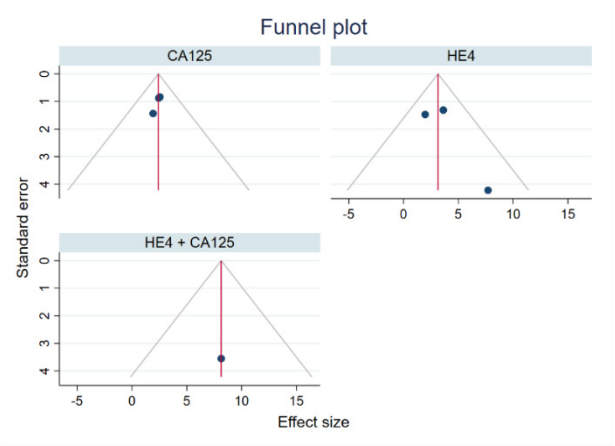
Supplementary Table 4: Sensitivity & Specificity Data

						Sensitivity			Specificity					With Recurrence		Without Recurrence	
Name of First Author	Year of publication	Sampling Time/ Recurrence Time	Biomarker	CutOff	Analysis Criteria	%	95% CI Min	95% CI Max	%	95% CI Min	95% CI Max	# of OC patients with recurrence	# of OC patients without recurrence	Biomarker > Cutoff	Biomarker < Cutoff	Biomarker > Cutoff	Biomarker < Cutoff
Chen L	2018	PTFM	HE4	70 pmol/L	diagnosis of recurrent ovarian cancer	87.6	76.6	95.6	92.4	81.1	97.8	52	51	46	6	4	47
Chen L	2018	PTFM	CA125	35 IU/ml	diagnosis of recurrent ovarian cancer	75.3	61.1	86.0	87.8	76.1	95.6	52	51	39	13	6	45
Chen L	2018	PTFM	HE4 + CA125	70 pmol/L + 35 IU/ml	diagnosis of recurrent ovarian cancer	93.5	84.1	98.8	94.2	83.8	98.8	52	51	49	3	3	48
Gong Z	2022		HE4	157 pmol/L	predicting poor prognosis	69.6	51.3	84.4	77.5	61.5	89.2	33	40	23	10	9	31
Gong Z	2022		CA125	175 kU/L	predicting poor prognosis	63.6	45.1	79.6	82.5	67.2	92.7	33	40	21	12	7	33
Innao P	2016	PTFM	HE4	200 %	Prediction of Recurrence	91.3	72.0	98.9	87.5	67.6	97.3	23	24	21	2	3	21
Innao P	2016	PTFM	CA125	200 %	Prediction of Recurrence	52.7	30.6	73.2	95.6	73.0	99.0	23	24	12	11	2	22
Kotowicz BU	2022	(T1)*	HE4	79.1 pmol/L	detecting recurrence	80.0	44.4	97.5	72.7	50.6	87.9	10	25	8	2	7	18
Kotowicz BU	2022	(T1)*	CA125	30.7 IU/mL	detecting recurrence	80.0	44.4	97.5	100.0	86.3	100.0	10	25	8	2	0	25
Kotowicz BU	2022	(T2)*	HE4	90.4 pmol/L	detecting recurrence	100.0	76.8	100.0	76.9	51.9	95.7	14	15	14	0	3	12
Kotowicz BU	2022	(T2)*	CA125	25.6 IU/mL	detecting recurrence	100.0	76.8	100.0	86.7	59.5	98.3	14	15	14	0	2	13
Li R	2022	PTFM	HE4	64.14 pmol/l	detecting recurrence	80.0	69.9	87.9	83.8	73.4	91.3	85	74	68	17	12	62
Li R	2022	PTFM	CA125	24.3 IU/ml	detecting recurrence	84.7	75.3	91.6	94.6	86.7	98.5	85	74	72	13	4	70
Nassir M	2016	(rec12)*	HE4	49.5 pmol/l	diagnosis of recurrence in responders after 1st line chemotherapy	100.0	82.4	100.0	49.0	33.3	64.5	19	43	19	0	22	21
Nassir M	2016	(rec12)*	CA125	20 IU/ml	diagnosis of recurrence in responders after 1st line chemotherapy	78.9	54.4	94.0	90.7	77.9	97.4	19	43	15	4	4	39
Nassir M	2016	(rec12)*	HE4 + CA125	49.5 pmol/l + 20 IU/ml	diagnosis of recurrence in responders after 1st line chemotherapy	73.0	48.8	90.9	100.0	91.8	100.0	19	43	14	5	0	43
Rong Y	2021	(m6 rec6)*	HE4	70 pmol/L	diagnosis of recurrence in 6 months	62.5	35.4	84.8	83.6	73.0	91.2	16	73	10	6	12	61
Rong Y	2021	(m6 rec6)*	CA125	35 U/ml	diagnosis of recurrence in 6 months	43.8	15.2	64.6	97.3	90.5	99.7	16	73	6	10	2	71
Rong Y	2021	(m3/1 rec6)*	HE4 + CA125	70 pmol/L + 35 U/ml	diagnosis of recurrence in 6 months	50.0	24.7	75.3	94.5	86.6	98.5	16	73	8	8	4	69
Rong Y	2021	(m6 rec24)*	HE4	70 pmol/L	DFS in 2 years	46.7	28.3	65.7	86.4	75.0	94.0	30	59	14	16	8	51
Rong Y	2021	(m6 rec24)*	CA125	35 U/ml	DFS in 2 years	23.3	9.9	42.3	96.9	88.3	99.6	30	59	7	23	2	57
Rong Y	2021	(m3/1 rec24)*	HE4 + CA125	70 pmol/L + 35 U/ml	DFS in 2 years	30.0	14.7	49.4	94.9	85.9	98.9	30	59	9	21	3	56
Shen ZY	2019	PTFM	HE4	105 pmol/L	diagnosis of recurrence	69.2	48.2	85.7	87.5	71.0	96.5	26	32	18	8	4	28
Shen ZY	2019	PTFM	CA125	35 U/ml	diagnosis of recurrence	80.8	60.6	93.0	90.6	75.0	98.0	26	32	21	5	3	29
Steffensen KD	2016	(m6)*	HE4	41 pmol/L	diagnosis of recurrence	90.0	79.0	96.8	25.8	11.9	44.6	55	33	50	5	24	9
Steffensen KD	2016	(m6)*	HE4 + CA125	41 pmol/L + 1 U/ml	diagnosis of recurrence	90.0	79.0	96.8	29.0	14.2	48.0	55	33	50	5	23	10
Sun J	2020	PTFM	HE4	184 pmol/mL	diagnosis of recurrence	70.4	56.4	82.0	93.3	68.1	99.8	54	15	38	16	1	14
Sun J	2020	PTFM	CA125	57.5 U/L	diagnosis of recurrence	77.8	64.4	88.0	86.7	59.5	98.3	54	15	42	12	2	13
Uno M	2023	PTFM	HE4	70 pmol/mL	diagnosis of recurrence	77.8	57.7	92.4	85.7	63.7	97.0	27	21	21	6	3	18
Uno M	2023	PTFM	CA125	35 U/L	diagnosis of recurrence	85.2	66.3	95.8	90.5	69.6	98.8	27	21	23	4	2	19
Uno M	2023	PTFM	HE4 + CA125	70 pmol/mL + 35 U/L	diagnosis of recurrence	92.6	75.7	99.1	76.2	52.8	91.8	27	21	25	2	5	16

OC: *Ovarian Cancer;* ***95 % CI Min:*** *Lower limit of the 95 % confidence interval;* ***95 % CI Max:*** *Upper limit of the 95 % confidence interval;* ***PTFM:*** *Post Treatment Follow-Up Analyte Measurement;* ***T1:*** *Treatment regime 1;* ***T2:*** *Treatment regime 2;* ***m3/1:*** *HE4 is analyzed from the serum sample collected at 3rd month of the treatment, CA-125 is analyzed from the serum sample collected at 1st month of the treatment;* ***m6:*** *respective biomarkers that are analyzed from the serum sample collected at 6th month of the treatment;* ***rec6:*** *detection of recurrence at the 6th month of the follow-up;* ***rec12:*** *detection of recurrence at the 12th month of the follow-up;* ***rec24:*** *detection of recurrence at the 24th month of the follow-up;* ***DFS:*** *Disease-Free Survival*

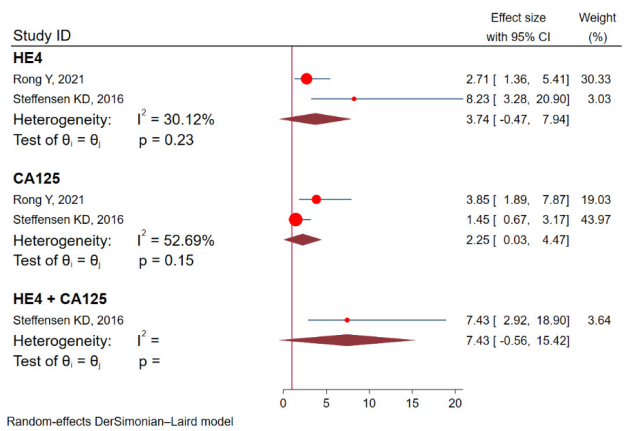
(The statistical data highlighted in gray, although not explicitly presented in the cited article, are iterated using Medcalc based on the statistical data readily presented within the cited article.

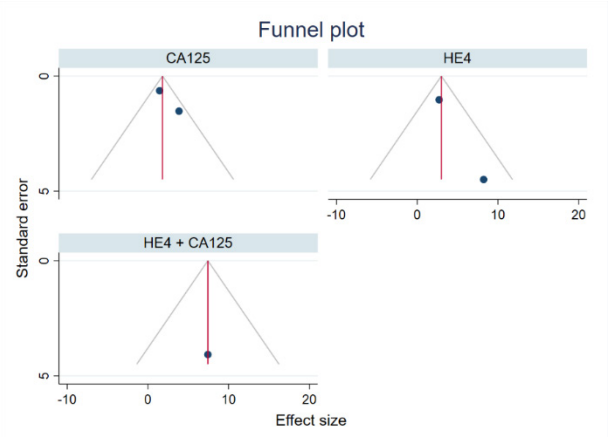




Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian–Laird

H0: beta1 = 0; no small-study effects
beta1 = 1.46
SE of beta1 = 0.870
z = 1.68
Prob > |z| = 0.0933

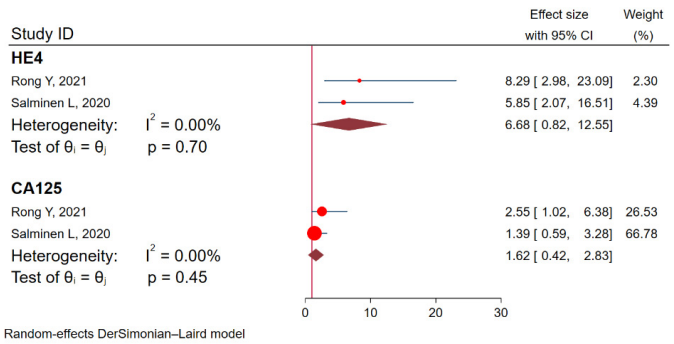


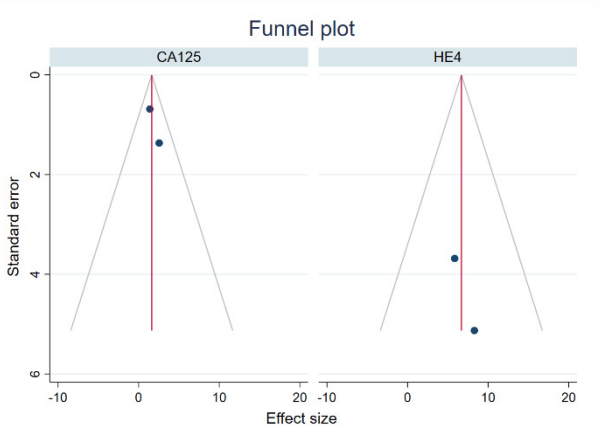


Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian–Laird

H0: beta1 = 0; no small-study effects
beta1 = 1.92
SE of beta1 = 0.791
z = 2.43
Prob > |z| = 0.0153

Figure 4: The association between serum values of HE4 and CA-125 with progression-free survival of ovarian cancer patients. Pooled univariate hazard ratios (**A, B**) and pooled multivariate hazard ratios (**C, D**) of serum HE4, CA125, or their combination regarding progression-free survival of ovarian cancer patients are seen as Forest graphs (**A, C**) and Funnel graphs together with the Egger-test scores (**B, D**).





Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian–Laird

H0: beta1 = 0; no small-study effects
beta1 = 1.54
SE of beta1 = 0.829
z = 1.86
Prob > |z| = 0.0629

Figure 5: The association between serum values of HE4 and CA-125 with overall survival of ovarian cancer patients. Pooled hazard ratios of HE4 and CA125 regarding overall survival of ovarian cancer patients are seen as Forest graphs (**A**) and Funnel graphs together with the Egger-test scores (**B, D**).

While three of the eligible studies reported hazard ratios for PFS (23,27,31) either by univariate or multivariate analyses, only two of the studies presented OS data (31,32) as shown in Figures 4 and 5. The univariate analysis of PFS suggests that serum positivity of both HE4 (PFS-UHR$_{HE4}$=3.14, CI=1.27–5.02, I^2=0.00 %, p=0.38) and CA-125 (PFS-UHR$_{CA-125}$=2.41, CI=1.31–3.51, I^2=0.00 %, p=0.93) increase the HR for PFS (Figure 4A-B). As the sample size for eligible studies was very small, heterogeneity in the studies cannot be significantly assessed through Egger's test and funnel plot analysis (Figure 4B). While the combination of the two biomarkers holds promise as an effective prognostic tool for the prediction of PFS (PFS-HR$_{HE4 + CA125}$=8.14, CI=1.18–15.11), insufficiency in the number of studies providing detailed statistical data hinders conclusive remarks (Figure 4A). Despite the limited number of eligible studies providing sufficient multivariate statistics, the multivariate analysis of PFS also suggests both biomarkers as indicators for worse PFS upon an increase in serum values (Figure 4C-D). The analysis of association between overall survival and the serum levels of HE4 and CA-125 indicate that increase in serum HE4 levels increase the risk for worse overall survival by 6.9 fold (OS-HR$_{HE4}$=6.68, CI=0.82–12.55, I^2=0.00 %, p=0.7), while the risk is increased 1.6 fold upon increase in serum CA-125 levels (OS-HR$_{CA-125}$=1.62, CI=0.42-2.83, I^2=0.00 %, p=0.45) (Figure 5).

Discussion

Recognizing the importance of timely intervention in recurrent OC for improving patient outcomes, gynecologic oncologists strongly emphasize recurrence monitoring during follow-up. Compared to pelvic and imaging examinations which suffer from subjectivity, low accuracy, and limited ability to detect small lesions, tumor markers provide a substantial benefit in monitoring patients for detection of OC recurrence.

Despite FDA approval of the combined use of HE4 and CA-125 in post-treatment monitoring (34), HE4 is a biomarker with limited clinical adoption across European countries and worldwide (35). European Society of Gynaecological Oncology (ESGO), the European Society for Medical Oncology (ESMO), and the European Society of Pathology (ESP) recommend routine oncological follow-up including imaging and/or CA-125 according to local practice and after discussion with the patient (35). To our knowledge, this meta-analysis which pooled data from 1026 patients across thirteen studies, is the first to examine the prognostic efficacy of CA-125 and HE4 in the detection of ovarian cancer recurrence simultaneously in the same patient cohort, enabling their direct comparison with one another, in addition to evaluation of their performance as a combined prognostic tool.

Here, pooled analyses of the eligible data confirm the findings of the previous studies, indicating that an increase in serum HE4 and CA-125 during the follow-up period is associated both with poor prognosis and poor survival in ovarian cancer.

Pooled AUC analysis of CA-125, HE4, and their combination indicated comparable efficacy in detecting OC recurrence (AUC_{HE4}=0.78; 95% CI=0.73–0.83; I^2=51.73%; p=0.03; AUC_{CA-125}=0.80; 95% CI=0.73–0.88; I^2=84.80%; p<0.001; $AUC_{HE4+CA-125}$=0.76; 95% CI=0.62–0.90; I^2=84.37%; p<0.001 Figure 2). The high level of heterogeneity among the studies examining these biomarkers individually or as a combined prognostic tool results in large and overlapping confidence intervals, defying the prominence of HE4-alone, CA-125-alone, or their combination as a better prognostic tool outperforming the others.

Pooled analysis of sensitivity and specificity of HE4 and CA-125 measurements indicate HE4 as a biomarker with higher sensitivity ($Sensitivity_{HE4}$: 80.7 [73-88.4]; $Sensitivity_{CA-125}$: 71.4 [60.2-82.7]) while indicating CA-125 as a biomarker with higher specificity ($Specificity_{HE4}$: 77.8 [68.9-86.6]; $Specificity_{CA-125}$: 94.5 [91.9-97.1]) in detecting recurrence in OC. With its higher sensitivity, HE4 may be able to identify recurrence in patients with negative CA-125 test results. Considering these results, it might be argued that HE4 has a higher potential as a recurrence tracker during the follow-up period, utilized in the initial screening phase limiting the false-negative results, and CA-125 might prove useful as a secondary parameter acting as a recurrence validator, decreasing the false-positive rate. Due to the limited number of available studies and high heterogeneity among eligible studies, the pooled analysis of the HE4 + CA-125 combination demonstrates limited improvement from individual biomarkers in terms of sensitivity or specificity ($Sensitivity_{HE4+CA-125}$=73.35 [56.16-90.54[; $Specificity_{HE4+CA-125}$=84.39 [73.07-95.70]). Additional data from new studies examining both biomarkers in parallel in the same patient population will be required to support this improvement to suggest the combination as a better indicator in predicting OC recurrence.

While pooled HR results suggest that the risk for worse progression-free survival (PFS) was greater than 3-fold upon increasing serum HE4, and close to 2.5-fold upon increase in serum CA-125, the limiting number of the eligible studies result in large and overlapping confidence intervals, precluding comprehensive comparison of their prognostic efficacy with one another.

The heterogeneity among the studies is attributable to several factors including variation in sample size, lack of standardization in the methods and cutoff values used to measure the analytes, variation in the recurrence intervals tracked, heterogeneity in the methods used during follow-up period for validation of cancer recurrence, etc.

Cao et al demonstrated a 2.6-fold increased risk of recurrence in OC patients with higher serum HE4 levels through a subgroup meta-analysis of five studies (36). However, the authors did not conduct subgroup analyses to assess the risk associated with increased CA-125 levels. Gu et al conducted a meta-analysis of 34 studies, demonstrating pooled specificity and sensitivity values of (0.93, 95% CI: 0.89–0.95) and (0.69, 95% CI:0.65–0.72), respectively, for CA-125 (37).

By utilizing EIA with a lower cutoff point (HE4: 41 pmol/L; CA-125: 1 U/ml), Steffensen et al. (23) achieved high sensitivity (90%) for HE4 and both tumor markers in combination in the early phase of OC (the first 6 months after first-line therapy), however, this approach compromised the specificity of the tests. In addition to the primary analysis, a secondary analysis was conducted using a cutoff value determined by a 50% increase after the first-line treatment in a six-month follow-up. They found that patients with elevated HE4 levels at the 3- and 6-month follow-up points experienced significantly shorter progression-free survival compared to those with elevated CA-125 levels, as demonstrated by substantially higher hazard ratios for HE4. They suggested in summary that a >50% early increase in HE4 post-treatment strongly predicts recurrence risk.

Rong et al. analyzed tumor markers using the ECLIA method (cut-off values HE4: 70 pmol/L; Ca125: 35 U/ml) during the initial six-month postoperative period while patients were undergoing first-line chemotherapy treatment (31). While they demonstrated that HE4 had a higher sensitivity than CA-125, their reported sensitivity was lower than our meta-analysis. This difference might be attributed to their analysis being restricted to the initial six months following surgery. They claimed that HE4 is a better predictor of platinum sensitivity than CA-125. Their data revealed a maximum AUC of 0.779 (p<0.001) for HE4 alone in predicting platinum sensitivity after the third chemotherapy cycle, compared to the maximum AUC=0.731 of CA125 (p=0.004) after the first cycle. Combining both biomarkers, they found that either HE4 clearance after the third cycle or CA-125 clearance after the first cycle yielded AUC, sensitivity and specificity were 0.788, 100, and 57.5% respectively. Notably, the absence of HE4 clearance after the third cycle and CA-125 clearance after the first cycle perfectly identified all platinum-resistant patients.

While the current study represents a pioneering contribution to the field, by evaluating statistically relevant and sufficient data from the studies examining both tumor markers in the same study population for the first time, it is afflicted by the limitations present in the studies currently available in the literature. A significant limitation is attributable to the high heterogeneity among studies regarding study periods, cut-off values, patient populations, and treatment regimens. Available literature had utilized diverse methods for the assessment of tumor markers and studies using varying cut-off levels had to be combined in the pooled analyses. Variation in the cut-off levels utilized in different studies results from the fact that the analysis methods used in the studies for measurement of either of the tumor markers are not yet standardized, traceable, or harmonized. Once the measurement methods become traceable, standardized, and harmonized, the homogeneity among the studies will increase, enabling the utilization of a mutual cut-off. Another limitation was caused due to the limited number of available studies. As the number of studies examining both biomarkers in parallel in the same patient population increases, it will be possible to evaluate the prognostic efficacy of these markers based on tumor stage or type. Larger prospective studies comparing both tumor markers in the same patient population are needed.

Conclusion

Frequent and meticulous surveillance of patients following cancer treatment is essential for early detection of recurrence. Our meta-analysis indicates comparable efficacy of both tumor markers in detecting OC recurrence, with HE4 as a feasible complementary tool in tracing OC recurrence and CA-125 as a recurrence validator. Given the substantial heterogeneity among studies, additional prospective trials assessing both biomarkers within the same patient cohort are imperative for definitive conclusions. In addition, the imperative to discover biomarkers with superior prognostic potential remains paramount. Earlier detection of cancer recurrence with higher accuracy will open possibilities for advanced therapeutic approaches.

Declarations

Funding

Not applicable

Conflict of Interest

The authors state no conflict of interest.

Ethics Approval

No ethical approval and patient consent were required for this study as all of the included studies had recruited patients that provided informed consent.

Availability of Data and Material

The raw data can be obtained on request from the corresponding author.

Author Contributions

Both authors contributed to the study conception and design, screening and selection of the studies, and data extractions. Statistical evaluation was performed by Ceyhan Ceran Serdar. The first draft of the manuscript was written by Şeyma Osmanlıoğlu, and both authors read and approved the final manuscript.

Acknowledgement

The authors sincerely thank Professor Muhittin Abdülkadir Serdar for his invaluable insights and constructive feedback on this study.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1574135

Exploring the Correlation Between Bone Marrow Edema in the Tibial Plateau and Surgical Preferences in Stage 3 Gonarthrosis Patients

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Received: 26.10.2024
Accepted: 12.11.2024

ABSTRACT

Purpose: This study investigated the association between bone marrow edema in the tibial plateau and surgical inclination in patients with stage 3 gonarthrosis.

Methods: A cohort of 40 patients diagnosed with stage 3 gonarthrosis underwent Magnetic Resonance Imaging (MRI) to assess the presence and severity of bone marrow edema in the tibial plateau. Demographic data, clinical history, and radiographic findings were collected, and chi-square tests and logistic regression analyses were used to evaluate significant relationships.

Results: A significant positive correlation was identified between age and edema presence ($r = 0.47$, $p < 0.01$), indicating an increased likelihood of edema with advancing age. No significant correlations were found between edema and BMI ($r = -0.06$, $p = 0.70$) or between BMI and age ($r = 0.08$, $p = 0.62$), suggesting that BMI does not relate significantly to either edema or age within this sample. Patients with more pronounced bone marrow edema were more likely to opt for surgery. Age and prior conservative treatment outcomes were identified as potential confounding factors influencing surgical decision-making.

Conclusion: The results highlight bone marrow edema in the tibial plateau as a factor associated with a greater inclination towards surgery in stage 3 gonarthrosis patients. These insights support a personalized approach to treatment, helping clinicians align interventions with individual patient profiles and preferences. Further research is recommended to explore additional factors impacting treatment choices in advanced knee osteoarthritis.

Keywords: Stage 3 gonarthrosis, Bone marrow edema, Tibial plateau

ÖZET

Başlık: Tibial Platodaki Kemik İliği Ödemi ile Evre 3 Gonartroz Hastalarının Cerrahi Tercihleri Arasındaki Korelasyonun İncelenmesi

Özet: Amaç: Bu çalışma, tibial platonun kemik iliği ödemi ile evre 3 gonartroz hastalarında cerrahi eğilim arasındaki ilişkiyi araştırmayı amaçlamaktadır.

Metod: Evre 3 gonartroz tanısı konulan 40 hastadan oluşan bir kohortta, tibial platonun kemik iliği ödemi varlığı ve şiddeti Manyetik Rezonans Görüntüleme (MRG) ile değerlendirildi. Demografik veriler, klinik geçmiş ve radyografik bulgular toplandı; anlamlı ilişkileri değerlendirmek için ki-kare testi ve lojistik regresyon analizleri kullanıldı.

Sonuçlar: Yaş ile ödem varlığı arasında anlamlı pozitif bir korelasyon ($r = 0.47$, $p < 0.01$) saptanmış olup, yaş arttıkça ödem görülme olasılığının arttığı gözlenmiştir. Ödem ile vücut kitle indeksi (BMI) ($r = -0.06$, $p = 0.70$) veya BMI ile yaş ($r = 0.08$, $p = 0.62$) arasında anlamlı bir ilişki bulunmamış, BMI'nin bu örneklemde ödem veya yaşla anlamlı bir bağlantısı olmadığı belirlenmiştir. Daha belirgin kemik iliği ödemine sahip hastaların cerrahi müdahaleyi tercih etme olasılığı daha yüksek bulunmuştur. Yaş ve önceki konservatif tedavi sonuçları, cerrahi karar alma sürecini etkileyen potansiyel karıştırıcı faktörler olarak belirlenmiştir.

Sonuç: Sonuçlar, tibial platonun kemik iliği ödeminin, evre 3 gonartroz hastalarında cerrahi eğilim ile ilişkili bir faktör olduğunu göstermektedir. Bu bulgular, tedavi yaklaşımlarının bireyselleştirilmesine katkı sağlayarak, klinisyenlerin müdahaleleri hastanın bireysel profiline ve tercihlerine göre uyarlamalarına yardımcı olabilir. İleri araştırmalar, ileri seviye diz osteoartriti tedavi seçimlerini etkileyen diğer faktörleri incelemek üzere önerilmektedir.

Anahtar Kelimeler: Evre 3 gonartroz, Kemik iliği ödemi, Tibial plato

Bone marrow edema (BME) in the tibial plateau is a condition commonly seen in patients with knee pain, often linked to trauma, overuse, or degenerative conditions such as osteoarthritis. Characterized by fluid accumulation within the bone marrow, BME can be visualized using MRI and is frequently associated with underlying bone stress or inflammation (1). This edema represents a response to increased mechanical loading or injury in the knee joint and may significantly impact both diagnosis and treatment strategies. In particular, its presence serves as an important marker of joint health, influencing not only the approach to conservative management but also surgical decision-making (2).

When it comes to surgical interventions, the detection of bone marrow edema in the tibial plateau plays a crucial role in determining the optimal course of action. Surgeons must carefully consider the extent of edema and its underlying cause before proceeding with procedures such as arthroscopy, osteotomy, or total knee arthroplasty (3). BME may suggest ongoing instability or mechanical stress in the joint, potentially affecting the outcome and recovery from surgery. As a result, its presence often leads to modifications in surgical planning, including the timing of the intervention, the type of procedure chosen, and postoperative management strategies aimed at reducing further joint damage and promoting healing (4).

Additionally, the presence of bone marrow edema may serve as a red flag for delayed or altered healing postoperatively. This can impact decisions regarding the intensity of rehabilitation and weight-bearing activity, as well as the use of adjunctive treatments to address inflammation and support recovery. Thus, the relationship between bone marrow edema in the tibial plateau and surgical preferences is a key consideration in ensuring favorable outcomes for patients undergoing knee surgery, especially in cases of complex or degenerative joint conditions.

Materials and Methods

In this study 40 patient's data were evaluated retrospectively. The radiographic grading system and MRI sagittal images were used. Between the years 2016-2022, 40 patients were included in the study group. Patients who had undergone surgery for tumoral, arthroscopic, or traumatic conditions related to the knee were excluded from the study. Siemens Healthcare Erlangen, Germany's 1.5 T Magnetom MRI equipment was used to get these pictures. To ensure the best possible contrast manual adjustments were made to accommodate each image's brightness, intensity, contrast, and gray value limitations. The maximal coronal thickness (depth) of the IPFP from the medial to the lateral surface was physically measured for each patient in our research for both the right and left knees. To evaluate correlations between these variables, Pearson correlation analysis was conducted, providing correlation coefficients (r) and significance levels (p-values) to determine the strength and direction of each relationship. Statistical significance was set at $p < 0.05$, with specific attention given to correlations where $p < 0.01$. All data analyses were performed using statistical software, ensuring accurate calculation of correlation coefficients and significance levels

The study was approved by the Ethics Committee of İstanbul Unıversıty Cerrahpasa, Cerrahpasa Faculty of Medicine (Date: 18.09.2024, decision number: 1094609)

Results

Table 1: Correlation analysis conducted between edema, bmi and age.

	Edema	Bmi	Age
EDEMA: Pearson Correlation	1,00	-,06	,47**
Sig. (2-tailed)		,70	,00
N	40,00	40,00	40,00
BMI: Pearson Correlation	-,06	1,00	,08
Sig. (2-tailed)	,70		,62
N	40,00	40,00	40,00
AGE:	,47**	,08	1,00
Sig. (2-tailed)	,00	,62	
N	40,00	40,00	40,00
***Correlation is significant at the 0.01 level (2-tailed).*			

Pearson correlation analysis was conducted to evaluate the relationships between edema, BMI, and age in the sample of 40 participants. A statistically significant positive correlation was found between edema and age ($r = 0.47$, $p < 0.01$), indicating that as age increases, the presence of edema also tends to increase. No significant correlations were found between edema and BMI ($r = -0.06$, $p = 0.70$), or between BMI and age ($r = 0.08$, $p = 0.62$). This suggests that, within this sample, BMI does not significantly relate to either edema or age. (Table 1)

Discussion

The results of the Pearson correlation analysis provide insights into the relationships between age, BMI, and edema within this sample. The positive, statistically significant correlation between edema and age ($r = 0.47$, $p < 0.01$) suggests that as individuals in the sample age, they are more likely to experience edema. This finding aligns with prior research indicating that aging is associated with increased prevalence of edema, likely due to age-related physiological changes such as decreased vascular elasticity, reduced venous return, and overall circulatory efficiency. These factors can contribute to fluid retention, especially in the lower extremities, increasing edema risk in older individuals.

However, the analysis found no significant relationship between BMI and edema ($r = -0.06$, $p = 0.70$), nor between BMI and age ($r = 0.08$, $p = 0.62$). This lack of significant association suggests that, in this sample, BMI does not play a substantial role in edema presence or in the aging process. Although BMI has been previously associated with various cardiovascular and metabolic risks that could hypothetically contribute to edema, this sample's data indicate that such effects may not be evident, or that other confounding factors are at play. Additionally, the non-significant relationship between BMI and age suggests that, within this population, increases in age do not necessarily correlate with changes in BMI. This could be due to lifestyle factors, sample characteristics, or variations in the body composition changes with age.

Overall, the findings highlight age as a potential contributor to edema risk, while BMI does not appear to have a direct association with either age or edema in this sample.

For this reason, total knee arthroplasty should not be immediately considered for these patient groups. Based on our findings, we believe that edema is not significant for making surgical decisions in these patients. Instead of surgical treatment, it may be more beneficial to follow these patient groups with physical therapy methods, weight loss, and NSAID use. When we look at gender groups, we see that women tend to have more muscle strength, which leads to higher bone marrow edema in women with a higher body mass index (6).

Postoperative recovery in patients with pre-existing bone marrow edema in the tibial plateau may be prolonged, as the edema reflects ongoing stress or inflammation in the joint. This condition could predispose patients to slower healing times and increased risk of complications, such as delayed bone healing or prolonged pain. Surgeons may need to consider strategies to minimize postoperative edema, such as careful rehabilitation protocols, anti-inflammatory therapies, and monitoring with follow-up imaging. The presence of bone marrow edema can also guide decisions about the intensity and timing of weight-bearing activities during recovery, with a more gradual approach recommended to avoid exacerbating joint stress. Thus, the management of bone marrow edema is critical not only for the surgical planning phase but also for optimizing long-term outcomes and patient satisfaction.

Bone marrow edema in the tibial plateau is a common finding in patients experiencing knee pain, often detected on MRI. This condition reflects an accumulation of fluid in the bone marrow, typically due to microtrauma, overload, or degenerative changes. The increased intramedullary pressure from fluid accumulation stimulates nociceptors within the bone, resulting in pain. edema in the tibial plateau may be associated with underlying injuries, such as subchondral fractures, meniscal tears, or ligamentous instability, all of which contribute to altered load distribution and increased stress on the bone. This biomechanical imbalance further exacerbates the edema and pain, creating a vicious cycle. In clinical practice, managing edema often involves addressing both the mechanical overload and underlying pathology to reduce pain and improve function.

Conclusion

This study's findings highlight a notable relationship between age and edema, suggesting that increased age is associated with a higher likelihood of edema presence within the sample.Future studies with larger and more diverse samples may provide further insight into these relationships and assess whether other factors might mediate or moderate the influence of age and BMI on edema.

Declarations

Funding

NONE

Conflicts of Interest/Competing Interests

The authors declare that they have no conflicts of interest.

Ethics Approval

This study was approved by the ISTANBUL UNIVERSITY CERRAHPAŞA RECTORATE Clinical Research Ethics Committee with the number E-83045809-604.01-1094609

Availability of Data and Material The data that support the findings of this study are available from the corresponding author, C.D.D. upon reasonable request.

Authors' Contributions: C.D.D. contributed to the conception and design of the study, data collection, data analysis, manuscript drafting and critical revision of the manuscript. A.C. contributed to the conception and design of the study, data collection, data analysis, manuscript drafting and critical revision of the manuscript.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1374171

Donation Decision-Making Process and Psychological Experiences of Families of Brain-Dead Donors from Turkey

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Received: 02.11.2023
Accepted: 13.09.2024

ABSTRACT

Purpose: Families play a key role in the decision to donate the organs of people with brain death. However, studies on the factors affecting the decisions of families and possible emotional difficulties they experience afterwards are insufficient. In our study, we aimed to investigate donor families' personal evaluations of the donation approval process and long-term psychological experiences in their families, such as prolonged grief, depression and restructuring of meaning.

Methods: A total of 24 first-degree relatives of donors who had brain death at least 6 months ago and who gave their consent for transplantation were included in the study. Demographic data form, Prolonged Grief Scale(PG-13), Grief and Meaning Reconstruction Inventory(GMRI), and Beck Depression Inventory(BDI) were administered to the participants.

Results: It was found that female gender increased the risk of depression by 13 times(OR=13, $p<0.05$) and the risk of prolonged grief by 5 times(OR=5.57, $p<0.05$). It was observed that the presence of a relative waiting for an organ transplant increased the risk of depression by 17 times(OR=17.0, $p<0.05$). It was determined that the risk of depression increased 1.26 fold by the increase in PG-13 scores($p<0.05$), while GMRI scores were not statistically significant in increasing the risk of depression($p>0.05$).

Conclusion: It is considered that in donor families, especially female gender and witnessing the experience of waiting for organ transplantation before donation may increase the risk of depression and grief. Programs that will facilitate access to psychological counseling services for all donor families in the long term is needed.

Key words: Organ donation, Brain death, Transplantation, Depression, Donor, Family

ÖZET

Amaç: Aileler, beyin ölümü gerçekleşen kişilerin organlarının bağışlanması kararında kilit rol oynamaktadır. Ancak ailelerin kararlarını etkileyen faktörler ve sonrasında yaşadıkları olası duygusal zorluklar üzerine yapılan çalışmalar yetersizdir. Çalışmamızda donör ailelerin, bağış onam süreciyle ilgili kişisel değerlendirmelerini ve uzun vadede ailelerdeki uzamış yas, depresyon ve anlamı yeniden yapılandırma gibi psikolojik deneyimleri araştırmayı amaçladık.

Yöntem: En az 6 ay önce beyin ölümü gerçekleşen kişilerin nakil onamını veren birinci derece yakınlarından toplam 24 gönüllü çalışmaya dahil edildi. Katılımcılara demografik veri formu, Uzamış Yas Ölçeği (UYÖ-13), Yas ve Anlam Yeniden Yapılandırma Envanteri (YAYYE) ve Beck Depresyon Envanteri (BDE) uygulandı.

Bulgular: Çalışmamızda kadın cinsiyetin depresyon tanısı riskini 13 kat (OR=13, $p<0,05$), uzamış yas tanısı alma riskini ise 5 kat arttırdığı (OR=5,57, $p<0,05$), öncesinde organ nakli bekleyen bir arkadaşın varlığının ise depresyon riskini 17 kat artırdığı (OR=17.0, $p<0.05$) bulunmuştur. UYÖ-13 skorlarının artmasıyla depresyon riskinin 1,26 kat arttığı ($p<0,05$), YAYYE skorlarının ise depresyon riskini arttırmada istatistiksel olarak anlamlı olmadığı belirlendi ($p>0,05$).

Sonuç: Olası sonuçlar göz önüne alındığında; donör ailelerinde özellikle kadın cinsiyetin ve bağıştan önce organ nakli beklemeye aşina olmanın depresyon ve yas riskini arttırabileceği düşünülmektedir. Bu sebeple başta bu özellikte olan aileler olmak üzere tüm donör ailelerin uzun vadede psikolojik danışmanlık hizmetlerine erişimini kolaylaştıracak programların geliştirilmesini önermekteyiz.

Anahtar Kelimeler: Organ bağışı, Beyin ölümü, Nakil, Depresyon, Donör, Aile

Although the number of patients waiting for organ transplantation is increasing in the world, the transplantation rates are still insufficient. Socio-economic status, differences in cultural and religious beliefs, level of knowledge about donation and brain death, and the deceased person's preference for organ transplantation may affect donation decisions of families (1,2). It is affirmed that poor communication with family negatively affects the transfer decisions and a clear, understandable, empathetic, informative, supportive communication style with families at the appropriate time and environment is important, and thus it may be beneficial to provide communication training to health professionals working in organ donation coordination team (3,4). On the other hand, it has been shown that the quality of communication established with the healthcare team during this period has a positive effect on the subsequent psychological processes of families who give consent (4).

While most people who mourn the loss of a loved one can return to their daily routines and functions, some may experience psychiatric disorders such as depression, prolonged grief and post-traumatic stress disorder (5). The symptoms observed in the grief process of people diagnosed with prolonged grief disorder(PGD) are more severe and take a longer time. Although 6 months have passed since the loss, the symptoms do not subside and there is clinically significant impairment in social, occupational and other areas of functioning (6). Studies show that grief reactions can vary according to the type of death, the type of relationship with the deceased, and the personality traits of those left behind (7).

Studies have shown that restructuring meaning after bereavement can be a protective factor for prolonged grief (8). Restructuring of meaning enables re-meaning of the world, learning after loss, personal growth, exploring new roles, and adapting. Therefore, the individual searches for answers to various questions and obtain different explanations. Interventions to reconstruct meaning have been shown to have positive effects on the treatment of chronic grief (9).

Considering the lack of literature, in the present study we aimed to evaluate the experiences of the relatives who lost their first-degree family member due to brain death and gave consent for organ donation, in terms of their experiences with the donation process and their subsequent levels of depression, prolonged grief, and restructuring of meaning.

Material and Method

Participants and Procedure

First-degree relatives of brain-dead donors between 2011 and 2021 who gave consent for transplantation were included in the study. According to the criteria for prolonged grief disorder, it was required that at least 6 months have passed since the bereavement. The contact information of the families was obtained through the Bursa Region Organ Donors database of the Ministry of Health Organ Transplantation Institution(OTI). It was observed that there were 96 donors in the 10-year period covered by the study. Fourty six relatives of donors could not be reached because their contact information was not up-to-date. Fifty relatives of donors were contacted by phone and 24 of them agreed to participate in the study. A questionnaire prepared with Google Forms was sent to the relatives of donors who agreed to participate in the study. Ethics committee approval was obtained from Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee.

Measurement Tools

Demographic data form: This form, which includes items to question the sociodemographic variables (such as age, gender, education,etc.) and the experience during decision-making process (such as closeness to the deceased, the age of the deceased, cause of death, beliefs about having sufficient knowledge about brain death and the donation process, environmental support for transplantation, time after transplantation,etc.), was prepared by the researchers and applied to all participants.

Beck Depression Inventory (BDI): It is a self-report scale that evaluates depression from cognitive, emotional and physiological aspects (10). The cut-off score was determined as 17 in the Turkish validity and reliability study (10). An increase in the scores obtained from the scale indicates an increase in depressive symptoms.

Prolonged Grief Scale (PG-13): It is used to diagnose and to measure symptom severity of prolonged grief, and its Turkish validity and reliability study was conducted by Işıklı et al (11). The PG-13 contains 11 Likert type questions and two "yes/no" questions, which evaluate symptoms of separation distress and other cognitive-emotional behaviors specific to PGD. The increase in the total scores obtained from the 11 items of the scale indicates an increase in the severity of the symptoms of prolonged grief (6).

Grief and Meaning Reconstruction Inventory (GMRI): Its Turkish validity and reliability were performed by Keser and Işıklı (12). Exploratory Factor Analysis showed that the Turkish version of the scale has 27 items and 4 sub-dimensions as continuing bonds, personal growth, emptyness-meaninglessness and sense of peace. As the scores obtained from the scale increase, the level of restructuring of meaning increases.

Statistical Analysis

Study data were analyzed with the IBM Statistical Package for the Social Sciences for Windows 26.0 package program(SPSS 26.0-IBM, NY, USA). Demographic and clinical characteristics of the participants were evaluated with descriptive statistical analyzes such as number, percentage, and median. The relationship between the BDI, GMRI and PG-13 scores were analyzed by Spearman Correlation Analysis. To investigate the effects of clinical variables about deceased and donation process on the risk of depression and prolonged grief, Univariate Binary Logistics Regression Analysis was performed. The efficiency of PG-13 and GMRI scores in increasing the risk of depression diagnosis, and the efficiency of BDI and GMRI scores in increasing the risk of prolonged grief diagnosis was examined by Multivariate Binary Logistic Regression Analysis. A value of $p<0.05$ was accepted as significant for all analysis.

Results

The sample of our study consists of first-degree relatives of 24 donors who gave transplant approval. Of the participants, 14 were male (58.3%) and 10 were female (41.7%). A total of four participants (16.7%), three women and one man, were diagnosed with prolonged grief. A total of 6 people (25%), five women and one man, and 75% of those diagnosed with prolonged grief received a score of 17 or higher on the BDI. It has been observed that an average of 2,6 years have passed since the loss. Other sociodemographic and clinical data are presented in Table 1. As a result of Chi-Square and Mann Whitney U tests, it was concluded that there was no statistically significant difference($p>0.05$) in terms of regret and demographic and clinical characteristics.

Table 1: Sociodemographic and clinical characteristics of participants

Characteristics (N=24)		n	%
Gender	Male	14	58,3
	Female	10	41,7
Education status	Primary education	14	58,3
	Higher education	10	41,7
Closeness to the person you lost and to whom you gave approval for the transfer	Parents (Mother or Father)	12	50
	Spouse	2	8,3
	Child	3	12,5
	Brother/Sister	7	29,2
Cause of death	Disease resulting in sudden death	15	62,5
	Suicide	1	4,2
	Human caused	1	4,2
	Traffic accident	3	12,5
	Industrial accident	2	8,3
	Other	2	8,3
How death happens	Sudden unexpected death	23	95,8
	Expected death	1	4,2
Did the person you lost have a known preference regarding organ transplantation?	Yes	7	29,2
	No	17	70,8
Did you find the attitude of the hospital staff empathetic, respectful and supportive during the donation process?	Yes	23	95,8
	No	1	4,2
Do you believe you have enough information about brain death and the entire donation process?	Yes	19	79,2
	No	5	20,8
Have you ever regretted your transplant decision?	Yes	4	16,7
	No	20	83,3
Have you ever needed to consult anyone other than healthcare professionals when deciding on donation?	Yes	13	54,2
	No	11	45,8
If you have consulted, please indicate who you consulted (relative, religious official, etc.)	Relative(s)	8	61,5
	Religious official	5	38,5
Having diagnosis of depression	Yes	6	25
	No	18	75
Having diagnosis of prolonged grief	Yes	4	16,7
	No	20	83,3
Age of the participants	18-24	1	4,2
	25-34	8	33,3
	35-44	5	20,8
	45 yaş üstü	10	41,7
Age of deceased	Mean±SD	51,42±16,98	
	Min.-Max.	23-87	

SD: Standart deviation, Min.-Max.: Minimum-Maximum

Univariate Binary Logistic Regression Analysis demonstrated that female gender increases the risk of depression by 13 times (OR=13,p<0.05) and the risk of prolonged grief by 5 times (OR=5.57,p<0.05), while presence of a friend waiting for an organ increased the risk of depression 17 times (OR=17.0, p<0.05). Sociodemographic characteristics were not statistically significant factors in increasing the risk of prolonged grief (p>0.05)(Table 2).

Table 2: Factors that increase the risk of diagnosis of depression and prolonged grief

	Depression		Prolonged grief	
	OR	%95 CI	OR	%95 CI
Age (18-44)	1,60	0,23-11,28	2,46	0,22-27,84
Gender (Female)	13,00*	1,20-140,73	5,57	0,48-64,09
Education status (High school and below)	1,60	0,23-11,08	0,67	0,08-5,75
Relationship (Sibling)	2,50	0,24-2,50	1,29	0,11-15,00
Age of the deceased	0,98	0,92-1,04	0,98	0,92-1,05
Relatives' choice of donation (Yes)	1,30	0,18-9,48	0,78	0,07-9,08
Adequate information about the donation process (Yes)	0,40	0,05-3,27	0,75	0,06-9,27
An acquaintance waiting for an organ (Yes)	17,00*	1,30-223,14	1,89	0,14-24,79
Social support for donation decision(Yes)	2,50	0,36-17,32	1,00	0,12-8,56
Organ donation week participation (Yes)	0,13	0,01-1,33	1,00	0,12-8,56
Time since loss	1,06	0,90-1,25	0,94	0,81-1,08
Having Regret (Yes)	0,99	0,99-1,00	0,99	0,99-1,00

OR: Odds Ratio, Univariate Binary Logistic Regression Analysis, CI: Confidence Interval

According to correlation analysis, a statistically significant positive correlation was found between BDI and PG-13(r=0.672,p<0.001) scores, and a negative correlation between BDI and GMRI meaningless-emptyness subscale(r=-0.480,p=0.018) scores. There was no significant correlation between BDI scores and GMRI scores(r=-0.199,p=0.350). There was a statistically significant negative correlation between PG-13 scores and GMRI total scores(r=-0.410, p=0.046) and sense of peace(r=0.-518,p=0.010) subscale scores.

Multivariate Binary Logistic Regression Analysis revealed that increased PG-13 scores increased the risk of depression diagnosis by 1.26 times (p<0.05,95%CI:1.03-1.54), and that GMRI scores were not a statistically significant variable in increasing the risk of depression (p>0.05)(Table 3). It was found that BDI and GMRI scores were not statistically significant variables in increasing the risk of prolonged grief (p>0.05)(Table 4).

Table 3: The effect of PG-13 and GMRI scores on the risk of depression

	β	OR	%95 CI
PG-13	0,23	1,26*	1,03-1,54
GMRI	0,04	0,37	0,95-1,15

OR: Odds Ratio, Multivariate Binary Logistic Regression Analysis, CI: Confidence Interval, PG-13: Prolonged Grief Scale, GMRI: Grief and Meaning Reconstruction Inventory
** p<0,05statistically significant*

Table 4: The effect of BDI and GMRI scores on the risk of prolonged grief

	β	OR	%95 CI
BDI	0,23	1,26	0,91-1,74
GMRI	-0,18	0,83	0,67-1,04

OR: Odds Ratio, Multivariate Binary Logistic Regression Analysis, CI: Confidence Interval, BDI: Beck Depression Inventory, GMRI: Grief and Meaning Reconstruction Inventory

Discussion

Making the decision to donate organs alone after their loss can be challenging for family members. Previous experiences have suggested that the donation decision is largely determined by the way of mutual interaction between the family of donor and healthcare team, and inadequate communication may be one of the reasons

for negative decisions (3). In our study, 79.2% family members of donors stated that they were adequately informed about brain death and donation process, and 95.8% families found the attitude of the hospital staff to be favorable. Studies show that the concept of brain death can still be confusing for families, less so in families who consent to donation (13). Families who are expected to make quick decisions in the acute period may understand the medical dimension of the concept of brain death better in the following period and tend to view their level of knowledge less in the first period. It has been shown that organ donation volunteerism increases with the training provided (14). We recommend that awareness meetings and training on organ donation be increased throughout society. For this reason, when giving information to families; it is thought that it may be beneficial to use explanatory brochures, offer them to participate in brain death tests, and give them time to ask questions and consider (15). The fact that eight of the volunteers who participated in our study stated that they consulted other family members before making the decision may be related to the need to alleviate the burden of making decisions alone and to be supported. Five participants stated that they consulted religious officials to decide on organ donation. On the other hand, the fact that families who did not consent to transplantation were not included in our study limited the evaluation of the effect of religious beliefs on the decision.

Families may be indecisive about donation, so they may experience regret and even complicated grief afterwards (16). In a comprehensive study, regret was found in 10% of those who gave consent for transplantation and in one third of those who did not (17). In our study, 16.7% of participants stated that they regretted giving their consent for organ donation. Although in the literature regret is associated with sudden loss of a loved one, not knowing the choice of transplantation, not clearly understanding the concept of brain death, and situations where the family is indecisive about consent, in our study, a statistical evaluation could not be made between regret and other variables due to the small size of the population (17). In our study, no relationship was found between regret and sociodemographic characteristics, depression and prolonged grief. This difference may be due to the small sample size of the study group.

Another important finding is that the presence of an acquaintance awaiting an organ transplant beforehand increases the risk of depression in donor families by 17 times, but has no effect on prolonged grief. It is an important finding that waiting in line for organ transplantation makes people and their relatives prone to depression. Witnessing the waiting process for organ transplantation may predispose people and their relatives to depression. On the other hand, establishing a clear causal relationship is difficult due to the nature of depression. However, we recommend not to ignore such past information in donor families and to be cautious about subsequent depression processes.

In our study, the average time since loss was found to be 2.6 years. Although loss-related grief processes and depression are expected to decrease with the time elapsed after the loss, no significant relationship was found between these variables and duration in our study (18). The changes in grief and depression over the course of time can be seen more clearly through longitudinal studies that include acute and chronic period follow-up after transplantation.

Seventy percent of te participants said that the death of their relatives were sudden and unexpected, and they did not know whether they had any preference for organ donation. It has been shown that if the decisions are known in advance, they act in accordance with this decision at a rate of 93%, even if their families do not think alike (19). In cases where the deceased person's preference is unknown, it is thought that the recognition of these people as altruistic and willing to help other people motivates their families in the decision to donate (20). For this reason, although the preferences of the donors in our study are not clearly known, their relatives may have given their consent for donation.

Families of donors may have difficulties in coping with the sudden death of a loved one, the donation decision-making process, and the aftermath and thus, are at risk for many psychiatric problems. Although the participants in our study stated that they did not have a psychiatric disease and did not receive psychological support, 16.7% of them met the diagnostic criteria of PGD. This can be explained by the fact that people culturally meet their mourning processes as usual and tend to ignore their psychological needs. There are culture-specific aspects to the bereaved person's psychological reactions to loss and the way they interpret them (21). Although different rates were found in previous prevalence studies, a recent comprehensive meta-analysis reported the prevalence of PGD as 10.3% (22). In addition to studies reporting that the rate of PGD in families who gave donor consent was similar to those who did not, there are also results showing

that there is a high rate as 46% of donor families with a diagnosis of complicated grief (23). In a study conducted in our country, the PGD rate was found to be 11.4% and differences in prevalence rates may be related to factors such as the variety of measurement tools used and the cultural characteristics of donor families (11).

In our study, it was found that female gender increased the risk of being diagnosed with prolonged grief by 5 times and the risk of being diagnosed with depression by 13 times. It was found that educational status, relationship level, age of the deceased, sufficient information about the donation process, and the time elapsed after the loss were not effective factors in increasing the risk of long-term grief diagnosis. There are studies in the literature showing that female gender, being single, low education level, advanced age and poverty pose risks for PGD (24). The different results in our study may be due to the small sample size.

It is known that the female gender is a risk factor for the development of depression (25). This predisposition is suggested to be related to the biological structure, and socio-cultural characteristics of women. Men's less use of emotion-focused coping strategies after negative life events and less likelihood of being affected by the thoughts and emotions of others may be related to this result (26).

The overlap of some of the symptoms of PGD and major depression and the high comorbidity rates between the two disorders pose a diagnostic challenge (27). It is thought that accepting complicated grief as a subset of major depression and trying to treat it may lead to underdiagnosis of prolonged grief, being untreated, or misdiagnosed and treated as depression and anxiety (23). Therefore, in our study, symptoms of depression and PGD were evaluated with two different scales. In consistent with the literature, a good linear correlation was observed between the PGS and the BDI scores. In multiple regression analysis, it was found that the increase in the PGS scores increased the risk of depression diagnosis by 1.26 times but the increase in the BDI scores did not increase the risk of prolonged grief. This supports that although both diagnoses can be comorbid, they are two different clinical conditions and clinicians should carefully question the comorbidity of depression in the follow-up of donor families diagnosed with prolonged grief.

One of the factors that play an important role in the resolution or chronicity of the grieving process is restructuring the meaning after loss (12). In the literature, studies on the restructuring processes of the meaning of donor families are rare. Communication with healthcare professionals and positive hospital experience have been shown to be positively and significantly correlated with post-traumatic growth (28). In our study, a negative correlation was found between PGD and sense of peace subdimensions of reconstructing of meaning in donor families. The thought that death relieves the pain of the loved one and puts her at peace, as well as the preparedness of both the deceased and the person who gave consent for the death, may reduce the risk of prolonged grief. For this reason, informing the relatives of the patient in advance about the patient's medical condition and the risk of death and the possibility of organ donation, and thus giving the families more time to discuss the donor decision, may reduce the risk of prolonged grief of donor family members. However, in Regression Analysis, reconstructing of meaning was not found to be a statistically significant variable in increasing the risk of both PGD and depression. In the light of the previous literature on the positive relationship between prolonged grief and restructuring of meaning, there is a need for more comprehensive studies investigating the effect of restructuring of meaning in assessing the risk of prolonged grief and depression in donor families.

While some studies report that organ donation has a positive effect on the grieving process, others do not support this relationship (29,30). In addition, it has been stated that the effects of the organ donation decision on the psychological well-being of the family individuals are affected by the nature of the social, cultural, and spiritual factors and the qualification of the bereavement (30). It is known that there are many families who describe themselves as happy and peaceful because of their decision to donate, although thinking that their relatives' organs are living with other people can sometimes cause emotional turmoil for families. Donating the organs of their loved ones can make donor family members feel that they are continuing their legacy through the organ recipient. Furthermore, the feeling that help and favors are given to those in need can increase families' ability to cope with bereavement.

Limitations

Due to the pandemic conditions, our study was planned as an online survey study. The limitations of our study are the lack of face-to-face interviews, the small sample size, and the inability to compare the findings with families

who did not give consent for transplantation. Another limitation of our study is that there is a wide time interval from six months to ten years between the donation decision and the evaluation.

Conclusion

Our results revealed that female gender and being familiar with awaiting organ transplantation before donation are important variables in terms of depression risk in donor families, and reconstructing of meaning is not an effective factor in increasing the risk of both PGD and depression. It can be argued that comprehensive studies involving participants from different religions and cultures, and comparing families who accept and do not accept to be a donor will make significant contributions to the field. It can be recommended to evaluate donor families in terms of depression risk, especially those who are female and have an acquaintance who is waiting for an organ transplant, to develop programs that will facilitate the access of risky individuals to psychological counseling services, and to train health professionals who provide information transfer to use strategic communication methods.

Declarations

Funding

There is no specific funding related to this research.

Conflicts of interests

The authors declare no conflict of interest.

Ethical Approval

The ethics committee approval date 08.09.2021 and protocole number: 2011-KAEK-25 2021/09-06.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author's contributions

EMA, HAK, IC study concept and design; FT, MA data collection, EMA, IC data analysis and draft the manuscript; HAK, EMA, IC contributed to the data analysis/ interpretation and prepare the table; HAK, EMA, IC, KÖ, SO contributed to writing the manuscript. All authors read and approved the manuscript.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1568533

Value of Repeated Transurethral Resection in Superficial Bladder Cancer

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Received: 17.10.2024
Accepted: 21.10.2024

ABSTRACT

Introduction: Repeat transurethral resection (re-TURBT) has been proposed as a method to improve staging accuracy and reduce the likelihood of recurrence by detecting residual tumor tissue. The purpose of this study is to evaluate the efficacy of re-TURBT in patients with superficial bladder cancer.

Materials and Methods: This prospective study included 100 patients with superficial bladder cancer (Ta and T1 stages) treated at the Urology Clinic of Istanbul Fatih Sultan Mehmet Training and Research Hospital between January 2005 and December 2006. Following the initial TURBT, all patients underwent re-TURBT within 4 to 6 weeks. Pathological findings from both procedures were analyzed to identify residual tumor presence and changes in tumor stage. Patients were followed up for 24 months to monitor recurrence rates and progression to muscle-invasive disease.

Results: Re-TURBT revealed residual tumor tissue in 40% of patients, with higher detection rates in T1 and Grade II tumors. Patients with residual tumors had a significantly higher recurrence rate (40%) compared to those without residual tumors (15%). Additionally, 20% of patients with residual tumors progressed to muscle-invasive bladder cancer, while no progression was observed in patients without residual tumors.

Conclusion: Re-TURBT plays a vital role in improving staging accuracy and reducing recurrence in patients with superficial bladder cancer. The presence of residual tumors significantly increases the risk of recurrence and progression, highlighting the importance of re-TURBT, especially in high-risk patients. These findings support the routine use of re-TURBT in managing superficial bladder cancer.

Keywords: Bladder cancer, transurethral resection, re-TURBT, residual tumor, recurrence, staging accuracy

ÖZET

Giriş: Tekrar transüretral rezeksiyon (re-TURT), mesane kanserinde evreleme doğruluğunu artırmak ve rezidüel tümör dokusunu tespit ederek nüks olasılığını azaltmak için bir yöntem olarak önerilmiştir. Bu çalışmanın amacı yüzeyel mesane kanseri olan hastalarda re-TURT etkinliğini değerlendirmektir.

Gereç ve Yöntemler: Bu prospektif çalışmaya Ocak 2005-Aralık 2006 tarihleri arasında İstanbul Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi Üroloji Kliniği'nde tedavi edilen yüzeyel mesane kanserli (Ta ve T1 evreleri) 100 hasta dahil edildi. İlk TURT'u takiben, tüm hastalara 4 ila 6 hafta içinde yeniden TURT uygulandı. Her iki prosedürden elde edilen patolojik bulgular rezidüel tümör varlığını ve tümör evresindeki değişiklikleri belirlemek için analiz edildi. Hastalar nüks oranlarını ve kas invaziv hastalığa ilerlemeyi izlemek için 24 ay boyunca takip edildi.

Bulgular: Re-TURT hastaların %40'ında rezidüel tümör dokusu ortaya çıkardı ve T1 ve Grade II tümörlerde daha yüksek saptama oranları vardı. Rezidüel tümörü olan hastalarda nüks oranı (%40), rezidüel tümörü olmayanlara (%15) kıyasla anlamlı derecede yüksekti. Ek olarak, rezidüel tümörlü hastaların %20'si kas invaziv mesane kanserine ilerlerken, rezidüel tümörü olmayan hastalarda ilerleme gözlenmedi.

Sonuç: Re-TURT, yüzeyel mesane kanserli hastalarda evreleme doğruluğunu artırmada ve nüksü azaltmada hayati bir rol oynamaktadır. Rezidüel tümörlerin varlığı nüks ve progresyon riskini önemli ölçüde artırarak, özellikle yüksek riskli hastalarda re-TURT'un önemini vurgulamaktadır. Bu bulgular, yüzeyel mesane kanseri tedavisinde re-TURT'un rutin kullanımını desteklemektedir.

Anahtar Kelimeler: Mesane kanseri, transüretral rezeksiyon, re-TURT, rezidüel tümör, nüks, evreleme doğruluğu

Bladder cancer is one of the most common malignancies affecting the urinary system, with approximately 90% of cases being classified as transitional cell carcinoma (1). While the majority of these tumors are superficial at the time of diagnosis, they possess a significant tendency for recurrence, with approximately 70-80% of superficial tumors recurring during follow-up. Furthermore, 20-30% of these cases may progress to become invasive, posing a severe threat to the patient's prognosis (1). The high recurrence and progression rates highlight the need for effective treatment strategies to manage bladder cancer recurrence and prevent progression (2).

Transurethral resection of bladder tumors (TURBT) is the standard procedure for both diagnosing and treating bladder cancer. It allows for the removal of macroscopic tumors and provides tissue for pathological evaluation, including tumor grading and staging. However, initial TURBT may not always result in complete removal of all cancerous tissues, and in some cases, residual tumor cells remain. This has led to the practice of repeat transurethral resection (re-TURBT), which is performed to ensure complete tumor removal, improve staging accuracy, and reduce recurrence rates (3). Studies have reported residual tumor detection rates of 15% to 76% in re-TURBT procedures, and its role in managing superficial bladder cancer remains an area of active research (4,5).

The purpose of this study is to evaluate the efficacy of re-TURBT in patients with superficial bladder cancer. By assessing the pathological findings and recurrence rates in patients who undergo re-TURBT, this study aims to determine whether this procedure provides additional benefits in disease management. The results could have significant implications for the treatment protocols of bladder cancer, particularly in terms of staging accuracy and recurrence prevention.

Materials and Methods

This prospective study was conducted at the Urology Clinic of Istanbul Fatih Sultan Mehmet Training and Research Hospital. A total of 100 patients diagnosed with superficial transitional cell carcinoma (TCC) of the bladder were included in the study between January 2005 and December 2006. The inclusion criteria were patients diagnosed with Ta and T1 stages of bladder cancer, with no evidence of muscle invasion on the initial TURBT. Patients with a history of muscle-invasive bladder cancer, prior radical treatments, or those who did not undergo re-TURBT were excluded from the study.

All patients underwent an initial TURBT for diagnostic and therapeutic purposes. After the initial TURBT, patients were scheduled for a repeat TURBT within 4 to 6 weeks. During the re-TURBT, the primary objectives were to remove any residual tumor tissue and to provide further histopathological material to assess for deeper invasion. The re-TURBT was performed using the same approach as the initial TURBT, with a focus on the original tumor site and surrounding areas.

The resected specimens from both the initial and repeat TURBT were sent for pathological evaluation. All patients received intravesical mitomycin in the early postoperative period (first 24 hours). Tumors were graded based on the World Health Organization (WHO) classification and staged using the TNM classification. Residual tumor presence, grade, and stage were documented, along with any changes between the initial and re-TURBT findings.

Patients were followed up for a period of 24 months after re-TURBT. Follow-up evaluations included cystoscopy at regular intervals (every 3 months for the first year and every 6 months thereafter). Recurrence rates, progression to muscle invasion, and complications related to the procedure were recorded. Data collected from both the initial and re-TURBT procedures were analyzed to determine the impact of re-TURBT on clinical outcomes, including tumor recurrence and accurate staging.

Statistical Analysis

The Statistical Package for the Social Sciences version 25 (SPSS IBM Corp., Armonk, NY, USA) program was used. Normality of distribution of the variables was checked by Shapiro-Wilk test. Independent student t test was used for comparison of the normally distributed variable between the groups, and Mann Whitney u test was used for non-normally distributed data. Quantitative data are given as mean ± standard deviation values. The data were analyzed at a 95% confidence level, and a P value of less than 0.05 was accepted as statistically significant.

Results

A total of 100 patients were included in the study, all diagnosed with superficial bladder cancer. The median age of the patients was 65 years, with a male-to-female ratio of approximately 3:1. The majority of tumors were classified as Ta (60%) with the remaining classified as T1 (40%). The following sections outline the key findings from the initial TURBT and re-TURBT procedures, as well as the recurrence rates and progression during follow-up.

Table 1 summarizes the distribution of cases with residual tumor detected after Re-TURBT, categorized by tumor grade and stage. For Grade I tumors, no residual tumors were detected in Ta stage (0/9, 0%). However, in Grade II tumors, 23.1% of Ta cases (6/26) and 57.1% of T1 cases (4/7) had residual tumors. Overall, in the entire group, the residual tumor rate was 0% for Grade I tumors and 30.3% (10/33) for Grade II tumors, giving a total residual tumor rate of 23.8% across all cases. This highlights the significant difference in residual tumor presence between Grade I and Grade II tumors.

Table 2 shows the changes in tumor stages after initial resection and Re-TURBT. The majority of tumors initially classified as Ta GII (61.9%) remained in the same category, with only 19.2% progressing to T1 GII and 3.8% progressing to T1 GIII. In T1 GII cases (16.6% of total), stage progression occurred in 14.2% of cases for each of the following categories: T1 GIII, T2 GII, and T2 GIII. These findings indicate that a significant portion of tumors remain in the same stage after Re-TURBT, although there are cases of progression, particularly in higher-grade tumors.

The cases were evaluated in terms of tumor diameter and multifocality. The mean tumor diameters of the patients with and without residual tumor detected in Re-TURBT were 3.85 cm and 1.62 cm, respectively. The tumor diameters in patients with residual tumor detected were significantly higher than those in whom no residual tumor was detected in the second resection ($p<0.001$) (figure 1a). In terms of multifocality, the mean bladder tumor foci numbers in patients with and without residual tumor detected in Re-TURBT were 4.88 and 1.62, respectively. The tumor foci numbers in patients with residual tumor detected were significantly higher than those in whom no residual tumor was detected in the second resection ($p=0.0016$) (figure 1b).

Table 1: Distribution of cases with residual tumor detected after Re-TURBT

	Grade I	Grade II	Residual Tumor / Total Tumor number (%)
Ta	0 / 9 (0 %)	6 / 26 (23.1 %)	6 / 35 (17.1 %)
T1	-	4/7 (57.1 %)	4/7 (57.1 %)
Residual Tumor / Total Tumor number (%)	0 / 9 (0 %)	10 / 33 (30.3 %)	10 / 42 (23.8 %)

Table 2: Changes in tumor stages after initial resection and Re-TURBT

	Initial TURT (n = 42)	Ta GI	Ta GII	T1GII	T1GIII	T2GII
Ta GI	9 (21.4%)	-	-	-	-	-
Ta GII	26 (61.9%)	-	5/26 (19.2%)	1/26 (3.8%)	-	-
T1 GII	7 (16.6%)	-	1/7 (14.2%)	1/7 (14.2%)	1/7 (14.2%)	1/7 (14.2%)

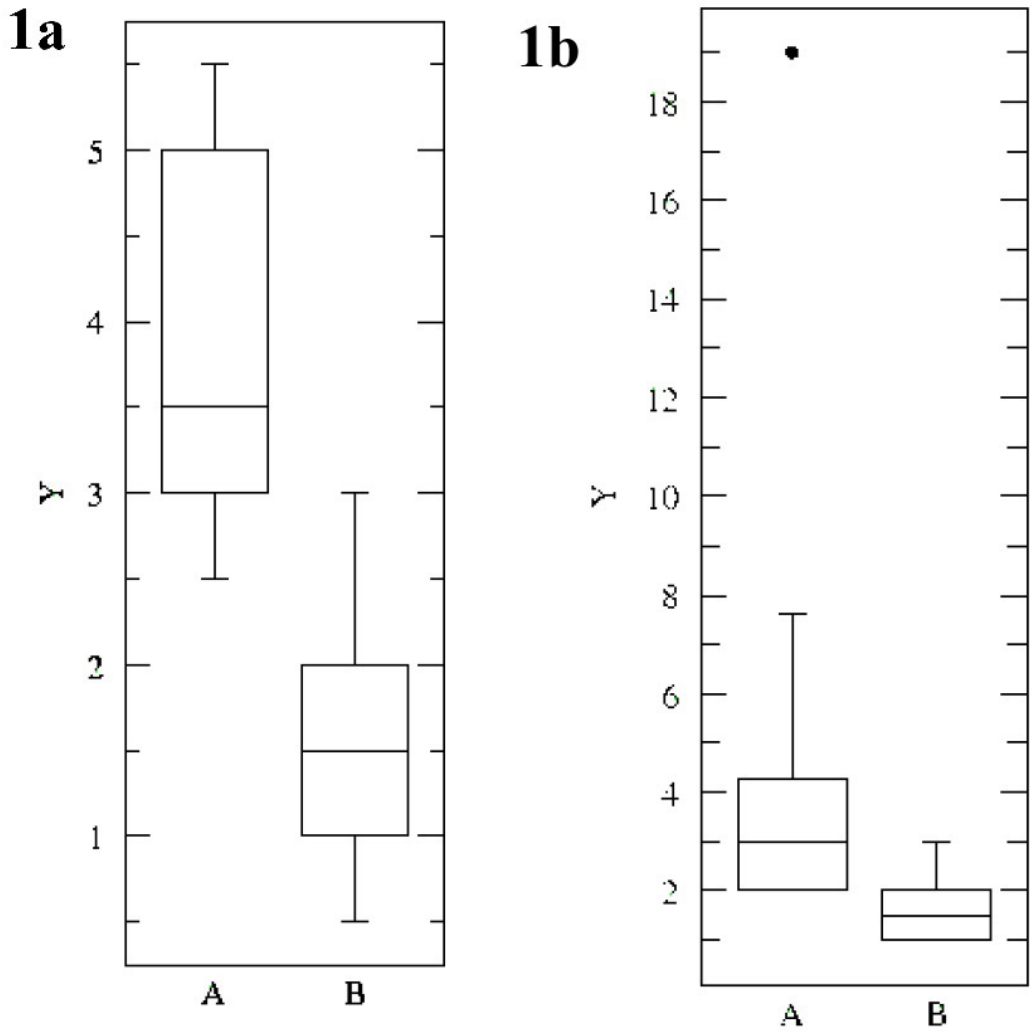

Figure 1: Relationship between the risk of detecting residual tumor in the second resection and the tumor diameter and number in the patients' first resection, 1a: tumor diameter graph, 1b: tumor number graph, A: residual tumor +, B: residual tumor -

Discussion

Bladder cancer remains a significant challenge due to its high recurrence rates and potential for progression to muscle-invasive disease (6). In our study, we found that repeat transurethral resection played a crucial role in identifying residual tumors and improving staging accuracy. Residual tumor was detected in 40% of patients who underwent re-TURBT, consistent with prior reports that found residual tumor rates ranging from 15% to 76% in patients undergoing a second resection (3,7). This reinforces the need for re-TURBT in the management of superficial bladder cancer.

The role of re-TURBT in accurately staging bladder cancer is well-documented in the literature. Our study found that 15% of patients experienced upstaging to muscle-invasive disease during re-TURBT, similar to findings from other studies (8). Accurate staging is crucial because patients with undetected muscle-invasive disease are at a higher risk for disease progression and poorer outcomes. By identifying these cases early through re-TURBT, appropriate treatment plans, such as radical cystectomy, can be initiated sooner, improving long-term survival (9).

Our results also demonstrated a significant correlation between residual tumor presence during re-TURBT and recurrence rates. Patients with residual tumors had a 40% recurrence rate, while those without residual tumors had only a 15% recurrence rate. This finding aligns with previous studies, which have shown that patients with incomplete initial TURBT or residual tumor presence are more likely to experience tumor recurrence (10). The higher recurrence rate in these patients underscores the importance of thorough tumor resection and careful follow-up.

In terms of progression to muscle-invasive bladder cancer, our study found that 20% of patients with residual tumors progressed to muscle-invasive disease during the follow-up period. None of the patients without residual tumors progressed. These findings suggest that residual tumor presence is a significant risk factor for progression, further supporting the role of re-TURBT in preventing disease advancement. Similar findings have been reported in other studies, highlighting the importance of early detection and intervention (11,12).

One of the key advantages of re-TURBT is its ability to improve the accuracy of pathological staging, which is crucial for determining appropriate treatment strategies. Our study confirmed that re-TURBT led to more accurate staging in a subset of patients, allowing for more aggressive treatment when necessary. This is consistent with findings from European and American guidelines that recommend re-TURBT as a standard practice in high-risk non-muscle invasive bladder cancer (13).

Despite the benefits of re-TURBT, some studies have questioned its necessity in all cases. For example, studies such as those by Thompson et al. have suggested that re-TURBT may not always be required in patients with small, low-grade Ta tumors (14). However, our study's findings indicate that even in superficial bladder cancer cases, re-TURBT can play a vital role in reducing recurrence and improving staging, especially in higher-risk cases. Further studies are needed to determine the exact criteria for patient selection in re-TURBT protocols.

The limitations of this study include its relatively small sample size and the short follow-up period of 24 months, which may not fully capture long-term recurrence and progression rates. Additionally, this study was conducted at a single center, which may limit the generalizability of the findings. Additionally, cost analysis was not performed in our study. Finally, patients were not subjected to subgroup analysis according to different demographic characteristics. Future studies with larger, multicenter cohorts and longer follow-up periods are needed to validate these results and provide more robust evidence for the role of re-TURBT in superficial bladder cancer management.

Conclusion

In conclusion, our study demonstrates that re-TURBT plays a critical role in the management of superficial bladder cancer by improving tumor staging accuracy and reducing recurrence rates. Residual tumor presence is a significant predictor of disease recurrence and progression, highlighting the importance of thorough tumor resection. Our findings support the use of re-TURBT, particularly in high-risk patients, as an essential tool for better disease management.

Figure Legends:

Figure 1. Relationship between the risk of detecting residual tumor in the second resection and the tumor diameter and number in the patients' first resection

Funding

There is no funding in this study

Conflicts of interest/Competing interests

There is no conflicts of interesst in this study for all authors

Availability of data and material

Appropriate

Authors' contributions

Hakan Cakir: Substantial contributions to the conception or design of the work, analysis, interpretation of data for the work, drafting the work or revising it critically for important intellectual content.

N. Doğu Güner: Final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Turgut Alp: Final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

M. İhsan Karaman: Drafting the work or revising it critically for important intellectual content.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1413949

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Audiology / Odyoloji

Can Auditory Brainstem Responses Be a Screening Tool to Assess the Brainstem for Post-Covid-19 ?

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Received: 03.01.2024
Accepted: 26.09.2024

ABSTRACT

Purpose: The aim of this study was to investigate whether auditory pathways at the brainstem level are affected in volunteers with normal hearing infected with SARS-CoV-2 virus, which is thought to localize in the brainstem and cause symptoms such as loss of smell and taste.

Methods: A total of 60 volunteers (120 ears), 30 (21 females and 9 males; M: 24.5±5.5) infected (study group) and 30 (18 females and 12 males; M: 20.7±2) never infected (control group), aged 17-45 years, were included in the study. The study group consisted of individuals who had Covid-19 and had at least one of the symptoms known to occur with the localization of the virus in the brainstem, such as nausea-vomiting, loss of smell-taste, weakness-fatigue.

The latency and amplitude values of auditory brainstem responses elicited at 80 dB nHL with LS-CE chirp stimuli were compared between the two groups. I, III, and V-wave latencies, I-III, III-V, and I-V interpic latencies, I, III, and V-wave amplitudes, and V/I amplitude ratio parameters were evaluated in the ABR test.

Results: Although no statistically significant difference ($p>0.05$) was observed between the study group and the control group in all parameters, it was found that the amplitudes of the waves were lower in the study group compared to the control group.

Conclusion: Although the findings did not show any significant results, the study group's worse amplitudes may indicate the presence of brainstem damage.

Keywords: Covid-19, Auditory Brainstem Responses, LS-CE-Chirp, SARS-CoV-2.

ÖZET

Amaç: Bu çalışmanın amacı, beyin sapında yerleşerek koku ve tat kaybı gibi semptomlara neden olduğu düşünülen SARS-CoV-2 virüsü ile enfekte olan normal işitmeye sahip gönüllülerde beyin sapı seviyesindeki işitsel yolakların etkilenip etkilenmediğini araştırmaktır.

Yöntemler: Çalışmaya yaşları 17-45 arasında değişen 30 (21 kadın ve 9 erkek; Ort: 24.5±5.5) enfekte (çalışma grubu) ve 30 (18 kadın ve 12 erkek; Ort: 20.7±2) hiç enfekte olmamış (kontrol grubu) olmak üzere toplam 60 gönüllü (120 kulak) dahil edildi. Çalışma grubu Covid-19 geçiren ve virüsün beyin sapında lokalizasyonu ile ortaya çıktığı bilinen bulantı-kusma, koku-tat kaybı, halsizlik-yorgunluk gibi semptomlardan en az birine sahip bireylerden oluşmuştur.

LS-CE chirp uyaranlarla 80 dB nHL'de ortaya çıkan işitsel beyin sapı yanıtlarının latans ve amplitüd değerleri iki grup arasında karşılaştırıldı. ABR testinde I, III ve V dalga latansları, I-III, III-V ve I-V interpik latansları, I, III ve V dalga amplitüdleri ve V/I amplitüd oranı parametreleri değerlendirildi.

Sonuçlar: Çalışma grubu ile kontrol grubu arasında tüm parametrelerde istatistiksel olarak anlamlı bir fark ($p>0.05$) gözlenmemesine rağmen, çalışma grubunda dalga amplitüdlerinin kontrol grubuna göre daha düşük olduğu saptandı.

Sonuç: Bulgular anlamlı sonuçlar göstermemekle birlikte, çalışma grubunun daha kötü amplitüdlere sahip olması beyin sapı hasarının varlığına işaret edebilir.

Anahtar Kelimeler: Covid-19, İşitsel Beyin Sapı Yanıtları, LS-CE-Chirp, SARS-CoV-2.

Severe Acute Respiratory Syndrome Coronavirus 2- SARS-CoV-2 (1), which emerged in Wuhan, China, in December 2019, caused an illness with symptoms such as fever, fatigue, dry cough, sore throat, and nasal congestion, with a clinical picture similar to that of influenza and the common cold: Coronavirus Disease-19 (Covid-19) (2). Over time, SARS-CoV-2 was observed to affect not only the respiratory center but also the central nervous system, causing neurological symptoms such as loss of taste and smell, headache, nausea, and vomiting (3).

The cellular target of SARS-CoV-2 is angiogensin converting enzyme 2 (ACE-2)(4). The immune system damage caused by SARS-CoV-2 has led to many theories, including vascular invasion, ischemia, infection of the auditory pathway, and that neurons and glia contain the ACE-2 receptor (5). Consistent with these theories, studies have suggested that the SARS-CoV-2 virus may affect the auditory and vestibular systems (6). It was thought that it may be possible to use the auditory brainstem response-ABR to assess brainstem damage caused by SARS-CoV-2 using auditory pathways (7). Our study was designed to investigate the impact of ABR testing on the hearing of Covid-19 survivors at the brainstem level, which causes significant neurological symptoms such as nausea and vomiting, muscle pain, headache, fatigue, and taste and smell disturbances.

Materials and Methods

Our cross-sectional study was conducted in the laboratory of the Department of Audiology, Faculty of Health Sciences, Üsküdar University with the approval of Üsküdar University Ethics Committee with decision number 2021-34 and date of 25.02.2021. Inclusion criteria;

- Age between 18-45 years to minimize the possible effects of aging on the hearing system(8),
- Bilateral type A (9) and 0.3-1.4 cc compliance; tympanogram with ±50 daPa values (10)
- Obtaining ipsilateral and contralateral reflexes in the range of 500-4000 Hz bilaterally was considered normal (11),
- Bilateral pure tone average (500-4000 Hz) obtained as ≤ 15 dB HL (12),
- Normal *Distortion product otoacoustic emissions (*DPOAE) test results (13)
- No diagnosed neurological, genetic, or systemic disease,

Different from the control group;

- The study group had a history of at least 1 "PCR test positive" in the previous 3 months,
- Mild to moderate illness and not hospitalized
- Experienced at least one of the symptoms of nausea-vomiting, muscle pain, headache, weakness, loss of taste and smell, which are thought to occur with the involvement of the brainstem pons region in the disease (14),
- Voluntary subjects who agreed to participate in the study were included in the study.

Data Collection Tools

A detailed medical history was obtained from all participants, and otoscopic examination, immittance evaluation, pure tone audiometry test, otoacoustic emission measurement (DPOAE), and ABR test were performed**.**

Acoustic Immittancemetry

Otoscopic control was performed prior to tympanometric assessment. Tympanometry and acoustic reflex testing were performed using the Interacoustics® Titan Handheld (Denmark). Bilateral type A tympanogram (0.3-1.6 cc compliance; ±100 daPa) (9) and bilateral ipsilateral and contralateral reflexes between 500-4000 Hz (10) were considered normal.

Pure Tone Audiometry Test

Participants' air conduction thresholds at frequencies of 125-8000 Hz were measured with supraaural headphones using an Interacoustics® AC40 clinical audiometer (Denmark). For all air conduction thresholds between 125-8000 Hz, it was ensured that there was no difference of 15 dB or more between consecutive thresholds and that all thresholds were within normal hearing limits (-10-15 dB). Bilateral pure tone averages (500-4000 Hz) ≤ 15 dB HL were considered normal (12).

Distortion Product Otoacoustic Emissions

The functionality of the receptor cells in the inner ear was assessed by DPOAE measurement using the Otodynamics/ Echoport ILO292 USB=2 device. The result was considered normal if the signal-to-noise ratio was 6 dB or greater at 4 of the measured frequencies (13)

Auditory Brainstem Response

The ABR test was performed in all participants with the lights off, with the patient in a calm supine position and/or in natural sleep. In the test using Ambu NeurolineTM 720 electrodes, the resistance difference between the electrodes was 2 kΩ or less and the resistance value at each electrode was 3 kΩ or less. The ER-3A insert headphones were placed in the ear canal, and a LS-CE-Chirp stimulus was sent at an intensity of 80dB nHL. The responses were recorded as a minimum of 3000 sweeps at the rate of 21.1 per second in alternating polarity. Double-trace records were taken in order to ensure the reliability of the response. Absolute latencies of waves I, III and V, inter-wave latencies, amplitudes of wave I and V, and the amplitude ratios V/I were determined.

Statistical Analysis

SPSS 25.0 package programme was used for statistical data analysis in the study. In this study, G*Power 3.1.9.4 program was used to calculate the sample size. According to the program, assuming an effect size = 0.8, significance level = 0.05 and power = 0.80, the minimum sample size was found to be at least 21 for each group.

The normality analysis of the distributions of I., III. and V. wave latency and amplitude values and I-III, III-V and I-V interpic latency measurements was performed with the Kolmogorov-Smirnov test and it was found that they did not fit the normal distribution. Therefore, Mann Whitney U test was used in the comparisons between the experimental and control groups. Significance level (α=0.05) was accepted in statistical comparisons (15).

Results

Gender differences were not analyzed due to non-homogeneous data distribution. Figure 1 presents the observed symptoms in the study group.

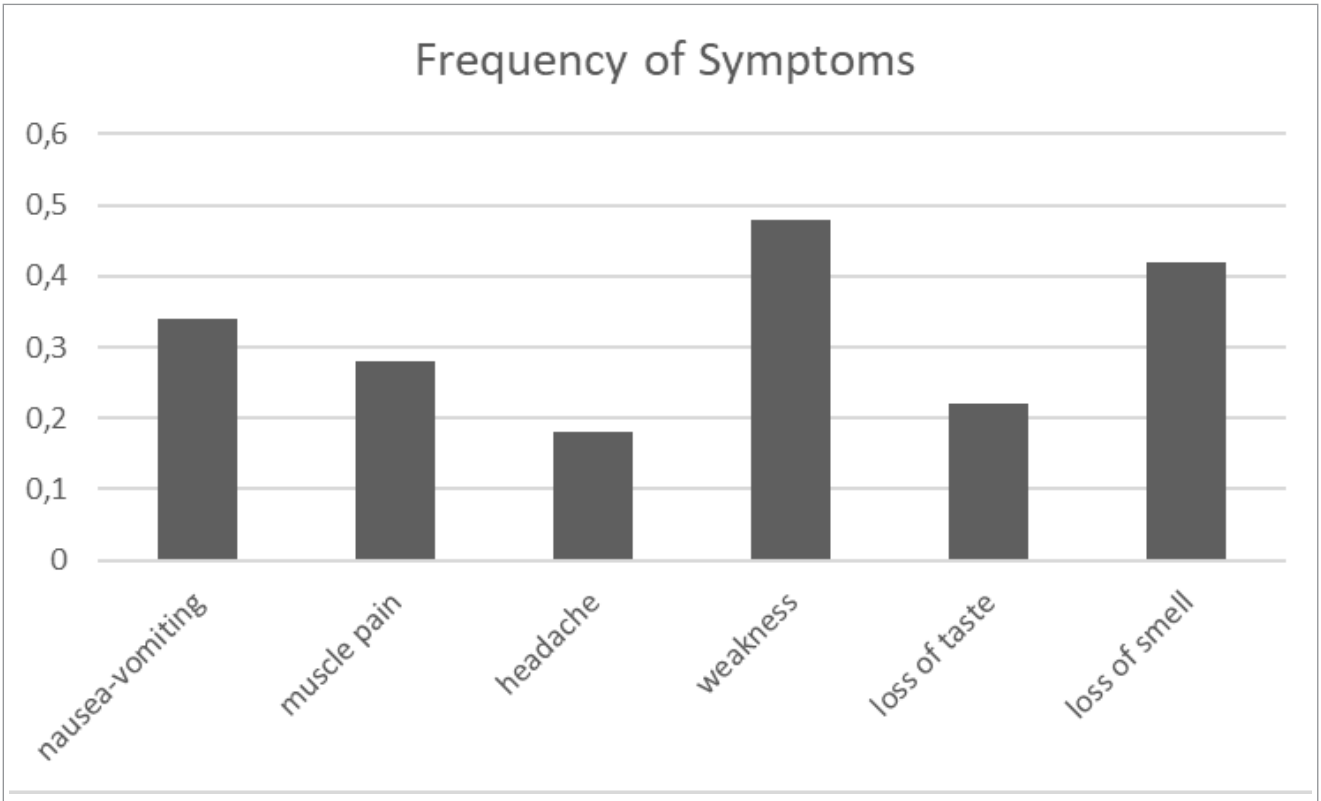

Figure 1: Frequency of neurological symptoms and other symptoms in the study group

Table 1: Latency and interpic latency values of I., III. and V. waves in the study and control groups

Parameter Latency (ms)	Control Group (M ± SD) (N:30)		Test Group (M ± SD) (N:30)		P-value**	
	Right	Left	Right	Left	Right	Left
Wave I	1.45 ± 0.13	1.48 ± 0.14	1.41 ± 0.18	1.44 ± 0.09	0.224	0.213
Wave III	3.57 ± 0.16	3.59 ± 0.17	3.53 ± 0.13	3.54 ± 0.15	0.438	0.311
Wave V	5.19 ± 0.20	5.21 ± 0.28	5.14 ± 0.19	5.16 ± 0.18	0.522	0.322
I–III interpeak latency	2.11 ± 0.19	2.10 ± 0.13	2.11 ± 0.20	2.07 ± 0.22	0.970	0.382
III–V interpeak latency	1.63 ± 0.16	1.62 ± 0.17	1.67 ± 0.17	1.69 ± 0.19	0.342	0.447
I–V interpeak latency	3.74 ± 0.22	3.72 ± 0.25	3.79 ± 0.21	3.77 ± 0.16	0.527	0.958

*Mann Whitney U test SS: standard deviation N: number of individuals **Significant difference (p<0.05).*

Table 2: Amplitude values of I., III. and V. waves in the study and control groups

Parameter	Control Group (M ± SD) (N:30)		Test Group (M ± SD) (N:30)		P-value**	
	Right	Left	Right	Left	Right	Left
Wave I	0.32 ± 0.12	0.31 ± 0.12	0.29 ± 0.13	0.28 ± 0.11	0.387	0.280
Wave III	0.37 ± 0.11	0.33 ± 0.11	0.33 ± 0.13	0.31 ± 0.11	0.135	0.496
Wave V	0.80 ± 0.23	0.74 ± 0.19	0.77 ± 0.13	0.78 ± 0.14	0.988	0.171
V/I	2.85 ± 1.34	2.91 ± 1.47	3.30 ± 1.61	3.51 ± 1.85	0.379	0.257

*Mann Whitney U test SS: standard deviation N: number of individuals **Significant difference (p<0.05).*

In ABR test; latency values of I., III. and V. waves, I-III, III-V, I-V interpic latency values, amplitudes of I., III. and V. waves and V/I amplitude ratio parameters were evaluated (see Table 1 and Table 2). No statistically significant difference was observed between the study group and the control group (p>0.05).

However, lower results were obtained in the I. and III. wave amplitudes in the right and left ears and in the V. wave amplitude in the right ear in the study group compared to the control group.

Discussion

Viral infections affect the peripheral hearing and vestibular system by involving the corti, stria vascularis and spiral ganglia (16). Viral infections such as cytolamegalovirus, rubella and measles can cause both acquired and congenital hearing loss (17). There have been many studies suggesting that coronaviruses can also cause hearing loss (18,19). However, most of the studies are related to peripheral hearing and vestibular system.

In many autopsy studies, it has been reported that RNA residues of the virus are found intensively in the brainstem region (14). The same studies have emphasized the brain stem damage's potential lethality level. However, our observations of brainstem damage in patients with varying degrees of disease with today's technological capability reveal multiple queries requiring resolution.

The extensive damage to the brainstem raises the probability of impacted central auditory pathways in the area. In this study, our aim was to exclude cochlear pathologies and concentrate solely on the brainstem by incorporating the requirement of normal DPOAE outcomes in our inclusion criteria. Although no statistically significant difference in latencies of I, III, and V waves and latencies between I-III, III-V, and I-V waves was observed between the experimental and control groups in ABR testing studies conducted in individuals with Covid-19 (20), Groiss et al., (2020) argued that the patient should be evaluated for brainstem involvement even if the disease is asymptomatic (21). One of the studies conducted before the Covid-19 pandemic stated that brainstem function can be assessed with ABR. Gedik et al., (2021) evaluated I, III and V wave latencies, I-III, III-V, I-V inter-wave latencies, I and V wave amplitude values and V/I amplitude ratio (22) . Significant difference was found only in prolongation of III-V inter-wave latency (p<0.05). On the other hand, although they did not find a statistically significant

difference, they stated that there were prolongations in the latency values of the study group compared to the control group.In our study, latencies of I, III, and V waves, latencies between I-III, III-V, I-V waves, amplitudes of I, III, and V waves, and V/I amplitude ratios were examined. Although no statistically significant difference was observed between the two groups (p>0.05), the study group had lower amplitudes of I and III waves in the right and left ears and of V wave amplitude in the right ear compared to the control group.

It was thought that the lack of significant differences between groups may be due to the fact that individuals in the study group survived the disease without any medical intervention and support (such as the need for intensive care and the use of ototoxic drugs). Although not significant, this difference in amplitudes suggests the presence of brainstem damage, albeit not at a significant level, in participants whose cochlea was considered healthy by DPOAE. A study evaluating otoacoustic emissions after COVID-19 infection reported that the absence of symptoms does not guarantee that the cochlea is functioning properly (23) while another of the following studies also confirmed damage to the cochlea using otoacoustic emissions testing (24). Another study showing prolongation of latency in brainstem evoked potentials in people who developed sensorineural hearing loss after Covid-19 attributed this to neuronal damage caused by the disease. Öztürk et al. (2022), also reported a similar association (8). Celesia, (2015) reported that in the case of brainstem dysfunction, wave morphology, amplitude, and latency may be affected, and outcomes associated with a weak (<0.5) amplitude ratio between V/I waves may be observed (24). In our study, no significant difference was observed in the V/I amplitude ratio between individuals in the study group with symptoms that can be considered neurological symptoms, such as loss of taste and smell, and individuals in the control group. This, as well as other results of the ABR, suggests that the study group may have survived the disease at a mild to moderate level.

Conclusion

This study investigated the effect of possible damage in the pons region of the brainstem, where the auditory pathways and nuclei are located, on ABR responses in individuals with Covid-19. The biggest difference of our study from other studies in the literature is the presence of at least one neurological symptom thought to originate from the pons region in all individuals included in the study. As a result, it was revealed that the auditory brainstem responses of adult volunteers who had undergone Covid-19 with neurological symptoms were not different from those of people who had not previously undergone Covid-19. However, the low amplitudes of the study group suggest the onset of brainstem damage. The study may be supported by other studies with more participants and may allow us to have an idea about the brainstem of people who have had Covid-19 with ABR scanning.

Limitation

The emergence of new variants of the virus causing the disease every day causes changes in the diversity and frequency of symptoms. In this study, since the variants that the study group was infected with were not questioned, no comparison between variants was made. In addition, since the distribution was not homogeneous, comparison between genders was not analysed.

Declarations

Funding

this study received no funding support

Conflict Of Interest The authors

have no conflict of interest to declare.

Author Contribution

MBB: Project development, data collection, manuscript writing,

DŞC: data analysis, literature review, critical review, manuscript writing,

ETE: data collection, literature review.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1455530

Hard Tissue Changes on Soft Tissue Harmony in Non-Extraction Camouflage Treatments for Angle Class III Malocclusion

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Received: 19.03.2024
Accepted: 25.10.2024

ABSTRACT

Purpose: The aim of this retrospective study was to observe the harmony between hard and soft tissue alterations on lateral cephalograms of patients with Class III malocclusion following orthodontic treatment.

Methods: Fifteen patients (7 male, 8 female; mean age: 21.4±0.49 years) who had Class III non-extraction camouflage treatment with intermaxillary elastics were included in the study. Pretreatment and posttreatment lateral cephalograms were evaluated for hard and soft tissue changes using NemoStudio NX-Pro software. Student's t-test, Pearson correlation analyses, and linear regression analyses were performed. Statistical significance was set at $p<0.05$.

Results: Strong negative correlations were identified between SN-GoMe values and UL Thickness (p=0.004), Pog'-TVL (p=0.012), and LLA-TVL (p=0.018), also between overbite and UL-E Line (p=0.013), H angle (p=0.002). UI-SN parameter showed strong positive correlation withand UL-E Line (p=0.014), and H angle (p=0.004). UI-OP showed strong positive correlation with H angle (p=0.004). The linear regression analysis showed that each unit increase in SN-GoMe caused 0.523-unit decrease in UL Thickness (p=0.004), UI-SN caused 0.177-unit increase in LL-E Line (p=0.039). Moreover, overbite caused 0.835-unit decrease in H angle (p=0.027) and 0.749-unit increase in G-Sn-Pog' (p=0.032).

Conclusion: Since changes in SN-GoMe angle, UI-SN angle, and overbite have a greater impact on soft tissues compared to other hard tissue alterations, they can provide clinicians with crucial information when planning Class III camouflage treatments.

Keywords: Orthodontics, Cephalometry, Angle Class III Malocclusion

ÖZET

Amaç: Bu retrospektif çalışmanın amacı, Sınıf III maloklüzyona sahip hastaların ortodontik tedavi sonrası lateral sefalogramlarında üzerinden sert ve yumuşak doku değişiklikleri arasındaki uyumu incelemektir.

Yöntem: Çalışmaya intermaksiller elastiklerle Sınıf III çekimsiz kamuflaj tedavisi uygulanan 15 hasta (7 erkek, 8 kadın; ortalama yaş: 21,4±0,49 yıl) dahil edilmiştir. Hastaların tedavi öncesi ve tedavi sonrası lateral sefalogramları NemoStudio NX-Pro yazılımı kullanılarak sert ve yumuşak doku değişiklikleri açısından değerlendirilmiştir. Student's t-testi, Pearson korelasyon analizi ve lineer regresyon analizleri uygulanmıştır. İstatistiksel anlamlılık seviyesi $p<0,05$ olarak belirlenmiştir.

Bulgular: SN-GoMe ile UL Kalınlığı (p=0,004), Pog'-TVL (p=0,012), LLA-TVL (p=0,018) arasında, overbite ve UL-E çizgisi (p=0,013), H açısı (p=0,002) arasında negatif yönde güçlü korelasyon bulunmuştur. UI-SN ile UL-E çizgisi (p=0,014) ve H açısı (p=0,004) arasında pozitif yönde güçlü korelasyon bulunmuştur. UI-OP ve H açısı arasında negatif yönde güçlü korelasyon bulunmuştur (p=0,004). Doğrusal regresyon analizi, SN-GoMe' deki bir birimlik artışın UL kalınlığında 0,523 birimlik bir azalmaya neden olduğunu (p=0,004) ve UI-SN' deki bir birimlik artışın LL-E çizgisinde 0,177 birimlik bir artışa neden olduğunu (p=0,039) göstermiştir. Ayrıca overbite'deki bir birimlik artışın, H açısında 0,835 birimlik bir azalmaya (p=0,027), G-Sn-Pog' değerinde ise 0,749 birimlik bir artışa neden olduğu (p=0,032) bulunmuştur.

Sonuç: SN-GoMe açısı, UI-SN açısı ve overbite değişiklikleri, yumuşak dokular üzerinde diğer sert doku değişikliklerine göre daha fazla etkiye sahip olduğundan, çekimsiz Sınıf III kamuflaj tedavisini planlamasında klinisyenlere önemli bilgiler sağlayabilir.

Anahtar Kelimeler: Ortodonti, Sefalometri, Angle Sınıf III Maloklüzyon

Class III malocclusion is a complex deformity that has skeletal or dental components. Treatment options vary depending on the growth and development period (1). In skeletal Class III malocclusion, the stage of growth and development and residual growth after treatment are important factors for treatment stability (2). The aim of early orthopedic treatment is to achieve the proper development of skeletal and dentoalveolar structures to reduce the possibility of a need for complex orthodontic treatment or orthognathic surgery. On the other hand, residual growth potential can result in the relapse of the corrections that have been achieved earlier, or orthognathic surgery may be needed later on in severe cases (3).

After the active growth period of the patient, the decision for the treatment protocol depends on the severity of the case. Patients with acceptable facial profiles and mild Class III malocclusion can be treated with orthodontic camouflage to disguise the jaw discrepancy (4). However, orthognathic surgery is the only way to reach successful results for patients with unacceptable facial profiles and severe dentoskeletal discrepancies (5).

Today, the number of people seeking orthodontic treatment is increasing because social media is more involved in our lives, and patients realize that aesthetic results can be obtained with orthodontic treatment (6, 7). Therefore, the individual treatment plan of each patient should be prepared in a way that will positively contribute to the patient's facial aesthetics (8).

The conventional Class III camouflage treatment concept is the proclination of maxillary anterior teeth and the retroclination of mandibular anterior teeth to achieve a more balanced occlusion. Extraction is also indicated depending on the degree of crowding and the anchorage protocol (9). Various factors such as soft tissue phenotypes, as well as the position and angulation of the teeth, may contribute to the individual's facial harmony and balance (10). In the literature, the effects of different treatment protocols on soft tissues in different malocclusions have been examined (11-14). The differences between orthognathic surgery and camouflage treatment, as well as camouflage treatments with and without extraction, have been investigated in Class III malocclusion cases (15-18). However, to the best of our knowledge, no study has focused on hard-soft tissue interactions in patients receiving non-extraction Class III camouflage treatment, while it is clinically observed that the tooth movements and hard tissue changes induced in these treatments cause soft tissue response. Thus, this study aimed to examine the effects of hard tissue changes on soft tissues in patients who underwent Class III non-extraction camouflage treatment and provide information for clinicians to use in their orthodontic practice by determining which hard tissue changes affect soft tissues more.

Methods

Sample

This retrospective study was approved by the Ethics Committee of Marmara University, Faculty of Medicine (30.05.2025-09.2022.1465). Lateral cephalograms of patients who underwent Class III camouflage treatment between the years 2016 and 2022 were selected from the archive of … University, Department of Orthodontics.

The G*Power (Version 3.1.7, Heinrich-Heine-Universität, Düsseldorf, Germany) software was used for calculating the minimum required sample size based on the results of a previous study. The required sample size was calculated to be at least 13 patients (α=0.05, power of 90%, and effect size=0.87 according to 1.6 mm retrusion in LL-E Line in a previous study) (18).

The inclusion criteria were as follows:

- Age between 19 and 30
- Cervical vertebral maturation stage 5 or 6 according to cephalograms
- Angle Class III molar and canine relationship,
- ANB angle -5° and 0°,
- Wits appraisal between -11.8 mm and -3.4 mm,
- Overjet between -4 mm and 2 mm,
- Overbite between -1.5 mm and 4.5 mm
- Acceptable facial profile,
- Non-extraction comprehensive orthodontic treatment,
- High-quality pretreatment and posttreatment orthodontic records.

The exclusion criteria were as follows:

- Extracted or missing teeth,
- Non-compliant patients,

- Dentofacial anomalies or syndromes such as cleft lip and palate,
- Files with missing information or missing orthodontic records.

Following the screening of cases based on the inclusion and exclusion criteria, the final sample consisted of 15 patients (7 male, 8 female; mean age: 21.4±0.49 years). The mean treatment duration of the patients was 3.26±0.23 years.

According to the information obtained from the files, lateral cephalograms were taken before (T0) and after treatment (T1). All patients had been treated in a university hospital where treatment plans had been determined by a council of experienced specialists. 0.018″-slot fixed appliances were used. Following the leveling and aligning stages, 6.5 oz. Class III elastics with a diameter of 3/16″ were applied on 0.016x0.022′-in stainless steel wire in all patients to correct the anteroposterior relationship, and the patients were seen at 4-week intervals. At the end of the treatment, Class I molar and canine relationships, normal overjet and overbite, and maximum intercuspation were achieved. All patients were given fixed retainers.

Cephalometric Evaluation

One researcher (G.Y.) traced all lateral cephalograms using the NemoStudio NX-Pro software v.10.4.2 (Nemotec, Madrid, Spain). The calibration of lateral cephalograms at the two time points was further established with reference to the Sella-Nasion length for each patient. The cephalometric analyses that were used to evaluate skeletal, dental, and soft tissue changes are given in Table 1 and Figure 1.

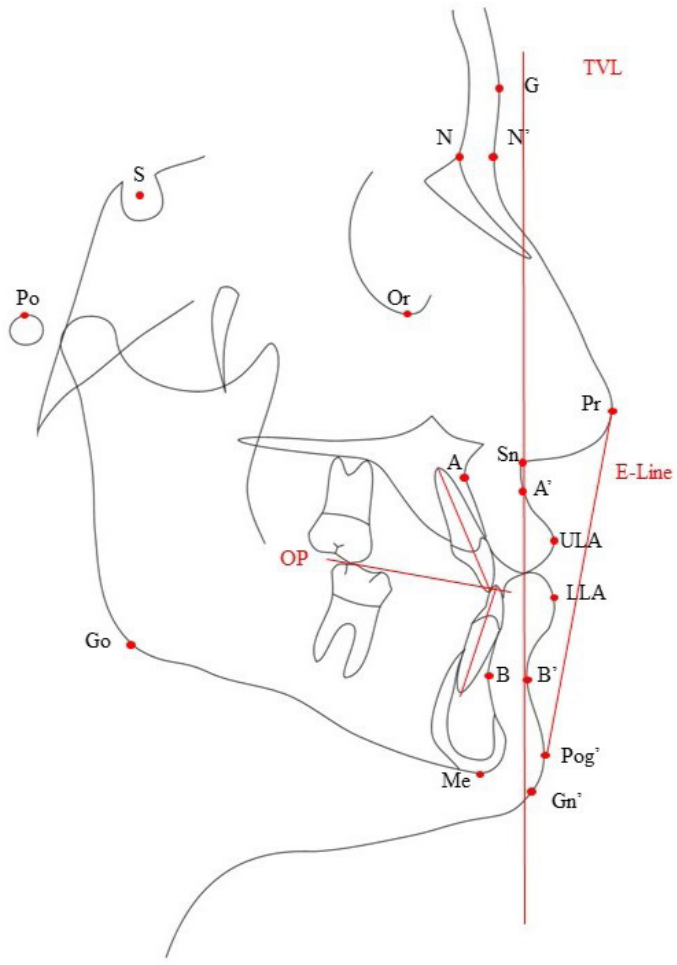

Figure 1: Landmarks used in cephalometric analysis

Table 1: Cephalometric measurements and definitions

CEPHALOMETRIC MEASUREMENTS	DEFINITION
	SKELETAL-SAGITTAL
SNA (°)	Angle formed between S, N, and A points
SNB (°)	Angle formed between S, N, and B points
ANB (°)	Arithmetic difference of SNA angle and SNB angle
Wits (mm)	Distance between projections from points A and B, drawn perpendicular to the functional occlusal plane
ACB-Corpus Length (mm)	Distance between S and N-distance between Go and Gn
N⊥A (mm)	A true vertical line dropped from N and horizontal distance parallel to this true vertical line measured from point A
	SKELETAL-VERTICAL
SN-GoMe (°)	Angle formed between S-N line and Go-Me line
FMA (°)	Angle formed between Po-Or line and Go-Me line
SN-OP (°)	Angle formed between S-N line and the functional occlusal plane
	DENTAL
UI-SN (°)	Angle formed between S-N line and upper centrals axis line
IMPA (°)	Angle formed between lower central axis line and Go-Me line
UI-OP (°)	Angle formed between upper central axis line and the functional occlusal plane
LI-OP (°)	Angle formed between lower central axis line and the functional occlusal plane
I-I (°)	Angle formed between upper central axis line and lower central axis line
Overjet (mm)	Distance between the incisal edges of maxillary and mandibular incisors, parallel to the functional occlusal plane
Overbite (mm)	Distance between the incisal edges of maxillary and mandibular incisors, perpendicular to the functional occlusal plane
	SOFT TISSUE
Nasolabial Angle (°)	Angle formed by a line tangential to the base of the nose and a line tangential to the upper lip
UL-E Line (mm)	Distance between upper lip anterior (ULA) to E-Line (line between pronasale and pogonion)
LL-E Line (mm)	Distance between lower lip anterior (LLA) to E-Line (line between pronasale and pogonion)
UL Thickness (mm)	Horizontal thickness of upper lip overlying the incisors at the level of vermilion border
UL Base (mm)	Lip thickness near the base of alveolar process, about 3 mm below point A
UL Strain (mm)	Arithmetic difference between upper lip base and upper lip thickness
LL Thickness (mm)	Horizontal thickness of upper lip overlying the incisors at the level of vermilion border
LL Base (mm)	Lip thickness near the base of alveolar process, at about point B
LL Strain (mm)	Arithmetic difference between lower lip base and lower lip thickness
H Angle (°)	Angle formed between N' and Pog', tangential to the upper lip anterior
Soft Tissue Profile (°)	Angle formed between soft G, Sn, and Pog'
A'-TVL (mm)	Distance from A' to True Vertical Line
B'-TVL (mm)	Distance from B' to True Vertical Line
Pog'-TVL (mm)	Distance from Pog' to True Vertical Line
ULA-TVL (mm)	Distance from ULA to True Vertical Line
LLA-TVL (mm)	Distance from LLA to True Vertical Line
UL Angle (°)	Angle formed between ULA, Sn, and Pog'

Statistical Analyses

The SPSS software for Windows (version 22.0, IBM Corp, Armonk, NY, USA) was used for the statistical analyses. The Shapiro-Wilk test was used to assess the conformity of the parameters to normal distribution. Student's t-test was used to evaluate changes over time. Pearson's correlation analysis was used to determine the correlations between soft and hard tissue changes. Linear regression analysis was performed to examine the effects of hard tissue changes on soft tissue changes using the enter method. Statistical significance was set at $p<0.05$.

Results

All parameters were re-measured at one-month intervals by the same researcher (G.Y.). The intraclass correlation coefficient (ICC) was calculated for each variable to evaluate the accuracy of the measurements, and it varied from 0.868 to 1.000, revealing a high level of agreement.

The changes in skeletal and dental parameters observed as a result of treatment are shown in Table 2. Significant increases in Wits, UI-SN angle, overjet, and overbite and significant decreases in ACB-Corpus, SN-GoMe, SN-OP, and UI-OP were observed (Table 2) ($p<0.05$).

Table 2: Treatment effects on skeletal and dental parameters in T0-T1

Parameters	T0	T1	ΔT0-T1	p
SNA (°)	79.87±4.21	80±4.75	0.13±1.25	0.685
SNB (°)	81.07±4.38	80.87±4.31	-0.20±1.15	0.510
ANB (°)	-1.20±1.26	-0.87±1.30	0.33±0.90	0.173
Wits (mm)	-6.25±2.5	-4.13±1.92	2.13±1.68	**0.000***
ACB-Corpus (mm)	9.65±8.24	6.01±7.56	-3.64±4.66	**0.009***
N⊥A (mm)	-2.89±3.76	-2.59±4.23	0.30±1.27	0.376
SN-GoMe (°)	36.4±6.64	35.13±6.59	-1.27±1.39	**0.003***
SN-OP (°)	16.93 ±5.7	14.87±5.22	-2.07±2.09	**0.002***
UI-SN (°)	106.8±6	111.73 ±6.9	4.93±6.09	**0.007***
IMPA (°)	85.47±4.39	85.33±6.47	-0.13±5.21	0.922
UI-OP (°)	56.8±4.44	52.2±4.65	-4.60±4.15	**0.001***
LI-OP (°)	72.53±6.09	71.8±8	-0.73±5.73	0.628
I-I (°)	131.4±7.77	127.87 ±9.43	-3.53±9.52	0.173
Overjet (mm)	0.72±1.55	2.93±0.69	2.21±1.84	**0.000***
Overbite (mm)	0.55±1.68	1.79±0.78	1.25±1.70	**0.013***

*Student's t-test, T0: Initial, T1: Post-treatment, SD: Standard deviation, *p<0.05*

In the evaluations of hard and soft tissue changes with Pearson's correlation analysis, the degree of change in SN-GoMe angle had strong negative correlations with the degrees of changes in UL Thickness, Pog'-TVL, and LLA-TVL ($p=0.004$, $p=0.012$, and $p=0.018$, respectively) and a moderate negative correlation with the degree of change in B'-TVL ($p=0.048$) (Table 3, Figure 2a).

Table 3: Evaluation of the relationships between hard and soft tissue measurements

Soft Tissue Parameters		Wits	ACB-Corpus	SN-GoMe	SN-OP	UI-SN	UI-OP	Overjet	Overbite
Nasolabial angle	r	0.010	-0.119	-0.097	-0.099	-0.405	0.404	**-0.554**	**0.513**
	p	0.972	0.673	0.732	0.726	0.135	0.135	**0.032***	**0.041***
UL-E Line	r	-0.208	0.201	-0.242	0.044	**0.619**	**-0.552**	0.259	**-0.621**
	p	0.456	0.472	0.385	0.876	**0.014***	**0.033***	0.352	**0.013***
LL-E Line	r	-0.197	0.197	-0.393	-0.069	**0.537**	-0.471	0.020	-0.323
	p	0.482	0.482	0.147	0.806	**0.039***	0.076	0.943	0.240
UL Thickness	r	-0.266	0.108	**-0.698**	-0.123	-0.246	0.349	-0.446	0.277
	p	0.338	0.702	**0.004***	0.663	0.376	0.203	0.095	0.318
UL Base	r	-0.329	-0.212	-0.409	-0.269	0.317	-0.256	0.101	0.059
	p	0.231	0.447	0.130	0.332	0.250	0.357	0.720	0.833
UL Strain	r	-0.088	-0.260	0.153	-0.146	0.455	-0.476	0.413	-0.152
	p	0.756	0.349	0.585	0.604	0.088	0.073	0.126	0.590
LL Thickness	r	0.248	0.073	-0.347	-0.315	-0.009	0.195	0.338	-0.113
	p	0.372	0.796	0.205	0.252	0.975	0.486	0.218	0.688
LL Base	r	-0.249	-0.146	-0.452	-0.129	0.142	-0.096	-0.374	0.354
	p	0.371	0.604	0.091	0.648	0.615	0.735	0.169	0.196
LL Strain	r	-0.349	-0.149	0.079	0.212	0.077	-0.217	**-0.514**	0.326
	p	0.202	0.596	0.780	0.447	0.784	0.436	**0.040***	0.235
H angle	r	-0.099	0.224	0.025	0.140	**0.701**	**-0.702**	0.465	**-0.733**
	p	0.726	0.422	0.930	0.618	**0.004***	**0.004***	0.081	**0.002***
G-Sn-Pog'	r	-0.021	-0.396	-0.031	-0.218	-0.438	0.439	-0.434	**0.554**
	p	0.939	0.144	0.911	0.435	0.102	0.101	0.106	**0.032***
A'-TVL	r	-0.171	-0.251	-0.131	-0.109	0.105	-0.040	0.199	-0.086
	p	0.543	0.366	0.641	0.699	0.709	0.889	0.477	0.759
B'-TVL	r	-0.129	-0.359	**-0.499**	-0.493	0.149	0.008	-0.467	0.417
	p	0.646	0.189	**0.048***	0.062	0.597	0.976	0.079	0.122
Pog'-TVL	r	-0.338	-0.458	**-0.627**	-0.341	-0.060	0.202	-0.369	**0.511**
	p	0.218	0.086	**0.012***	0.213	0.831	0.469	0.175	**0.041***
ULA-TVL	r	-0.261	-0.129	-0.131	-0.036	0.466	-0.402	0.242	-0.353
	p	0.347	0.648	0.641	0.897	0.080	0.137	0.384	0.197
LLA-TVL	r	-0.291	-0.161	**-0.600**	-0.333	0.399	-0.291	-0.158	0.099
	p	0.293	0.567	**0.018***	0.225	0.141	0.293	0.574	0.726
UL angle	r	-0.211	-0.082	-0.079	0.063	0.411	-0.372	0.348	-0.372
	p	0.451	0.771	0.778	0.823	0.128	0.172	0.204	0.173

*Pearson's correlation analysis, *p<0.05*

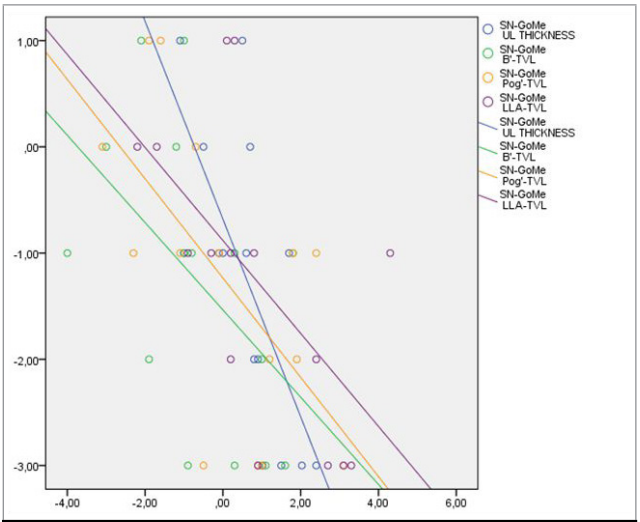

Figure 2a: Scatter plots showing the correlations between SN-GoMe and soft tissue variables

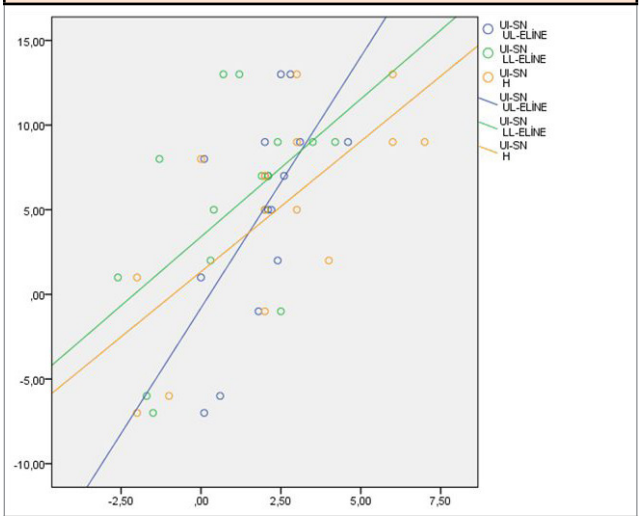

Figure 2b: Scatter plots showing the correlations between UI-SN and soft tissue variables

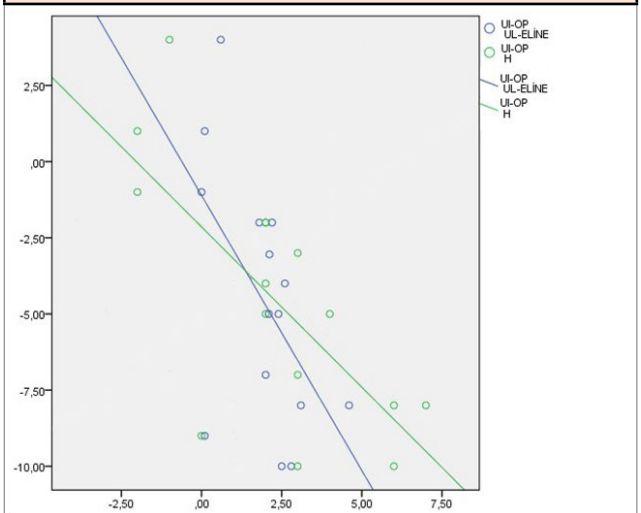

Figure 2c: Scatter plots showing the correlations between UI-OP and soft tissue variables

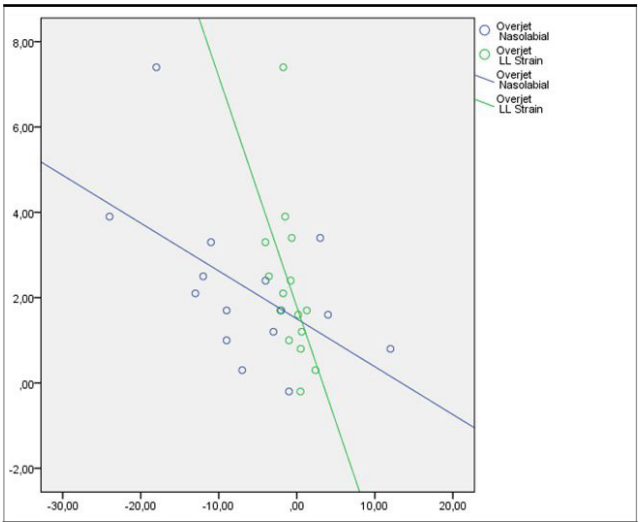

Figure 2d: Scatter plots showing the correlations between Overjet and soft tissue variables

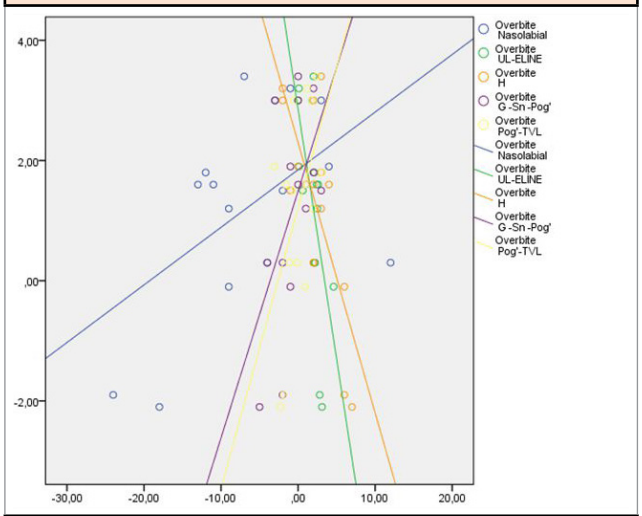

Figure 2e: Scatter plots showing the correlations between Overbite and soft tissue variables

The change in UI-SN angle had strong positive correlations with UL-E Line and H angle (p=0.014 and p=0.004, respectively) and a moderate positive correlation with LL-E Line (p=0.039) (Table 3, Figure 2b). The change in UI-OP angle had a strong negative correlation with H angle (p=0.004) and a moderate negative correlation with UL-E Line (p=0.033) (Table 3, Figure 2c).

The change in overjet had moderate negative correlations with nasolabial angle and LL Strain (p=0.032 and p=0.040, respectively) (Table 3, Figure 2d). Moreover, while the change in overbite had moderate positive correlations with nasolabial angle, G-Sn-Pog', and Pog'-TVL (p=0.041, p=0.032, and p=0.041, respectively), it showed strong negative correlations with UL-E Line and H angle (p=0.013 and p=0.002, respectively) (Table 3, Figure 2e).

Finally, linear regression analysis was performed to investigate the effects of significant correlation values. It was observed that a one-unit increase in SN-GoMe angle corresponded to a 0.523-unit decrease in UL Thickness, and a one-unit increase in UI-SN angle corresponded to a 0.177-unit increase in LL-E Line (p=0.004 and p=0.039, respectively) (Table 4). Additionally, a one-unit increase in overbite corresponded to a 0.835-unit decrease in H angle and a 0.749-unit increase in G-Sn-Pog' (p=0.027 and p=0.032, respectively) (Table 4).

Table 4: Linear regression analysis of the significant correlation values

		β_0 (95% CI)	Std. Error	t	p	R^2	Adjusted R^2
Nasolabial angle	(Constant)	-3.861 (-15.482 – 7.76)	5.333	-0.724	0.483	34.7%	
	Overjet	-1.889 (-5.19 – 1.413)	1.515	-1.246	0.236		23.9%
	Overbite	1.413 (-2.163 – 4.989)	1.641	0.861	0.406		
UL-E Line	(Constant)	1.927 (0.688 – 3.166)	0.563	3.423	**0.006***	49.7%	35.9%
	UI-SN	0.096 (-0.171 – 0.363)	0.121	0.792	0.445		
	UI-OP	0.02 (-0.353 – 0.394)	0.17	0.121	0.906		
	Overbite	-0.3 (-0.723 – 0.124)	0.192	-1.558	0.148		
LL-E Line	(Constant)	0.067 (-1.213 – 1.347)	0.592	0.113	0.912	28.8%	23.3%
	UI-SN	0.177 (0.01 – 0.344)	0.077	2.293	**0.039***		
UL Thickness	(Constant)	-0.032 (-0.625 – 0.561)	0.275	-0.117	0.909	48.7%	44.7%
	Sn-GoMe	-0.523 (-0.845 - -0.201)	0.149	-3.51	**0.004***		
LL Strain	(Constant)	-0.303 (-1.691 – 1.085)	0.642	-0.471	0.645	26.4%	20.8%
	Overjet	0.49 (0 – 0.98)	0.227	2.161	0.05		
H Angle	(Constant)	1.99 (-0.119 – 4.099)	0.958	2.077	0.062	69.3%	61%
	UI-SN	0.002 (-0.452 – 0.457)	0.206	0.011	0.991		
	UI-OP	-0.299 (-0.934 – 0.337)	0.289	-1.034	0.324		
	Overbite	-0.835 (-1.555 - -0.115)	0.327	-2.554	**0.027***		
G-Sn-Pog'	(Constant)	-1.534 (-2.921 - -0.146)	0.642	-2.388	**0.033***	30.7%	25.4%
	Overbite	0.749 (0.075 – 1.422)	0.312	2.402	**0.032***		

*Linear regression analysis, *p<0.05*

Discussion

When it comes to the treatment of skeletal Class III malocclusion in adults, the patient's opinion about their profile is an important determiner (1). If the main problem is profile according to the patient, orthognathic surgery may be the only treatment option (19).

One of the main factors affecting the results of the treatment is soft tissue alteration induced by orthodontic tooth movements. Therefore, during the camouflage treatment, the procedure should be planned considering the effects of tooth movements on the soft tissues (20).

The aim of this study was to examine the effects of hard tissue changes that occur during camouflage treatment on soft tissues. Although 3D imaging techniques provide more detailed information, cephalograms are more commonly used tools in clinical practice. The cephalometric measurements that were preferred in this study are widely used all over the world and provide the clinician with information about the general diagnosis at first glance (21, 22). If the nature of the relationship between hard and soft tissues is known during treatment planning, a more accurate plan can be established. In this study, except for Wits, none of the sagittal skeletal values were subjected to the Pearson's correlation test since none of them showed a significant change according to the Student's t-test. However, it should be noted that all patients were mild to moderate skeletal Class III adult cases, so significant differences were not expected in their sagittal skeletal values (23).

The soft tissue and lip profile may be impacted by elements like elastic strength, bracket presripciton and torque selection, anchorage regimen, and extraction during treatment. Despite the fact that the literature has a variety of studies looking at soft tissue alterations, no publication uses a comparable methodology (24-26).

Li et al. reported that the impact of soft and hard tissue parameters on soft tissue evaluation of skeletal Class III patients are yet unknown. They also emphasized on the need of further investigation regarding the contribution of incisor positions in facial harmony during the camouflage treatment of skeletal Class III malocclusions (27). In the vertical dimension, as the SN-GoMe angle increased, a decrease in UL Thickness and increases in Pog'-TVL, LLA-TVL, and B'-TVL values were observed, which might be due to the posterior rotation of the mandible. Moreover, these correlations were found to be strong. The increase in Pog'-TVL and LLA-TVL are expected to contribute to the improvement of the lip profile in skeletal Class III patients, but the decrease in UL Thickness may create an effect that complicates the profile aesthetics. The benefits of these strong effects to the treatment should be considered well during the first examination of the patient. Therefore, if there is the right indication, a slight increase in the vertical dimension could be considered to help improve the profile.

In this study, a strong correlation was found between the UI-SN angle values of the patients and their UL-E Line and H angle values, which showed that the higher the incisor inclination was, the more the upper lip moved forward as expected. As a morphological feature in skeletal Class III patients, the upper lip is turned back and inward, and the lower lip is turned anteriorly and outward, which is aimed to be improved after the orthodontic treatment (28). Therefore, if the maxillary incisor angles are not suitable for camouflage treatment, the desired improvement in the lip profile may not be achieved. Additionally, there was a moderate correlation between UI-SN and LL-E Line in our study. So, maxillary incisor inclination may also affect the prominence of the lower lip. Since maxillary incisor proclination can affect both lips, the clinician should examine the initial lip posture accordingly to improve the lip profile.

Similar to the UI-SN angle findings, UI-OP had a strong correlation with H angle and UL-E Line, but at this point, the occlusal plane's inclination must be considered. The results of this study showed that the upper lip becomes more prominent as the occlusal plane becomes steeper.

Additionally, there was a moderate negative correlation between overjet and nasolabial angle, which showed that the increase in overjet caused a decrease in the nasolabial angle as expected. The relationship between overjet and nasolabial angle on different mechanics and malocclusions has also been reported to be similar to the results in our study (29, 30). Moreover, a moderate negative correlation was found between overjet and LL Strain. It is a mechanically predicted outcome and has been mentioned in the literature before that the lower lip becomes protruded more as overjet increases (31). Therefore, the clinician is advised to make sure that the applied mechanics should only be kept at a level for relieving lower lip incompetency, not over-protruding the lip and disturbing the patient's profile. The overbite change results had strong negative correlations with UL-E Line and H angle and moderate positive correlations with nasolabial angle, G-Sn-Pog', and Pog'-TVL. As an increase in the maxillary incisor angle will cause a decrease in overbite, a decrease in UL-E Line and nasolabial angle and an increase in H angle would be a predictable outcome as in this study. In the examinations of the influence of overbite changes on hard tissues, the correlation seen in G-Sn-Pog' and Pog'-TVL changes was normal. This result was important in terms of the improvement of the lip profile, as well as the compensation of the deficiency in the upper lip profile caused by maxillary retrusion.

As seen in Table 3, it is clear that H angle was highly correlated with multiple hard tissue changes (UI-SN, UI-OP, and overbite). The hard tissue measurements that affected multiple soft tissues with strong correlations were SN-GoMe (UL Thickness, Pog'-TVL, LLA-TVL) and UI-SN angles (UL-E Line, LL-E Line, and H angle). Therefore, if profile improvement is anticipated following camouflage treatment, the Sn-GoMe and UI-SN angles are the hard tissue values that need the utmost attention. Overbite is also the parameter the most correlated with soft tissue parameters (UI-E Line, H angle, Nasolabial angle, G-Sn-Pog', Pog'-TVL). However, it should be considered that it affected only 2 soft tissues with strong correlation values.

In the further analyses in our study, it was revealed that a 1° increase in the SN-GoMe angle reduced the UL Thickness by 50%. This finding showed us how important vertical control is in this patient group, for whom it is necessary to preserve and perhaps even improve the upper lip profile. It was also observed that a 1° increase in the UI-SN angle made the lower lip more protruded by nearly 20%. Although it has been reported in the literature that the upper incisor angle and overjet affect the lower lip,

this strong relationship should not be ignored clinically (32). Due to the nature of camouflage treatment in Class III malocclusion cases, the maxillary incisor angle is increased to improve the upper lip profile. In individuals whose lower lip is more prominent due to underlying skeletal problems, treatment planning should be made by keeping this in mind while ensuring balance between the lips. The results of the linear regression analysis in this study showed that the overbite value was highly compatible with two different soft tissue parameters. The common point of both soft tissue parameters was the Pogonion point. In this context, it should not be forgotten that an increase in overbite during treatment will bring the Pogonion forward, and therefore, worsen the soft tissue profile which is already compromised.

Even though the most commonly used analyses were preferred in cephalometric evaluations, 3D measurements may have superiority over 2D imaging while facilitating the understanding of different aspects of hard and soft tissue interactions in future studies.

Conclusion

Due to their close associations with soft tissues, SN-GoMe angle, UI-SN angle, and overbite are among the cephalometric criteria of utmost importance in Class III camouflage treatment planning. It would be advantageous for clinicians to select the biomechanics they will employ by considering these cephalometric characteristics if they aim to improve the lip profile and obtain better cosmetic outcomes.

Declaration

Funding

Not applicable.

Conflicts of interest / Competing interest

Not applicable.

Ethical approval

…… University Faculty of Medicine Clinical Research Ethics Committee (30.05.2023, 09.2022.1465)

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Concept: EB, GY; Design: EB, EOO; Data Collection: GY, BT; Analysis: EB, EOO; Literature: EOO, BT; Writing: EB, GY, BT.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1359894

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Health Institutions Management / Sağlık Kurumları Yönetimi

Effects of the COVID-19 Pandemic on the Health of Nursing Staff: Qualitative Research

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ABSTRACT

Purpose: To explore the effects of the COVID-19 pandemic on the physical, psychological, social, and spiritual health of nursing team members and to identify the coping measures adopted by them.

Methods: This is a descriptive study with a qualitative approach. The study involved 42 Brazilian nursing professionals. Data were collected between June and July 2022 and analyzed through content analysis.

Results: Three themes identified: (I) Effects of the pandemic on the health of nursing professionals, (II) Major difficulties faced by nursing professionals during the pandemic, and (III) Protection measures adopted by nursing professionals during the pandemic. Also, eleven sub-themes emerged. Participants stated that the COVID-19 pandemic affected their physical, psychological/mental, social, and spiritual health. The lack of material and human resources, increased demand and professional devaluation, social distancing, facing death, insufficient information and the lack of social commitment were cited as the main problems faced by the participants. Nursing professionals resorted to different measures to protect their health.

Conclusion: The health of nursing professionals was significantly impacted during the COVID-19 pandemic. It was determined that nursing professionals and health institutions need to be better prepared to face crises. Continuing education should be developed to train nursing staff for future outbreaks better. Health administrators and nurse managers play key roles in safeguarding the physical and psychosocial health of nursing staff by ensuring adequate and high-quality personal protective equipment, offering occupational health training, and establishing psychosocial support programs.

Keywords: COVID-19, qualitative research, nurse administrators, nursing staff, occupational health, pandemics.

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ÖZET

Amaç: Araştırmanın amaçları, COVID-19 pandemisinin hemşirelik ekibi üyelerinin fiziksel, psikolojik, sosyal ve ruhsal sağlıkları üzerindeki etkilerini belirlemek ve benimsedikleri başa çıkma önlemlerini ortaya çıkarmaktır.

Yöntem: Bu, nitel bir yaklaşımla yapılan tanımlayıcı bir çalışmadır. Çalışma, 42 Brezilyalı hemşirelik profesyonelini içermektedir. Veriler Haziran-Temmuz 2022 tarihleri arasında toplanmış ve içerik analizi yöntemi kullanılarak analiz edilmiştir.

Bulgular: Üç tema ortaya çıktı: (I) Pandeminin hemşirelik profesyonellerinin sağlığı üzerindeki etkileri, (II) Pandemi sırasında hemşirelik profesyonellerinin karşılaştığı ana zorluklar ve (III) Pandemi sırasında hemşirelik profesyonelleri tarafından benimsenen başa çıkma yöntemleri. Ayrıca on bir alt tema belirlenmiştir. Katılımcılar, COVID-19 pandemisinin fiziksel, psikolojik/zihinsel, sosyal ve ruhsal sağlıklarını nasıl etkilediğini bildirdi. Donanım ve insan kaynağı eksikliği, artan talep ve profesyonel devalüasyon, sosyal mesafe, ölümle karşı karşıya kalma, yetersiz bilgi ve sosyal taahhüt eksikliği, katılımcıların karşılaştığı başlıca sorunlar olarak belirtilmiştir. Hemşirelik profesyonelleri sağlıklarını korumak için farklı yöntemlere başvurmuşlardır.

Sonuç: Hemşirelik profesyonellerinin sağlığı, COVID-19 salgını sırasında büyük ölçüde etkilenmiştir. Hemşirelik profesyonellerinin ve sağlık kurumlarının krizlere karşı daha hazırlıklı olmaları gerektiği belirlenmiştir. Hemşirelik profesyonelleri gelecekteki salgınlar için daha iyi yetiştirmek için sürekli eğitim geliştirilmelidir. Sağlık yöneticilerinin ve yönetici hemşirelerin, yeterli ve kaliteli kişisel koruyucu donanım sağlayarak, iş sağlığı konusunda eğitim vererek ve psikososyal destek programları geliştirerek hemşirelerin fiziksel ve psikososyal sağlığını korumada kilit rollere sahip oldukları unutulmamalıdır.

Anahtar Kelimeler: COVID-19, nitel araştırmalar, yönetici hemşireler, hemşirelik profesyonelleri, iş sağlığı, pandemi.

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Received: 13.09.2023
Accepted: 26.09.2024

The routine of the world population changed at the end of December 2019 with the emergence of the Coronavirus of Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) (1), popularly known simply as coronavirus. The Coronavirus Disease 2019 (COVID-19) became a pandemic a few months after its emergence (1), posing a threat not only to the health sector but also to the economy of several countries. It is a fact that the entire world was severely affected by the COVID-19 pandemic, but health professionals were, and continue to be, the most threatened by this disease (2), which even today, more than three years after its emergence, continues to cause the death of many people around the world (3).

Health professionals, especially nursing team members, continue to be affected by the pandemic in several dimensions. The fear of contracting the virus and contaminating others, the difficulty of carrying out their functions due to constantly using Personal Protective Equipment (PPE), or even the lack of them, the prejudice, ignorance, and violence of society accusing healthcare workers of spreading the virus, the feeling of powerlessness in the face of terminally ill patients, and the sadness when witnessing the death of co-workers are some of the challenges brought by COVID-19 to the daily lives of nursing professionals (4). In addition, the workload of nursing professionals has increased (2) due to a large number of infected patients and the lack of staff for various reasons such as sick leave, old age, or even death.

Brazil was one of the countries hardest affected by the COVID-19 pandemic. By August 2022, 34,096,935 cases of the disease and 680,786 deaths had been confirmed; thus, the country occupies the third position in the number of cases worldwide (3). Among Brazilian health professionals, nursing team members, such as technicians, assistants, and nurses, were respectively the most affected by the disease (5). Studies conducted in Brazil identified a very high number of health professionals infected with SARS-CoV-2 when compared to surveys conducted in other countries (6).

Even in non-pandemic periods, the work environment of nursing staff presents several risk factors for workers' health (2), as it is a favorable place for the development of infections, stress, anxiety, and depression, among others. Thus, the health of nursing professionals, which is routinely under threat, was even more affected by the chaotic scenario of the pandemic. The physical health of nursing professionals was affected by the presence of the virus, the use of PPE (7) and also the lack of such equipment (8), and the violence of society (9). Psychological health was threatened by fear, anxiety, and stress, which in some cases triggered diseases such as depression and burnout (2,7,8). Social health was threatened by the economic crisis (2), discrimination (9), and social distancing (2). In addition, spiritual health was also affected by the uncertainties and fears surrounding the pandemic period (10). It is essential to highlight that to provide quality care to individuals and the community, nursing professionals must be healthy.

Nursing professionals have resorted to various measures to alleviate the problems brought about by the COVID-19 pandemic, such as support from family members and colleagues (11), in-service training, counseling programs (12), research on the topic (11) and religious resilience (13). The pandemic came to show once again that nursing professionals must be prepared for emergencies and crises, which can arise at any time in the health area. Understanding the importance of the topic, the present study aimed to explore the effects of the COVID-19 pandemic on the physical, psychological, social, and spiritual health of nursing team members and to identify the coping measures adopted by them.

Materials and Methods

Design

This is a descriptive study with a qualitative approach. This type of design was chosen because it explores participants' perspectives, thus allowing detailed information about their experiences (14). The study was based on the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist (15).

Participants

The population under study consisted of nursing staff (nurse assistants, nursing technicians, and nurses) working in different regions of Brazil. Social media applications were used to send individual instant messages inviting individuals who identified themselves as nursing professionals in their profiles to participate in the study. The messages included general information about the study and the researcher, the Informed Consent Form (ICF), and the data collection tool. In order to reach more participants who met the study's inclusion criteria, the snowball technique was also used (14), so nursing professionals who agreed to participate in the study indicated other possible participants.

The study was developed through the written responses of 42 participants to questions related to their experiences during the COVID-19 pandemic. Members of the nursing team who had worked in Brazil for at least three years and who had signed the ICF, thus accepting participation in the study, were included. Nursing professionals not working in Brazil during the pandemic were not included.

Data Collection

The researcher is a female RN with a Ph.D. and works as an Assistant Professor. Her cultural background is similar to that of the participants of this study. The researcher took a course on qualitative research methods and has experience with qualitative studies.

Unlike most qualitative research in which data are collected through face-to-face interviews or focus groups, in this study, online Google Forms were used. The use of online and telephone approaches is becoming more common for the development of qualitative research, and Google Forms makes it possible to reach participants in different geographical regions easily and quickly (16), which was fundamental for the present study. Additionally, it facilitates the capture of spontaneous written responses, which are not influenced by the dynamics between the interviewer and interviewee. Data were collected between June and July 2022.

The data collection tool was composed of two parts; the first questions referred to the participants' sociodemographic characteristics, such as age, gender, marital status, position at work, working unit, and years of working experience, among others. The second part of the tool was composed of questions related to the COVID-19 pandemic, formulated based on the scanned literature (2,7,8,10). Examples of questions: (I) Have you been diagnosed with COVID-19? (II) Have you worked directly with COVID-19 patients? (III) What were the effects of the COVID-19 pandemic on your health? (IV) What are the most significant difficulties you face/faced during the COVID-19 pandemic? (V) What measures do you use/have used to protect your health (physical/mental/social/spiritual) during the COVID-19 pandemic? In addition, there was a space for a free comment on the subject at the end of the data collection tool.

The data collection instrument was pilot-tested with nursing professionals who evaluated the research instrument positively and did not give any suggestions for improvement in the format or wording; therefore, no changes were made. The data obtained from these participants were not included in the study. These four participants were recruited through social media applications. The data collection tool was written in Portuguese. Upon reaching 40 participants, data saturation was achieved (14). However, two more participants were included in the study.

Data Analysis

Participants' sociodemographic characteristics were summarized (Table 1). The responses of the 42 participants were read repeatedly and content analysis was used to analyze the data (14). The researcher read several times, line by line, the responses of the participants to immerse herself fully in the data. The data were coded manually by identifying themes, main ideas, similarities, and differences. The identified themes and sub-themes have been checked many times by the researcher. The interpretation of the narratives was completed through deep reflections on the research purposes.

Rigor

Creditability, confirmability, dependability, and transferability were used to increase reliability and validity. A variety of participants was provided; detailed information about the researcher was given; the data collection tool was pilot-tested, and prolonged engagement with the data was ensured. An important point for the credibility of the study is that participants' responses were provided in writing. The narratives, coding, sub-themes, and themes were read and reread many times. A specific routine was followed for data collection**,** and reflexivity was maintained, thus avoiding opinions on the interpretation of data. In addition, purposive sampling was used, data saturation was reached, and comprehensive analysis was provided.

Results

Most participants (90.5%) were female; 40.5% of participants were between 46 to 55 years old; 40.5% had a postgraduate degree; 45.2% were married; 64.3% were nurses; 23.8% were working in emergency rooms and 30.9% of participants had between 21 and 25 years of work experience. The characteristics of the participants are presented in Table 1. Participants were from seven different states of Brazil.

Table 1: Characteristics of nurse participants

Variable		N	%
Gender	Female	38	90.5
	Male	4	9.5
Age	18-25	1	2.4
	26-35	3	7.1
	36-45	16	38.1
	46-55	17	40.5
	56-65	4	9.5
	66+	1	2.4
Marital Status	Divorced	5	12.0
	Married	19	45.2
	Separated	3	7.1
	Single	9	21.4
	Stable Union	6	14.3
Educational Level	High School	6	14.3
	Bachelor's Degree	13	30.9
	Postgraduate (Specialization)	17	40.5
	Master's Degree	6	14.3
Position at Work	Nursing Assistant	3	7.1
	Nursing Technician	12	28.6
	Nurse	27	64.3
Unity of Work	Central Sterilization Unit	2	4.8
	Diabetes Program	1	2.4
	Emergency Room	10	23.8
	Health Surveillance	1	2.4
	Home Care	1	2.4
	Intensive Care Unit	8	18.9
	Operation Room	2	4.8
	Outpatient	9	21.4
	Primary Health Care	2	4.8
	Ward	6	14.3
Work Experience	1-5 years	2	4.8
	6-10 years	2	4.8
	11-15 years	6	14.3
	16-20 years	9	21.4
	21-25 years	13	30.9
	26+	10	23.8

The first of the three themes that emerged is the effects of the pandemic on the health of nursing professionals. It was identified that the health of nursing professionals was affected in all its dimensions. Thus, this theme was divided into four sub-themes: "Effects on physical health", "Effects on psychological/mental health", "Effects on social health", and "Effects on spiritual health". Twenty-seven (64.3%) participants stated having been infected with COVID-19, and varied symptoms of the disease, such as headaches, muscle aches, and dizziness were reported by them. Participants also emphasized that even after a few months, they were unable to fully recover from the disease and still suffered from some symptoms, such as loss of smell. In the second sub-theme, the participants' narratives regarding the effects of the pandemic on psychological/mental health were presented. Fear and emotional exhaustion were the most common effects pointed out by the participants. In the third sub-theme, the effects of the pandemic on the social health of the participants were shown. It was reported that social isolation, one of the preventive measures adopted at the beginning of the pandemic, in addition to affecting the emotional health of the participants, also changed their social lives. Finally, the effects of the pandemic on the spiritual health of the participants were presented. Nursing professionals emphasized the fact that social isolation kept people away from their religious rituals. On the other hand, many of the participants stated that the pandemic served to increase faith and in this way, the emergence of the coronavirus positively affected their spiritual health.

The second theme is about major difficulties faced by nursing professionals during the COVID-19 pandemic and was organized into five sub-themes: "The lack of material and human resources", "Increased demand and professional devaluation", "Social distancing", "Caring and facing death", and "Insufficient information and the lack of social commitment". Problems related to the insufficiency of PPE and medical materials, staff shortages, and the lack of training are among the difficulties cited by the participants. The shortage of health professionals trained to work during the pandemic was also a problem experienced by nursing professionals. Several participants mentioned the increase in demand, physical and emotional exhaustion, and the devaluation of the profession. The need for social distancing and the use of public transport were other barriers emphasized by nursing professionals. Thirty-four (81%) participants reported having had direct contact with COVID-19 patients. Being close to sick patients and family members and facing constant deaths were other difficulties reported by the participants. The existence of insufficient information in professional and social contexts, including a lack of social commitment towards preventive measures, was also stated by nursing professionals when they mentioned the difficulties faced during the COVID-19 pandemic.

The last theme refers to the measures that nursing professionals have adopted to solve the problems arising from the COVID-19 pandemic. This theme was organized into two sub-themes: "Protecting physical health" and "Protecting psychological/mental, social and spiritual health". Most of the measures cited by nursing professionals to protect their physical health involve using PPE, practicing hygiene care, and boosting the immune system. Additionally, according to their responses, they engaged in physical exercises, listened to music, maintained social connections, relied on faith, utilized the Internet for communication, underwent psychotherapy, and prioritized delivering quality care to the community to protect their psychological, mental, social, and spiritual health. The three identified themes, eleven sub-themes, and examples of participants' quotes are shown in Table 2.

Table 2: Themes, Sub-themes and Quotes

Themes	Sub-themes	Quotes
Effects of the pandemic on the health of nursing professionals	Effects on physical health	*"I had mild symptoms such as headache, body aches, and low-grade fever."* (Participant 7) *"I lost my sense of smell. Until today, I don't smell things properly."* (Participant 12) *"I gained 20 kilos…"* (Participant 40)
	Effects on psychological/ mental health	*"I had insomnia; fear of getting infected by the virus; I experienced paranoia and mental exhaustion!"* (Participant 6) *"The psychological effects of Covid were enormous. I was afraid of acquiring the disease and dying, of contaminating my family members, or that they would contaminate themselves. I lost some co-workers and personal friends due to Covid. Many things happened in a short period of time and I didn't have time to elaborate everything because I was focused on surviving."* (Participant 21)
	Effects on social health	*"I started to avoid going out anywhere and I isolated myself a lot."* (Participant 17) *"With the increased workload due to the pandemic, and also with the circulation of the virus, I don't go out much or visit friends and relatives. My social life has changed a lot."* (Participant 39) *"I'm afraid of socializing."* (Participant 40)
	Effects on spiritual health	*"I got attached to God much more than before."* (Participant 3) *"My faith has decreased a lot. After the pandemic, I stopped going to church."* (Participant 39)
Major difficulties faced by nursing professionals during the pandemic	The lack of material and human resources	*"The lack of PPE and medical equipment for ventilatory assistance in the hospital, such as Ambu and venturi mask and constant changes in treatments and protocols were big problems."* (Participant 11) *"I believe that the lack of structure and trained professionals were great difficulties."* (Participant 41)
	Increased demand and professional devaluation	*"I think we should show more the value of the work of nursing professionals. One of the categories that didn't stop for a single minute on their strenuous journeys! (…) We are underutilized "heroes"! That's sad!"* (Participant 34) *"The work overload and the lack of appreciation… The pandemic greatly increased demand; on the other hand, there was no change in salary, nor increased benefits."* (Participant 39)
	Social distancing	*"Not being together with the people I love was very hard."* (Participant 1) *"I had a lot of difficulties while going to work due to the reduced in the amount of public transport."* (Participant 5)
	Caring and facing death	*"Seeing intubated patients awake and tied up because of the lack of sedatives are scenes that still torment me."* (Participant 8) *"Taking care of my father hospitalized in the ward for Covid was very traumatic."* (Participant 35)
	Insufficient information and the lack of social commitment	*"Patients were not committed to prevention."* (Participant 27) *"Disinformation from everyone, including both professional and social contexts, was a big problem."* (Participant 42)
Protection measures adopted by nursing professionals during the pandemic	Protecting physical health	*"I resorted to immunity boosting with vitamins."* (Participant 10) *"I protected myself using masks, coveralls and protective aprons, gloves, face shield."* (Participant 21)
	Protecting psychological/ mental, social and spiritual health	*"Having faith in the mission I was carrying out as a nurse was important."* (Participant 10) *"Talking to God and praying several times a day. Asking for the pandemic to end as soon as possible… Watching movies and listening to music helped me."* (Participant 32)

Discussion

Nursing staff participating in this study reported that the COVID-19 pandemic affected their health in several dimensions; thus, effects on physical, psychological/mental, social, and spiritual health were identified. The lack of material and human resources, increased demand and professional devaluation, social distancing, facing death, insufficient information and the lack of social commitment were cited as the main problems faced by the participants. Nursing staff resorted to different measures to protect their health in all dimensions.

Participants cited symptoms of COVID-19, such as headaches, muscle aches, and memory and sensory losses. The scientific literature states that the most common symptoms of COVID-19 are fever, dyspnea, and cough; however, infected individuals may present a variety of other signs and symptoms, including loss of smell, headache, and muscle pain (17). Although some participants reported tiredness due to increased workload, others related that their physical health was affected due to the sedentary lifestyle imposed by social isolation, which led to weight gain. The results of the present study align with those of previous studies, in which fatigue and discomfort due to increased workload and the constant use of PPE (8) and gain or loss of weight (18) were identified as effects of COVID-19 on the physical health of nurses.

Concerning psychological/mental health, the participants listed several symptoms and diseases that emerged due to the COVID-19 pandemic, such as fear, sadness, anxiety, panic attacks, and depression. Studies showed that in previous outbreaks such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS); anxiety, fear, insomnia, stress, and burnout were triggered in nurses who worked on the front lines (19,20). Regarding the COVID-19 pandemic specifically, the results of research carried out in different countries align with those found in this study. A survey conducted in China showed that nurses had high rates of anxiety, fear, depression and burnout in the first periods of the pandemic (7). Stress, fear, anxiety, and depression were identified in Turkish nurses during the COVID-19 pandemic (18). An interesting fact was also seen in a study carried out with Chinese nurses, in which a relationship was identified between skin damage caused by the constant use of PPE and the emergence of problems related to mental health, such as anxiety, fear, burnout, and depression (7).

Participants reported social distancing as a major threat to social health. Previous studies have also pointed to the pandemic's risks to health professionals' social well-being. In a study conducted in the United Kingdom (UK), health and social care professionals working during the COVID-19 pandemic stated that their social health was impaired due to social distancing that took them away from loved ones (21). Social interactions are essential for individuals to feel healthy, but the advent of the pandemic harmed humanity's social health. Even after the relaxation of protective measures such as social isolation, some people still have difficulties in socializing, alleging the emergence of agoraphobia, that is, the fear of being in open and crowded places (22), as pointed out by some participants in this study.

The spiritual health of the nursing staff participating in the present study was also affected. Still, unlike the other dimensions of health, it was identified that the pandemic caused both negative and positive effects on the spiritual health of nursing professionals. While some participants reported a decrease in faith, others stated that the pandemic period was a time of spiritual strengthening. Similarly, a study carried out with advanced clinical practitioners identified that the COVID-19 pandemic has impacted their spiritual well-being. Participants in the study exhibited low levels of spiritual well-being, and those with higher levels reported greater resilience (23). A study conducted in Saudi Arabia pointed to the importance of spiritual well-being for nurses facing the challenges of the pandemic (10).

Nursing professionals reported facing many barriers during the COVID-19 pandemic due to a lack of material and human resources. Similar results were identified in several studies carried out in different countries (8,12). The death of patients and loved ones, the existence of insufficient information, and the lack of social commitment were also cited by participants as the main problems encountered during the pandemic. These results are in line with several other international research findings. A study conducted in Iran identified that observing the health state of patients was a factor that negatively affected nurses' mental health (24). Nurse participants in a study conducted in Canada reported psychological distress due to constant policy changes and different information about the disease and protective measures (25). Problems due to the need for more sharing important information about COVID-19 with frontline nurses were also identified (12). Health and social care professionals working during the COVID-19 pandemic in the UK expressed their frustration due to members of the public not following social distancing and other guidelines (21).

Participants in this study pointed out that the lack of professional appreciation was also a problem faced during the pandemic; these findings align with a study carried out with nurses during the MERS epidemic in which participants reported feeling devalued as professionals (19). Participants also stated a need for governmental and institutional support. The importance of support from health institutions' administrators was pointed out in previous studies carried out with nurses during the COVID-19 pandemic (2,11,18).

Given so many problems and barriers, nursing professionals have adopted diversified measures to protect the different dimensions of health. These results are in accordance with previous studies carried out during the COVID-19 pandemic in which the use of PPE and hygiene care were reported as the main protective measures adopted by nurses (26,27). In many studies, qualified and sufficient PPE provision was shown as a measure that should alleviate nurses' psychological pressure (28,29).

Doing physical exercises, listening to music, watching movies, talking to friends, having faith in God, maintaining communication through the Internet, avoiding news about the pandemic, undergoing psychotherapy, and focusing on their mission as nursing professionals were measures reported by the participants to protect their psychological/mental, social, and spiritual health. These results are in line with those of previous studies conducted in different countries. Avoiding news about COVID-19 seems to have been an important measure, as nurse participants in a survey by Coffré and Aguirre (26) reported stress due to different news from social media. However, the most common and effective measure taken by nurses to protect psychosocial health during the COVID-19 pandemic was communication with family and colleagues. Regular rest and exercises were also strategies adopted by Chinese nurses (11). In another study conducted in China, nurses shared their sense of duty as healthcare providers, highlighting that witnessing patients' improvements was a source of resilience (30). Some studies also emphasized the importance of providing spiritual support for nurses during the COVID-19 pandemic (18,24). In addition, focusing on delivering the best possible care to the community during the pandemic was another important resilience strategy adopted by nurses (30). Nursing staff implemented several strategies to face the challenges arising from the COVID-19 pandemic. It is essential to note that nursing professionals need to feel healthy so that they can provide quality care. The support from health administrators and nurse managers is crucial in this process.

Limitations

In-depth analysis of participants' experiences was hindered because the data were collected through online self-report instruments. The lack of variety in terms of participants' gender can also be pointed out as a limitation of the study since most of the interviewees were female. Another limitation of the study is that only seven states of Brazil were represented. In addition, the data were analyzed by only one researcher, and although she has experience in qualitative research, this can be considered a weakness of this study.

Implications for Nursing Management

The results of this study, along with other research, show that the health of nursing professionals is significantly impacted during outbreaks. Nursing management must prioritize better preparation for crises through comprehensive planning and resource allocation. Continuing education and psychosocial support programs should be developed to protect nursing professionals' physical and psychosocial health. By focusing on these areas, nursing management can enhance the resilience and readiness of nursing professionals, ultimately leading to improved patient care during crises.

Conclusion

This study sought to explore the effects of the COVID-19 pandemic on the physical, psychological, social, and spiritual health of nursing team members and to identify the coping measures adopted by them. It was identified that the health of nursing professionals was negatively affected in all dimensions, but the COVID-19 pandemic also represented a spiritual strengthening. Several difficulties experienced during the COVID-19 pandemic were highlighted by nursing professionals, including the lack of material and human resources, as well as social distancing, which kept them away from loved ones. Participants utilized PPE, practiced hygiene, and bolstered their immune systems to protect their physical health. They safeguarded their psychosocial and spiritual well-being through sports, reading, socializing with friends, strengthening their faith, undergoing psychotherapy, and maintaining a focus on delivering quality care to the community.

Declarations

Conflicts of Interest

The author declares that there is no conflict of interest.

Availability of Data

Available upon request.

Funding

This study received no specific grant from any funding agency in the public commercial, or not-for-profit sector.

Ethics Approval

Ethical approval was obtained from the Research Ethics Committee of the Anna Nery School of Nursing – São Francisco de Assis School Hospital of the Federal University of Rio de Janeiro through the Brazil Platform (approval date: June 22, 2022; decision number: 5.481.843). The ethical principles for medical research on human subjects established by the Declaration of Helsinki were followed.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1488774

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Health Institutions Management / Sağlık Kurumları Yönetimi

Examination of Healthcare Quality Indicators with a Two-Stage Panel Data Analysis: The Case of Cancer Care

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ABSTRACT

Purpose: The aim of this study was to examine the quality of care for cancer patients using survival rates for breast, cervical, colorectal, lung, and stomach cancers.

Methods: The study population comprised OECD countries. Survival rates from breast, cervical, colorectal, lung, and stomach cancers, alcohol use, smoking, physical inactivity, and obesity rates, age, and income were selected as research data. A two-stage panel data analysis was performed. In the first stage, efficiency scores were found to be an indicator of the quality of cancer care through data envelopment analysis. Survival rates of cancer types were used as output variables to determine efficiency scores. In the second stage, the factors affecting efficiency were determined by panel tobit regression analysis.

Results: In the first stage, Australia, Canada, Finland, Iceland, Israel, Israel, Korea, the Slovak Republic and Turkey were found to be efficient in all years. In the second stage, it was found that alcohol consumption, smoking, and inactivity statistically decreased cancer activity ($p<0,05$).

Conclusion: To reduce the negative impact of smoking, alcohol consumption, and physical inactivity on the quality of cancer care, it is important to integrate smoking cessation programs into cancer treatment plans, to offer counseling and support to help patients reduce or stop drinking, and to encourage and facilitate regular physical activity for cancer patients.

Keywords: Efficiency, cancer care, healthcare quality indicators, panel data analysis.

ÖZET

Amaç: Bu çalışmanın amacı meme, serviks, kolonrektal, akciğer ve mide kanserleri için sağkalım oranlarını kullanarak kanser hastalarının bakım kalitesini incelemektir.

Yöntem: Çalışmanın evreni OECD ülkelerinden oluşmaktadır. Araştırma verileri olarak meme, servikal, kolonrektal, akciğer ve mide kanserlerinden sağkalım oranları, alkol kullanımı, sigara kullanımı, fiziksel inaktivite ve obezite oranları, yaş ve gelir seçilmiştir. İki aşamalı bir panel veri analizi kullanılmıştır. İlk aşamada, veri zarflama analizi yoluyla kanser bakım kalitesinin bir göstergesi olarak etkinlik skorları bulunmuştur. Kanser türlerinin sağkalım oranları, etkinlik skorlarını belirlemek için çıktı değişkenleri olarak kullanılmıştır. İkinci aşamada ise panel tobit regresyon analizi ile etkinliği etkileyen faktörler belirlenmiştir.

Bulgular: İlk aşamada, Avustralya, Kanada, Finlandiya, İzlanda, İsrail, Kore, Slovak Cumhuriyeti ve Türkiye›nin tüm yıllarda etkin olduğu bulunmuştur. İkinci aşamada ise alkol tüketimi, sigara kullanımı ve fiziksel inaktivitenin kanser etkinliğini istatistiksel olarak azalttığı tespit edilmiştir ($p<0,05$).

Sonuç: Sigara, alkol ve fiziksel hareketsizliğin kanser bakımının kalitesi üzerindeki olumsuz etkisini azaltmak için, sigarayı bırakma programlarının kanser tedavi planlarına entegre edilmesi, hastaların alkolü azaltmalarına veya bırakmalarına yardımcı olmak için danışmanlık ve destek sunulması ve kanser hastaları için düzenli fiziksel aktivitenin teşvik edilmesi ve kolaylaştırılması önemlidir.

Anahtar Kelimeler: Etkinlik, kanser bakımı, sağlık hizmetleri kalite göstergeleri, panel veri analizi.

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Received: 23.05.2024
Accepted: 07.08.2024

Cancer was the second leading cause of death after cardiovascular diseases in OECD countries, accounting for 24% of all deaths in 2019. The leading causes of cancer deaths were lung cancer (21%), colorectal cancer (11%), breast cancer (15% in women), and prostate cancer (10% in men). These four cancers account for 44% of all cancers diagnosed in OECD countries. Mortality rates from cancer have fallen in all OECD countries since 2000, but on average, the decline has been more modest than that for cardiovascular diseases (1).

The term "cancer", representing a range of heterogeneous diseases, refers to a diagnosis that is increasingly becoming a chronic condition diseases that can begin with the uncontrolled growth of abnormal cells in almost any organ or tissue of the body. The quality of cancer care is shifting from a model focused on the need for immediate treatment of the tumor to a more holistic approach to patient care to ensure both quantity and quality of life. Addressing these needs begins before the active treatment phase and continues after the transition to long-term survival (2).

The importance of healthcare quality is paramount as it has a direct impact on patient outcomes, safety and overall well-being. In the context of cancer care, quality healthcare is critical to improving survival rates. Quality care includes timely and accurate diagnosis, effective treatment protocols, skilled healthcare professionals and comprehensive follow-up care. These elements ensure that patients receive the best possible interventions, reduce the likelihood of complications and improve their chances of recovery (3).

When healthcare systems emphasize quality, they are better equipped to handle the complexities of cancer treatment, such as surgery, chemotherapy, radiation, and palliative care. This holistic approach not only improves patient experiences but also plays a crucial role in enhancing survival rates or life expectancy. On the other hand, poor or inconsistent care can result in delays in treatment, incorrect diagnoses, or less effective therapies, which can negatively impact patient survival. Thus, a dedicated focus on quality in healthcare is vital for attaining superior clinical outcomes, prolonging patient lifespans, and enhancing the overall quality of life for those undergoing cancer treatment (4).

The need to measure the quality of care is a challenge in all medical disciplines. Quality of care is particularly difficult to assess for the wide range of diseases that fall under the umbrella of cancer, which are often treated by different healthcare providers in, both inpatient and outpatient settings. To measure quality, it is necessary to monitor several healthcare professionals over long periods of time: clinical oncologists, surgeons, radiologists, oncology nurses, psychotherapists, occupational therapists, physiotherapists, etc. Attributing outcomes to individual professionals or to a single intervention is difficult, and the collection of important data from all sectors of the healthcare system is sometimes still not practical (5). Furthermore, not all aspects of quality of care are amenable to measurement, and often those that are easiest and least costly to measure have little relevance to quality improvement (6).

In this study survival rates from breast, cervical, colourectal, lung, and stomach cancers were used as healthcare quality indicators. Survival rates for breast, cervical, colorectal, lung and stomach cancers are key indicators of the quality and effectiveness of healthcare. These rates provide valuable insights into the success of early detection methods, such as screening programmes, and the effectiveness of different treatment options, including surgery, chemotherapy and radiotherapy. High survival rates typically indicate that a healthcare system is well equipped to diagnose and treat these cancers promptly and effectively, while low survival rates may indicate gaps in care, such as delayed diagnosis or inadequate treatment. Monitoring these rates helps healthcare providers and policymakers identify areas for improvement, allocate resources more efficiently, and prioritise research and public health interventions. In addition, tracking survival rates over time allows progress in cancer treatment and prevention efforts to be assessed, highlighting the impact of medical advances and public health initiatives. Ultimately, understanding and improving these survival rates is essential to reducing cancer-related mortality and improving patients' quality of life (7). These indicators were selected by taking into account OECD data. In addition, the two-stage panel data analysis method was used for assessing the data. This approach using DEA and Tobit regression provides a comprehensive framework for assessing and understanding efficiency, making it a valuable tool for researchers, policy makers and practitioners in various fields, including healthcare.

In this context, the main purpose of this study was to analyze the quality of cancer care in terms of different indicators.

Methods

Study Population and Sample Selection

The study population comprised OECD countries. The aim was to reach the whole population without sampling. However, because the data were missing from 9 countries, 26 countries were included in the study.

Variables of the Study

Information on the study's data, which were fully accessible because of the literature review, is presented below (Table 1). The years of the data cover five-year periods (2000-2004, 2005-2009, 2010, 2014) for cancer types and alcohol consumption, smoking, physical inactivity, and obesity, whereas for other variables it is 2014. This is because data on cancer sites are available for five years in the data source. In order to harmonize the data, the averages of the data on alcohol, smoking, physical inactivity and obesity were used, considering the corresponding year intervals. A summary of the data is presented below (Table 1).

Table 1: Study data

Variables	Measurement	Abbr.	Data from	Year
Breast cancer survival	Breast cancer 5-year net survival (%)	BreSur	OECD (https://stats.oecd.org/Index.aspx?QueryId=51882)	2000-2004; 2005-2009; 2010-2014
Cervical cancer survival	Cervical cancer 5-year net survival (%)	CerSur	OECD (https://stats.oecd.org/Index.aspx?QueryId=51882)	
Colonrectal cancer survival	Colorectal cancer 5-year net survival (%)	ColSur	OECD (https://stats.oecd.org/Index.aspx?QueryId=51882)	
Lung cancer survival	Lung cancer 5-year net survival (%)	LunSur	OECD (https://stats.oecd.org/Index.aspx?QueryId=51882)	
Stomach cancer survival	Stomach cancer 5-year net survival (%)	StoSur	OECD (https://stats.oecd.org/Index.aspx?QueryId=51882)	
Alkohol	Liters per capita (15+)	Alk	OECD (https://stats.oecd.org/Index.aspx?QueryId=51882)	
Smoking	% of population Daily smokers (15+)	Smo	WHO (https://www.who.int/data/gho/indicator-metadata-registry)	
Inactivity	Prevalence of insufficient physical activity (18+)	Inact	WHO (https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3416)	
Obesity	Prevalence of overweight among adults (BMI ≥ 25)	Obe	WHO (https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3416)	
Age	Population ages 15-64 (% of total population)	Age	Worldbank (https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?view=chart)	2014
Income	GDP per capita, PPP (current international $)	Inc	Worldbank (https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?view=chart)	

Research Model

In light of the data obtained, the model of the research (Figure 1) is presented below.

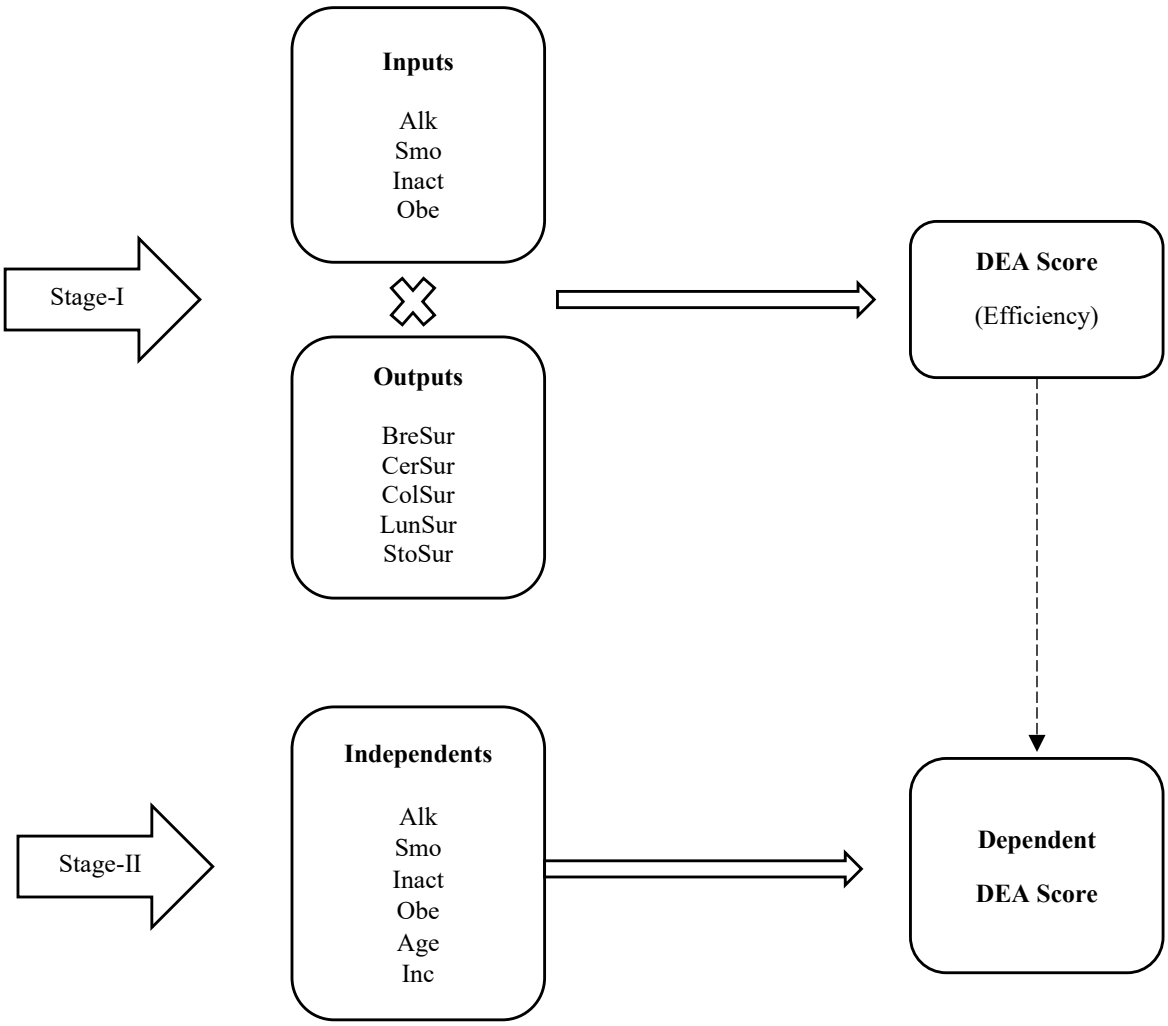

Figure 1: Research Model

Relationship between the Variables of the Study

The connection between alcohol consumption, smoking, physical inactivity, obesity, and cancer survival rates is intricate and substantial. Research has shown that these lifestyle choices can negatively impact cancer prognosis and survival chances. Both alcohol and smoking are established carcinogens, not only heightening the risk of developing various cancers but also exacerbating outcomes for individuals already diagnosed. Smoking, in particular, is linked to lower survival rates due to its role in cancer recurrence and additional complications. A sedentary lifestyle and obesity are also significant contributors, as they can cause metabolic and inflammatory issues that may impair the body's capacity to combat cancer. Obesity, in particular, is associated with lower survival rates across several cancer types, as it can interfere with treatment effectiveness and increase the risk of other health problems. Together, these lifestyle habits can compromise the immune system, reduce overall health, and weaken the body's resilience, leading to decreased survival rates for cancer patients. Therefore, addressing these factors is essential for enhancing cancer outcomes and survival. In addition, The relationship

between age, income and cancer survival is an important aspect of understanding cancer outcomes. In general, older age is associated with lower survival rates, as ageing often brings with it a higher likelihood of comorbidities and a reduced physiological reserve to withstand aggressive treatments. In addition, lower income levels can adversely affect cancer survival because they are often associated with reduced access to quality health care, timely screening and advanced treatments. Socioeconomic inequalities can also affect the ability to maintain a healthy lifestyle and access supportive care during and after treatment. As a result, both age and income are important factors that can influence the prognosis and overall survival of cancer patients. (8-10).

Data Analysis

The analysis of the data was carried out in two stages. In the first stage, the Data Envelopment Analysis (DEA) method was used to measure the relative efficiency of decision units (countries). DEA is a nonparametric method developed by Charnes et al. (11). In this method, the relative efficiency of the decision units is measured using inputs and outputs. Efficiency is assessed by weighting the most appropriate inputs and outputs for decision-making units (12). In DEA, which is based on linear programing, two different models are used: CCR (Charnes-Cooper-Rhodes) model and BCC (Banker-Charnes-Cooper) model (11). The BCC model expresses variable returns to scale. Accordingly, an increase in input will lead to a smaller or larger increase or decrease in output. Efficiency is evaluated between 0 and 1. If the value of the decision unit is equal to 1, the decision unit is considered efficient; if it is less than 1, it is considered inefficient (13). As the most commonly used model in DEA, the CCR model expresses constant returns to scale, which assumes that there are n decision units and each decision unit has the same type of input and output. In this model, all inputs and outputs are assumed to be positive. In this study, the BCC model was chosen because it compares both health services and countries. The model uses alcohol, smoking, physical inactivity, and obesity as input variables and cancers (breast, cervical, colourectal, lung, and stomach) survival rates as output variables. The reason for the selection of these variables is that they are thought to have an effect on cancer survival rates as stated in the literatüre (8-10). If the value of the decision unit is greater than 1, the decision unit is considered efficient. If the value of the decision unit is less than 1, the decision unit is considered inefficient (14).

In the second stage of the analysis, Tobit regression analysis was performed using the transformed DEA scores to determine the factors influencing the DEA scores. First, the independent and dependent variables for the Tobit regression analysis were determined. While alcohol, smoking, physical inactivity, obesity, age and income are selected as independent variables, the dependent variable is the DEA scores obtained in the first stage of the analysis, indicating the effectiveness of the service quality indicators. The Tobit regression model that was developed by Tobin is a powerful tool for determining the effect of independent variable(s) on dependent variable(s) when the dependent variable takes a value in a certain range (0-1 range) and is continuous (15). In cases where Tobit regression analysis is used as a second-stage analysis after DEA, it is recommended to apply [(1/VZA score)-1] transformation to the DEA scores. This makes it easier to ensure normality (16). The analysis is then censored at the zero (0) point from the left. In this case, the Tobit regression model shows the effects of the independent variables on inefficiency, but not efficiency. Accordingly, the effect of statistically significant independent variable(s) on efficiency as a result of the Tobit regression analysis is interpreted as the opposite sign of the coefficient of the relevant independent variable(s) (17).

One of the indicators of healthcare quality is efficiency. Therefore, in the first stage of the study, efficiency scores of cancer care of the countries were obtained through DEA and used as quality indicators. Secondly, tobit regression analysis was performed to determine the effect of lifestyle and sociodemographic variables in the study on the efficiency of cancer care quality.

DEA Solver Pro13 and EViews 9 were used to analyze the data.

Results

The DEA results of the first stage of the analysis are presented in Table 2. Accordingly, Australia, Canada, Finland, Iceland, Israel, Israel, Korea, the Slovak Republic, and Turkey were found to be efficient in all years.

Table 2: DEA results

	Years					
	2000-2004		2005-2009		2010-2014	
DMU's	Score	RTS	Score	RTS	Score	RTS
Australia	1,000	Constant	1,000	Constant	1,000	Constant
Austria	0,990	Increasing	0,987	Increasing	0,978	Increasing
Belgium	0,948	Constant	0,927	Increasing	0,925	Constant
Canada	1,000	Constant	1,000	Constant	1,000	Constant
Chile	0,882	Increasing	0,877	Increasing	0,875	Increasing
Czechia	0,933	Increasing	0,947	Increasing	0,950	Increasing
Denmark	0,922	Increasing	0,922	Increasing	0,922	Increasing
Estonia	0,886	Increasing	0,89	Increasing	0,889	Increasing
Finland	1,000	Constant	1,000	Constant	1,000	Constant
France	0,965	Constant	0,919	Decreasing	0,877	Increasing
Germany	0,933	Constant	0,922	Increasing	0,909	Increasing
Iceland	1,000	Constant	1,000	Constant	1,000	Constant
Israel	1,000	Constant	1,000	Constant	1,000	Constant
Italy	0,926	Constant	0,909	Increasing	0,895	Increasing
Korea	1,000	Constant	1,000	Constant	1,000	Constant
Lithuania	0,925	Increasing	0,917	Increasing	0,916	Increasing
Latvia	0,944	Increasing	0,957	Increasing	0,925	Increasing
Netherlands	0,932	Increasing	0,928	Increasing	0,926	Increasing
Norway	0,943	Increasing	0,962	Decreasing	0,961	Increasing
Portugal	0,892	Constant	0,869	Constant	0,844	Constant
Slovak Rep.	1,000	Increasing	1,000	Increasing	1,000	Increasing
Slovenia	0,958	Increasing	0,954	Increasing	0,951	Increasing
Spain	0,982	Increasing	0,981	Increasing	0,981	Increasing
Sweden	0,947	Increasing	1,000	Decreasing	0,993	Constant
Türkiye	1,000	Constant	1,000	Constant	1,000	Constant
United King.	0,930	Increasing	0,938	Increasing	0,939	Increasing
Mean	0,955		0,954		0,948	
SS.	0,038		0,042		0,048	

The descriptive statistics of the variables used in the study are presented in Table 3.

Table 3: Descriptives

	DEA Score	Alcohol	Smoking	Inactivite	Obesity	Age	Income
Mean	0.051	9.405	27.373	82.179	56.850	67.050	30512.26
SD	0.048	2.833	6.243	4.618	6.478	2.196	10700.09
Obs.	78	78	78	78	78	78	78

The correlation coefficients between the variables are presented in Table 4. Accordingly, it is determined that there is no multicollinearity problem that may prevent regression analysis.

Table 4: Correlations

	DEA Score	Alcohol	Smoking	Inactivite	Obesity	Age	Income
DEA Score	1.00						
Alkohol	0.35	1.00					
Smoking	0.43	0.25	1.00				
Inactivite	0.58	-0.10	-0.08	1.00			
Obesity	0.06	-0.22	0.01	0.08	1.00		
Age	-0.16	0.34	0.10	-0.48	-0.48	1.00	
Income	-0.18	-0.12	-0.53	0.07	0.01	-0.24	1.00

The results of the tobit regression analysis are presented below (Table 5). First, the regression model was found to be statistically significant ($p<0.05$). When analyzed for the variables, it was determined that alcohol consumption, smoking, and inactivity statistically decreased cancer activity (increased inactivity).

Table 5: Panel tobit regression analysis

Variables	Coefficient	Std. Error	z-Statistics	p
Alkohol	0.008	0.002	4.623	**<0.001**
Smoking	0.005	0.001	5.697	**<0.001**
Inactivite	0.009	0.001	7.973	**<0.001**
Obesity	0.001	0.001	0.970	0.331
Age	0.001	0.003	0.302	0.762
Income	7.536	4.930	1.527	0.126
C	-1.063	0.284	-3.741	0.001
Log likelihood: 90.962; Shwarz: -1.885; Hannan-Quinn: -2.030; Scale (p): 0.001				
Left censored obs.	25			
Right censored	53			
Total obs.	78			

Discussion

The aim of this study was to examine the quality of cancer care using survival rates for different types of cancer (breast, cervical, colorectal, lung and stomach). As a result of the analysis, alcohol consumption, smoking, and physical inactivity were found to negatively affect the quality of cancer care (inefficient care). There is by the way no significant difference was found with obesity, age and income as a result of the analysis.

When the literature was analyzed, it was found that similar results were obtained. Alcohol consumption significantly compromises the efficiency of cancer treatment. Ethanol and its metabolite, acetaldehyde, can interfere with the metabolism and action of various chemotherapy drugs, reducing their effectiveness and increasing the likelihood of adverse reactions (18,19). The study by Meadows and Zhang (20) included patients who consumed alcohol during and after cancer treatment and were at an increased risk of cancer recurrence and secondary primary cancers. Alcohol acts as a carcinogen, promoting the development of new cancers, particularly in the esophagus, liver, colon, and breast. Continued alcohol consumption can also contribute to primary cancer recurrence by creating a more conducive environment for cancer cell growth and survival. The study by Schwartz, et al (21) revealed that examining trends in alcohol consumption along with cancer incidence and mortality rates suggests that decreases in alcohol intake might reduce cancer risk. Managing the complications associated with alcohol consumption places a substantial strain on healthcare resources. Healthcare providers must allocate more time and resources to address these complications, which can detract from their ability to provide care for other patients. This inefficiency in resource utilization can negatively affect the overall quality of cancer care provided by healthcare institutions (22). These results elaborate on the adverse effects of alcohol consumption in cancer care, clearly demonstrating the repercussions of these effects on clinical outcomes. It also highlights the burden on health resources associated with alcohol consumption, another important factor affecting the efficiency of health systems and the quality of cancer care.

Smoking has a profound negative effect on the efficiency of cancer treatments. Research shows that smokers are less likely to respond to various cancer treatments, including surgery, radiotherapy, and chemotherapy. The presence of nicotine and other harmful substances in tobacco can reduce the body's ability to heal after surgery, increase the toxicity of treatments, and alter the pharmacokinetics of chemotherapy drugs (23). Peppone, et al (24) showed that patients who smoke during cancer treatment are at a higher risk of serious complications and side effects. Smoking intensifies respiratory problems, cardiovascular problems, and infections, which can lead to longer hospital stays and higher morbidity rates. Jassem (25) included smoking as having a negative impact on the quality of life of cancer patients. The addictive nature of nicotine and the physical dependence it creates can lead to chronic health problems and reduced overall well-being. This reduced quality of life can lead to lower adherence to treatment and poorer health outcomes. Selya, et al (26) found that the additional medical care required for smoking-related complications places a significant strain on healthcare resources. Hospitals and clinics must allocate more time and resources to manage these complications, which can detract from the care of other patients. This inefficiency in resource utilization can impact the overall quality of cancer care provided by healthcare institutions. It is stated that these studies address in detail the extensive effects of smoking on the effectiveness of cancer treatment, complications, quality of life and health resources. Highlighting the effects of smoking on these factors provides important information for shaping health policies and interventions.

Physical inactivity negatively impacts cancer care by contributing to poorer treatment outcomes and reduced quality of life. Regular physical activity improves the prognosis of cancer patients by enhancing immune function, reducing inflammation, and improving cardiovascular health. In contrast, a sedentary lifestyle can lead to weight gain, obesity, and associated metabolic complications, which can interfere with cancer treatment (27). Zhao, et al (28) reported that obesity is linked to increased risks of treatment-related complications and reduced efficacy of certain therapies. For example, excess body fat can alter the pharmacokinetics of chemotherapy drugs, making dosing more challenging and potentially less effective. Physical inactivity also contributes to fatigue and decreased physical function, which can reduce a patient's ability to tolerate and complete cancer treatment regimens. Physical inactivity can significantly impair the body's ability to tolerate cancer treatments, such as chemotherapy, radiation therapy, and surgery. Regular physical activity helps maintain cardiovascular and muscular health, which are crucial for enduring the rigorous demands of cancer treatment. Sedentary patients often have reduced muscle mass and cardiovascular fitness, leading to increased fatigue and a diminished

capacity to withstand the side effects of treatment (29). Physical inactivity is linked to poorer prognosis and lower survival rates in patients with cancer. Regular physical activity is associated with improved survival rates in various cancers, including breast, colorectal, and prostate cancers . In contrast, sedentary behavior can contribute to disease progression and lower survival rates. Physical inactivity promotes obesity and metabolic dysfunction, which are linked to a higher risk of cancer recurrence and mortality (30). These informations provide a detailed overview of the adverse effects of physical inactivity in cancer treatment and how physical activity can ameliorate these effects. These highlights the importance of promoting physical activity to improve treatment processes and informs the optimisation of healthcare services.

Conclusion

To reduce the negative impact of smoking on the quality of cancer care, it is important to integrate smoking cessation programes into cancer treatment plans. Healthcare providers should routinely screen for smoking and offer tailored smoking cessation interventions as part of comprehensive cancer care.

It is recommended that alcohol reduction strategies be included in cancer treatment plans. Healthcare providers should routinely screen for alcohol consumption and offer counselling and support to help patients reduce or stop drinking.

To mitigate the negative impact of physical inactivity on the quality of cancer care, healthcare providers should encourage and facilitate regular physical activity for patients with cancer. Incorporating exercise programes tailored to patients' abilities and treatment plans can improve physical functioning, enhance treatment tolerance, and improve overall well-being. Recommendations include

- Developing individualized exercise prescriptions that consider the patient's physical condition, cancer type, and treatment plan.
- Incorporating physiotherapy to help patients build strength, improve mobility, and manage treatment side effects.
- Counseling on the benefits of physical activity and practical ways to incorporate exercise into daily routines.

Limitations of the Study

There are some limitations in this study. First, it is important to know that the relationship between quality of cancer care and cancer treatment success does not depend only on these indicators. The treatment regimens used also important for treatment success. This factor should be taken into account when assessing the results. Second, the results of the study should be evaluated only by taking into account the relevant country group and the variables used. Different results can be obtained by using different country groups and variables. Finally, cancer survival rates were included in the study as included in the OECD database. It should be noted that the results may change when there are different groupings.

Implications for Theaory and Practice

The findings indicating that alcohol consumption, smoking, and inactivity significantly decrease cancer activity (interpreted as increasing inactivity) provide a nuanced perspective on how lifestyle factors impact cancer dynamics. These results contribute to the broader literature on the influence of lifestyle behaviors on cancer progression, challenging existing models by highlighting the complex relationship between these factors and cancer activity. This suggests that lifestyle behaviors not only play a role in cancer risk but also in its progression and the functional status of patients. The findings warrant further theoretical investigation into the mechanisms by which these lifestyle factors affect cancer biology and patient outcomes.

From a practical standpoint, these results underscore the importance of integrating lifestyle interventions into cancer treatment plans. Healthcare professionals should emphasize the need for screening and addressing alcohol consumption, smoking, and physical inactivity among cancer patients as part of a holistic approach to care. Encouraging healthier behaviors through resources for smoking cessation, reducing alcohol intake, and promoting physical activity can help mitigate the negative impacts on cancer activity and enhance overall patient health. Moreover, public health efforts should aim to educate the public about the harmful effects of these lifestyle factors on cancer progression, thereby empowering patients to make more informed health decisions.

Policymakers can leverage the findings of this study to shape public health initiatives and policies focused on

lowering cancer rates and enhancing patient outcomes. The study's identification of alcohol consumption, smoking, and physical inactivity as factors associated with increased inactivity in cancer patients underscores the need for focused interventions and prevention efforts. By implementing policies that encourage smoking cessation, moderate alcohol use, and greater physical activity, policymakers can address these risk factors. Moreover, investing in educational campaigns and support services that promote healthier lifestyle choices can help decrease cancer-related health issues and deaths. The empirical evidence provided by this study can be instrumental in formulating data-driven public health strategies and regulations to better manage and prevent cancer.

Declarations

Ethics Approval

In this study since secondary data were used, there is no need for ethics committee approval.

Conflicts of Interest

No conflicts of interest to declare.

Availability of Data and Material

Yes.

Funding

This study received no specific grant from any funding agency, commercial entity, or not-for-profit organization.

Acknowledgments

No to report.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1520732

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Health Institutions Management / Sağlık Kurumları Yönetimi

Applicability of Balanced Scorecard in Private and Public Hospitals: A Comperative Analysis

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ABSTRACT

Purpose: The aim of this article is to present research findings on the applicability of the Balanced Scorecard in private and public hospitals based on a survey conducted among managers and to provide recommendations based on the results obtained.

Methods: As part of the study, interviews were conducted with managers from private and public hospitals in Yalova, Istanbul University Cerrahpaşa Medical Faculty, and Medipol Mega Hospital. The Balanced Scorecard Infrastructure Suitability Survey was administered to 165 managers. Data collected from the surveys were analyzed.

Results: The analysis of the data revealed findings on the scores obtained by private and public hospital groups, as well as private and public university hospitals, regarding the measurement frequency of the four dimensions of the Balanced Scorecard.

Conclusion: The study concluded that private hospitals have a more favorable approach to the applicability of the Balanced Scorecard compared to public hospitals. Additionally, managers of public university hospitals were found to be more aware of performance measurement than managers of other public hospitals. It was also concluded that public hospitals should consider the practices in private hospitals regarding performance measurement.

Keywords: Hospitals, Administration, Employee Performance

ÖZET

Amaç: Bu makalede, Balanced Scorecard'ın özel ve kamuya ait hastaneler özelinde uygulanabilirliğe dair yöneticiler nezdinde yapılan bir anket çalışması ile birlikte araştırma bulgularına ulaşılması ve elde edilen sonuçlar doğrultusunda önerilerin sunulması amaçlanmıştır.

Yöntem: Çalışma kapsamında Yalova'daki özel ve kamu hastaneleri, İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi ve Medipol Mega Hastanesi yöneticileri ile görüşüldü ve 165 yöneticiye Dengeli Puan Kartı Altyapı Uygunluk Anketi uygulanmıştır. Anketlerden toplanan veriler analiz edilmiştir.

Bulgular: Analiz edilen veriler sonucu özel ve kamuya ait hastaneler grubu ile özel ve kamuya ait üniversite hastanelerinin Balanced Scorecard'ın 4 boyutuna ait ölçütlerin ölçüm sıklığı düzeylerinden aldıkları puanlara yönelik bulgulara ulaşılmıştır.

Sonuç: Çalışma sonucunda, Özel hastanelerin Balanced Scorecard'ın uygulanabilirliği konusunda Kamu hastanelerine nazaran daha uygun bir yaklaşım içinde oldukları, yine Kamu üniversite hastaneleri yöneticilerinin kamu hastanesi yöneticilerine kıyasla daha bilinçli oldukları, kamu hastanelerinin performans ölçümü konusunda özel hastanelerdeki uygulamaları dikkate alması gerektiği sonucuna ulaşılmıştır.

Anahtar kelimeler: Hastaneler, Yönetim, Çalışan Performansı

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Received: 23.07.2024
Accepted: 06.09.2024

The World Health Organization's strategy for evaluating health system performance begins with addressing a simple question: "What are health systems for?" The clear answer to this question is that health systems exist to enhance and sustain the health of the population. The World Health Report 2000 defines health systems as comprising all organizations, institutions, and resources aimed at improving health. The new strategy used by the WHO to evaluate health system performance has three main objectives: to enhance health, to ensure equity in competency and financing (1).

Contributing to the literature of healthcare management, Foss and Fine argue that hospitals have social responsibilities in promoting public health within their communities. They assert that understanding the community's health status is crucial for healthcare managers and institutions in the 21st century to be successful in planning, organizing, and delivering services to the community. Apart from engaging in public health, another significant activity hospitals should undertake is conducting institutional performance evaluations and implementing new approaches and tools such as the Balanced Scorecard (2).

The Balanced Scorecard is a systematic process aimed at setting goals aligned with the organization's vision and strategies, establishing balanced performance indicators/measures, evaluating performance, and thereby enabling the organization to achieve its long and short-term strategic goals (3). The objectives and measures in the Balanced Scorecard are not merely a collection of financial and non-financial measures serving a single function. These objectives and measures are derived from a detailed examination of the company's or department's mission and strategy (4). A well-prepared Balanced Scorecard reflects the organizational vision, facilitates its communication and better understanding, and provides a quick and comprehensive presentation of whether the organization is functioning effectively (5).

In the Balanced Scorecard, objectives and measures are determined considering the organization's vision and strategies. Business performance is evaluated in four different dimensions with the objectives and measures in the Balanced Scorecard (3). Thus, the Balanced Scorecard enables businesses to answer four fundamental questions:

• How do our customers perceive us? (customer dimension)

• In which areas should we excel? (operational dimension)

• Can we continue to improve and create value? (learning and growth dimension)

• How do we appear to our shareholders? (financial dimension) (6).

According to Kaplan and Norton, these four dimensions should not be seen as a ready-made jacket but rather as a mold or template. There is no mathematical theory that dictates that all four dimensions are necessary and sufficient. Some businesses may only use two or three of these dimensions, while others may add one or more dimensions depending on the conditions of the industry in which they operate and the company's strategy (7).

The Balanced Scorecard is a new management practice for healthcare organizations and hospitals in our country. Our study focuses on the readiness of healthcare organizations and hospitals in our country for Balanced Scorecard, based on their current practices and management understanding, with a mutual analysis focusing on both public and private sector hospitals. There are significant structural, strategic, and organizational differences between private and public hospitals in Turkey. With its findings, the study provides a new perspective on these differences through the Balanced Scorecard framework. The research aims to determine the applicability of the Balanced Scorecard in hospitals by examining the perceptions of managers in private and public hospitals in Yalova and two university hospitals in Istanbul, along

with assessing how ready hospitals are for the Balanced Scorecard with their current practices.

Materials and Methods

Sample Selection: This study was conducted with the ethical approval of the Istanbul University Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee, decision number 83045809/604.01/02-279751. As the sample for the study, a private and a public hospital in Yalova, and two university hospitals in Istanbul, one private and one public, were selected. The rationale for choosing one private and one public university hospital in Istanbul using stratified sampling is the absence of private or public university hospitals in Yalova, the existence of large-scale private and public university hospitals only in major cities like Istanbul in Turkey and the region, and Istanbul's leading role in the health economy. The reasons for selecting Cerrahpaşa Medical Faculty as the public university hospital in Istanbul are its affiliation with a long-established university like Istanbul University, its deep-rooted medical education, its highly specialized advanced health services, and its high bed capacity. On the other hand, the selection of Medipol Mega Hospital as the private university hospital was based on its comparable features with Cerrahpaşa Medical Faculty, such as its bed capacity, number of staff, and social security agreements, considering it is an appropriate private university hospital with four different branches (General, Cardiac Surgery, Oncology, and Dental Hospitals) at the start of the research.

Data Collection: The data used in the study were obtained from a survey conducted among managers of private and public hospitals in Yalova, Istanbul University Cerrahpaşa Faculty of Medicine and Medipol Mega Hospital, a private university hospital. Informed consent has been obtained from all participants prior to the study. The Balanced Scorecard Infrastructure Suitability Survey was used as the data collection tool in the research. The survey form was created based on the questionnaire prepared by Bardak and utilizing performance indicators used in the studies of Coşkun, Bekmezci, Kılınç et al. Kırgın, Chang et al., and Chen et al. (6,8,10,11,13). Criteria related to the four dimensions of the Balanced Scorecard (financial dimension, internal processes dimension, customer -patient and staff- dimension, and learning and growth dimension) are evaluated with a 5-point Likert scale (ranging from 1: Not Important at All to 5: Very Important, and from 1: Never Measured to 5: Always Measured). The validity and reliability of the survey have been demonstrated in previous studies (14, 15).

Statistical Analysis: The data obtained from the research were analyzed using the SPSS 17.0 program. The reliability (internal consistency) of the survey was measured with Cronbach's Alpha coefficient. Qualitative variables in the study are presented as percentages, while quantitative variables are shown as means with standard deviations. Descriptive statistics were used in the study, and the normal distribution of variables was checked with the Kolmogorov-Smirnov Normality test. Since the data did not show a normal distribution, non-parametric test,

Mann-Whitney U test were used to compare independent groups. The results were interpreted at a significance level of 5%.

Results

This section provides information about the hospitals participating in the research, including hospital classifications, the ages of private and public hospital group managers participating in the study, their educational backgrounds, managerial levels, job experiences, and the departments to which they are affiliated. Table 1 shows the distribution of managers according to their demographic characteristics.

Table 1: Distribution of Managers According to Demographic Characteristics				
Hospitals		**Frequency (n)**		**Ratio (%)**
Cerrahpasa Medical Faculty Hospital		52		31,5
Medipol Mega University Hospital		70		42,4
Yalova Oral and Dental Health Center		6		3,6
Yalova Çınarcık State Hospital		8		4,8
Yalova State Hospital		22		13,3
Yalova Private Atakent Hospital		4		2,4
Yalova Private Uzmanlar Hospital		3		1,8
Total		165		100,0
Hospital Groups		**Frequency (n)**		**Ratio (%)**
Cerrahpasa Medical Faculty Hospital		52		31,5
Medipol Mega University Hospital		70		42,4
Public Hospitals		36		21,8
Private Hospitals		7		4,2
Total		165		100,0
Hospital Groups		**Frequency (n)**		**Ratio (%)**
Public Hospitals Groups		88		53,3
Private Hospitals Groups		77		46,7
Total		165		100,0
Educational Status	**Public**		**Private**	
	Frequency (n)	**Ratio (%)**	**Frequency (n)**	**Ratio (%)**
High School	1	1,1	3	3,9
Associate Degree	0	0	8	10,4
Bachelor's Degree	37	42,0	29	37,7
Postgraduate	23	26,1	20	26,0
Phd	16	18,2	9	11,7
Others	8	9,1	3	3,9
Empty	3	3,4	5	6,5
Total	88	100,0	77	100,0
Manager Level	**Public**		**Private**	
	Frequency (n)	**Ratio (%)**	**Frequency (n)**	**Ratio (%)**
Medium Level	63	71,6	75	97,4
High Level	23	26,1	2	2,6
Empty	2	2,3		
Total	88	100,0	77	100,0
Work Experience	**Public**		**Private**	
	Frequency (n)	**Ratio (%)**	**Frequency (n)**	**Ratio (%)**
0-5 year	4	4,5	29	37,7
6-15 years	29	33,0	24	31,2
16-25 years	34	38,6	10	13,0
26 years and above	14	15,9	4	5,2
Empty	7	8,0	10	13,0
Total	88	100,0	77	100,0
Affiliated Unit	**Public**		**Private**	
	Frequency (n)	**Ratio (%)**	**Frequency (n)**	**Ratio (%)**
Administrative Services	21	23,9	4	5,2
Operational Tasks	27	30,7	56	72,7
Nursing Services	31	35,2	17	22,1
Empty	9	10,2	0	0
Total	88	100,0	77	100,0
Age Range	**Public**		**Private**	
	Frequency (n)	**Ratio (%)**	**Frequency (n)**	**Ratio (%)**
20-30	10	11,4	39	50,6
31-40	23	26,1	21	27,3
41-55	36	40,9	9	11,7
Age Over 55	0	0	0	0
Total	88	100,0	77	100,0

When we look at the distribution of the managers according to their demographic characteristics, it is seen that the managers of Cerrahpaşa Medical Faculty Hospital, Medipol Mega University Hospital, Yalova Oral and Dental Health Center, Yalova Çınarcık State Hospital, Yalova State Hospital, Yalova Private Atakent Hospital and Yalova Private Uzmanlar Hospital participated in the study. Accordingly, a total of 165 managers, including 52 managers (31.5%) from Cerrahpaşa Medical Faculty Hospital, 70 managers (42.4%) from Medipol Mega University Hospital, 6 (3.6%) managers from Yalova Oral and Dental Health Center, 8 (4.8%) managers from Yalova Çınarcık State Hospital, 22 (13.3%) managers from Yalova State Hospital, 4 (2.4%) managers from Yalova Private Atakent Hospital, and 3 (1.8%) from Yalova Private Uzmanlar Hospital participated in the survey.

An survey was conducted for all the managers at Yalova Oral and Dental Health Polyclinic, Private Yalova Atakent Hospital, Private Yalova Uzmanlar Hospital, and Çınarcık State Hospital, as well as for almost all the managers at Yalova State Hospital, Cerrahpaşa Medical Faculty Hospital, and Private Medipol Mega University Hospital. Positions such as Hospital Manager, Chief Physician, Deputy Chief Physician, Director, Assistant Director, and Administrative Services Officer fall under the Administrative Services class, while positions like Quality, Human Resources, Finance, Patient Services, and Marketing Officers are categorized under the Operational Services class. Nursing Services Managers and Directors are categorized under the Nursing Services class.

In this part of the research, questions were directed to the managers of private and public hospital groups based on the measurement frequency levels of the four dimensions of the Balanced Scorecard, and their responses were compared across various variables. The performance criteria consist of 10 financial, 15 internal process, 10 customer, and 8 learning and growth dimensions, totaling 43 indicators. Each indicator was evaluated according to a 5-point Likert scale. The values of the criteria indicate that as they approach 5, they increase, and as they approach 1, they decrease. The comparison of the scores obtained from the measurement frequency levels of the financial dimension criteria belonging to the Public Hospitals and Private Hospitals Group and to the Private and Public University Hospitals is shown in Table 2.

Table 2: Comparison of the Scores Obtained from the Measurement Frequency Levels of the Financial Dimension Criteria of Public Hospitals, Private Hospitals Group, and Private and Public University Hospitals.

Measurement Frequency Level	**Public Hospitals Group (77)**		**Private Hospitals Group (88)**		**Test Values**
	X	SD	X	SD	p*
Profitability of Capital	2,86	1,391	3,79	1,268	0,002
Asset Turnover Ratio	2,81	1,276	3,45	1,389	0,022
Personel Expenses	3,02	1,268	3,96	1,026	0,001
Medical Supplies Expense	3,44	1,173	4,04	0,958	0,103
Direct Cost of Patient Care Services	3,32	1,170	4,04	0,855	0,035
Cost per Patient Day	3,35	1,223	4,08	0,891	0,009
Average Cost per Outpatient	3,35	1,213	4,13	0,914	0,010
Average Daily Cost of an Inpatient	3,36	1,215	4,18	0,884	0,007
Ratio of Total Expenses to Total Revenues	3,25	1,196	3,86	1,085	0,031
Ratio of Total Debt to Total Revenue	3,26	1,208	3,77	1,146	0,076
Measurement Frequency Level	**Public University Hospital**		**Private University Hospital**		**Test Values**
	X	SD	X	SD	p*
Profitability of Capital	2,58	1,363	3,84	1,268	0,000
Asset Turnover Ratio	2,67	1,184	3,46	1,410	0,001
Personel Expenses	2,81	1,189	3,97	0,985	0,000
Medical Supplies Expense	3,31	1,164	4,04	0,915	0,024
Direct Cost of Patient Care Services	3,33	1,024	4,09	0,818	0,028
Cost per Patient Day	3,37	1,048	4,09	0,836	0,009
Average Cost per Outpatient	3,40	1,107	4,14	0,862	0,024
Average Daily Cost of an Inpatient	3,44	1,127	4,20	0,827	0,010
Ratio of Total Expenses to Total Revenues	3,12	1,215	3,91	1,060	0,001
Ratio of Total Debt to Total Revenue	3,17	1,232	3,91	1,018	0,001

*X=Mean SD= Standart deviation *Mann-Whitney U*

When looking at the frequency scoring related to the financial aspect by the managers of public hospital groups and private hospital groups, it is observed that the managers of the private hospital group received higher scores in all criteria. In the evaluations of frequency measurement related to the financial aspect in the private hospital group, the highest scores were observed for the criteria "Average Daily Cost per Inpatient," "Average Cost per Outpatient," and "Cost per Patient Day." In contrast, in the public hospitals group, the criteria "Medical Supply Expenses," "Average Daily Cost per Inpatient," "Cost per Patient Day," and "Average Cost per Outpatient" received the highest scores. Notably, criteria such as "Return on Equity" and "Asset Turnover" which are considered much more vital for the private sector, received higher scores in managerial evaluation compared to public hospitals, and it is seen that the difference in criteria like "Return on Equity" (Z=1.833 p=0.002) and "Asset Turnover" (Z=1.505 p=0.022) is statistically significant.

When comparing the frequency scoring related to the financial aspect by the managers of public hospital groups and private hospital groups, statistically significant differences were found in the criteria: "Personnel Expenses" (Z=1.978 p=0.001), "Direct Cost of Patient Care" (Z=1.421 p=0.035), "Cost per Patient Day" (Z=1.650 p=0.009), "Average Cost per Outpatient" (Z=1.627 p=0.010), "Average Daily Cost per Inpatient" (Z=1.685 p=0.007), and "Ratio of Total Expenses to Total Revenue" (Z=1.446 p=0.031).

When examining the frequency scoring related to the financial aspect for the managers of private and public university hospitals, statistically significant differences were found in all criteria. Accordingly, for "Return on Equity" (Z=2.140 p=0.000), "Asset Turnover" (Z=1.902 p=0.001), "Personnel Expenses" (Z=2.483 p=0.000), "Medical Supply Expenses" (Z=1.489 p=0.024), "Direct Cost of Patient Care" (Z=1.463 p=0.028), "Cost per Patient Day" (Z=1.647 p=0.009), "Average Cost per Outpatient" (Z=1.489 p=0.024), "Average Daily Cost per Inpatient" (Z=1.633 p=0.010), "Ratio of Total Expenses to Total Revenue" (Z=1.927 p=0.001), and "Ratio of Total Debt to Total Revenue" (Z=1.900 p=0.001), statistically significant differences were detected among the groups.

The comparison of the scores obtained from the frequency level of measurement criteria concerning internal processes for public hospitals, private hospitals, and private and public university hospitals is shown in Table 3.

When examining the scores for the internal process dimension criteria based on measurement frequency levels for private and public hospitals, it is observed that the following criteria received higher scores in the private hospital group and lower scores in the public hospital group, with the differences being statistically significant: "Readmission rate" (Z=2.089, p=0.000), "Postoperative length of stay" (Z=2.253, p=0.000), "Average number of surgeries per day per surgeon" (Z=1.665, p=0.008), "Cesarean section rate" (Z=1.488, p=0.024), "Waiting time for surgery date" (Z=1.685, p=0.007), "Bed occupancy rate" (Z=1.529, p=0.019), "Mortality rate" (Z=1.415, p=0.037), "Hospital infection rate" (Z=1.841, p=0.002), and finally "Annual malpractice and medical error count" (Z=1.997, p=0.001).

When comparing the internal process dimension criteria measurement frequency levels between private and public university hospitals, it is observed that the private university hospital scores higher on every measure compared to the public university hospital, with the differences being statistically significant.

Table 4. also presents a comparison of the scores based on measurement frequency levels for patient and staff dimension criteria between private and public hospitals.

Table 3: Comparison of the Scores Obtained from the Measurement Frequency Level of the Criteria Related to the Internal Processes Dimension of Public Hospitals, Private Hospitals, and Private and Public University Hospitals

Measurement Frequency Level	Public Hospitals Group (77)		Private Hospitals Group (88)		Test Values
	X	SD	X	SD	p*
Readmission rate	2,89	1,360	3,88	1,154	0,000
Postoperative length of stay	3,10	1,251	4,16	0,784	0,000
The average number of surgeries per surgeon per day	3,19	1,221	4,03	0,794	0,008
Cesarean section rate	2,84	1,355	3,60	1,042	0,024
Number of outpatient clinic rooms / number of outpatient clinic doctors	3,11	1,179	3,66	1,034	0,120
Ameliyat tarihi için bekleme süresi	2,89	1,343	3,79	1,004	0,007
Waiting time for surgery date	3,51	1,114	4,04	0,715	0,114
Average length of stay	3,44	1,081	3,92	0,929	0,052
Bed occupancy rate	3,60	1,000	4,00	0,903	0,019
Annual number of outpatients per docto	3,07	1,211	3,68	1,006	0,120
Annual number of inpatients per doctor	2,97	1,254	3,60	1,079	0,093
Annual number of emergency patients per doctor	3,11	1,188	3,52	1,034	0,577
Mortality rate	3,14	1,205	3,78	0,868	0,037
Hospital infection rate	3,66	1,060	4,29	0,723	0,002
Annual number of malpractice and medical errors	2,89	1,272	3,83	0,938	0,001
Measurement Frequency Level	**Public University Hospital**		**Private University Hospital**		**Test Values**
	X	SD	X	SD	p*
Readmission rate	2,83	1,339	3,81	1,179	0,000
Postoperative length of stay	3,12	1,149	4,12	0,796	0,000
The average number of surgeries per surgeon per day	3,31	1,076	4,07	0,748	0,016
Cesarean section rate	2,65	1,327	3,61	1,054	0,003
Number of outpatient clinic rooms / number of outpatient clinic doctors	3,00	1,103	3,70	1,040	0,013
Waiting time for surgery date	2,90	1,272	3,83	0,963	0,008
Waiting time for surgery date	3,58	1,036	4,04	0,690	0,315
Average length of stay	3,60	0,891	3,89	0,956	0,231
Bed occupancy rate	3,79	0,723	4,00	0,901	0,131
Annual number of outpatients per docto	2,98	1,180	3,70	0,968	0,025
Annual number of inpatients per doctor	2,94	1,178	3,63	1,066	0,033
Annual number of emergency patients per doctor	2,96	1,120	3,54	1,017	0,044
Mortality rate	3,17	1,115	3,77	0,871	0,061
Hospital infection rate	3,92	0,788	4,27	0,741	0,081
Annual number of malpractice and medical errors	2,98	1,196	3,87	0,883	0,003

*X=Mean SD= Standart deviation *Mann-Whitney U*

Table 4: Comparison of Scores for Patient and Staff Dimension Criteria Based on Measurement Frequency Levels for Private and Public Hospitals Groups, and Private and Public University Hospitals

Measurement Frequency Level	Public Hospitals Group (77)		Private Hospitals Group (88)		Test Values
	X	SD	X	SD	p*
Inpatient satisfaction	3,40	1,109	4,38	0,632	0,000
Outpatient satisfaction	3,32	1,273	4,39	0,634	0,000
Emergency patient satisfaction	3,20	1,332	4,26	0,839	0,000
Patient complaint rate	3,61	1,217	4,36	0,647	0,007
Number of new patients	2,42	1,404	3,83	1,248	0,000
Nurses' average response time to patient calls	2,13	1,437	3,82	1,073	0,000
Patient satisfaction	3,65	1,062	4,32	0,658	0,004
Outpatient wait times	2,63	1,526	4,10	0,882	0,000
Staff satisfaction	2,59	1,283	3,17	1,271	0,139
Staff turnover rate	2,58	1,354	3,22	1,273	0,017
Measurement Frequency Level	**Public University Hospital**		**Private University Hospital**		**Test Values**
	X	SD	X	SD	p*
Inpatient satisfaction	3,21	0,936	4,39	0,647	0,000
Outpatient satisfaction	2,81	1,329	4,41	0,649	0,000
Emergency patient satisfaction	2,77	1,308	4,26	0,869	0,000
Patient complaint rate	3,21	1,319	4,36	0,664	0,000
Number of new patients	2,04	1,137	3,91	1,147	0,000
Nurses' average response time to patient calls	1,88	1,132	3,97	0,884	0,000
Patient satisfaction	3,44	1,110	4,33	0,675	0,000
Outpatient wait times	2,33	1,438	4,21	0,635	0,000
Staff satisfaction	2,19	1,067	3,13	1,273	0,008
Staff turnover rate	2,65	1,251	3,29	1,253	0,179

*X=Mean SD= Standart deviation *Mann-Whitney U*

When comparing the scores for patient and staff dimension criteria based on measurement frequency levels between private and public hospital groups, statistically significant differences were found in the following criteria: "Inpatient satisfaction" (Z=2.372, p=0.000), "Outpatient satisfaction" (Z=2.349, p=0.000), "Emergency patient satisfaction" (Z=2.181, p=0.000), "Patient complaint rate" (Z=1.673, p=0.007), "Number of new patients" (Z=2.960, p=0.000), "Nurses' average response time to patient calls" (Z=3.724, p=0.000), "Patient satisfaction" (Z=1.779, p=0.004), "Outpatient wait times" (Z=3.204, p=0.000), and "Staff turnover rate" (Z=1.540, p=0.017).

When comparing the scores for patient and staff dimension criteria based on measurement frequency levels between private and public university hospitals, statistically significant differences were found in the following criteria: "Inpatient satisfaction" (Z=2.774, p=0.000), "Outpatient satisfaction" (Z=2.565, p=0.000), "Emergency patient satisfaction" (Z=2.459, p=0.000), "Patient complaint rate" (Z=2.053, p=0.000), "Number of new patients" (Z=3.635, p=0.000), "Nurses' average response time to patient calls" (Z=4.025, p=0.000), "Patient satisfaction" (Z=2.314, p=0.000), "Outpatient wait times" (Z=3.680, p=0.000), and "Staff satisfaction" (Z=1.654, p=0.008).

Table 5. shows the comparison of scores for learning and development dimension criteria based on measurement frequency levels between private and public hospital groups.

Table 5: Comparison of Scores for Learning and Development Dimension Criteria Based on Measurement Frequency Levels Between Private and Public Hospitals, and Private and Public University Hospitals Groups

Measurement Frequency Level	Public Hospitals Group (77)		Private Hospitals Group (88)		Test Values
	X	SD	X	SD	p*
Employee in-service training costs	2,05	1,164	2,42	1,268	0,242
Medical research expenses	1,86	0,985	2,46	1,238	0,055
Number of academic publications per medical staff member per year	1,90	0,959	2,38	1,166	0,067
Number of staff attending annual congresses and conferences (sent by the hospital)	2,01	0,977	2,43	1,193	0,340
Annual investment in information technology systems	2,35	1,204	2,58	1,074	0,113
Number of quality improvement teams	2,35	1,029	2,78	1,138	0,196
Number of committees and commissions established within the hospital	2,22	1,011	2,62	1,095	0,079
In-service training expenses	1,94	0,975	2,67	1,148	0,001
Measurement Frequency Level	**Public University Hospital**		**Private University Hospital**		**Test Values**
	X	SD	X	SD	p*
Employee in-service training costs	2,00	0,929	2,52	1,279	0,297
Medical research expenses	2,04	0,839	2,58	1,230	0,136
Number of academic publications per medical staff member per year	2,13	0,817	2,52	1,133	0,515
Number of staff attending annual congresses and conferences (sent by the hospital)	2,23	0,807	2,57	1,169	0,297
Annual investment in information technology systems	2,52	1,196	2,62	1,086	0,980
Number of quality improvement teams	2,29	0,800	2,83	1,124	0,324
Number of committees and commissions established within the hospital	2,19	0,864	2,65	1,082	0,732
In-service training expenses	1,94	0,725	2,77	1,152	0,022

*X=Mean SD= Standart deviation *Mann-Whitney U*

When comparing the scores for learning and development dimension criteria based on measurement frequency levels between private and public hospital groups, it is observed that private hospitals received higher scores in the following criteria: "Employee in-service training expenses," "Medical research expenses," "Number of academic publications per medical staff member per year," "Number of staff attending annual congresses and conferences," "Annual investment in information technology systems," "Number of quality improvement teams," "Number of committees and commissions established within the hospital," and "In-service training expenses." However, statistically significant differences were found only in the "In-service training expenses" criterion (Z=1.913, p=0.001).

When comparing the scores for learning and development dimension criteria based on measurement frequency levels between private and public university hospitals, it is observed that the private university hospital received higher scores in the following criteria: "Employee in-service training expenses," "Medical research expenses," "Number of academic publications per medical staff member per year," "Number of staff attending annual congresses and conferences," "Annual investment in information technology systems," "Number of quality improvement teams," "Number of committees and commissions established within the hospital," and "In-service training expenses." However, statistically significant differences were found only in the "In-service training expenses" criterion (Z=1.501, p=0.022).

Conclusions

It has been concluded that managers in the private hospital group have adopted a more customer-focused service approach, with financial dimension criteria being relatively more emphasized in private hospitals. Managers of public university hospitals score higher than their counterparts in other public hospitals and demonstrate greater awareness in performance measurement. Additionally, private hospitals are found to have a more suitable approach to implementing the Balanced Scorecard in the internal process dimension compared to public hospitals.

It can be said that the reason for this is that private hospitals are more aligned with the performance criteria in the four dimensions of the Balanced Scorecard—financial, customer, internal processes, and learning and growth—compared to all public hospitals. Additionally, among public hospitals, public university hospitals have a longer-established history, a more autonomous structure and more experienced managers compared to public hospitals under the Ministry of Health.

In public hospitals, compared to private hospitals, insufficient measurements are made in the internal process dimension. It is believed that organizing human resources and patient services units in public hospitals to align with the dynamics found in private hospitals would yield more effective results. For this, public hospitals need to undergo a restructuring of their human resources and patient services units, similar to those found in almost all private hospitals. The administrative organization, which remains at the level of 'personnel units' in human resources and 'secretarial services' in patient services, should be reorganized toward a modern human resources and patient services structure.

Similar to the financial dimension, it has been concluded that managers of public university hospitals score higher in the internal process dimension compared to other public hospital managers and are more aware of performance measurement. Accordingly, it is understood that a more merit-based process should be implemented when selecting individuals for managerial positions in Ministry of Health hospitals, and the criteria, particularly regarding education and experience, should be reviewed.

In public hospitals, compared to private hospitals, insufficient measurements are made not only in the internal process dimension but also in the patient and staff dimensions. The measurements that are conducted are limited to specific units. This indicates a negative situation regarding the applicability of the Balanced Scorecard in the learning and development dimension for both hospital groups. While the applicability of the Balanced Scorecard in the learning and development dimension is negatively impacted in both university hospital groups, private university hospital managers score higher in this dimension compared to public hospital managers. However, considering the low average of scores, it has been concluded that both university hospital groups face unfavorable performance measurement conditions in the learning and development dimension regarding the applicability of the Balanced Scorecard. This result indicates that the performance of both public and private university hospital employees, particularly academic staff, does not adequately reflect the institution's mission. It also suggests that more investment is needed in enhancing employee performance, as well as in institutional infrastructure and technology.

It has been concluded that public university hospitals should consider the practices in private university hospitals, ensure coordination between public university hospitals and other public hospitals, and initiate pilot implementations in public university hospitals based on measurement results. The experiences gained from these pilot implementations should be transferred to other public hospitals.

Funding

The author(s) received no financial support

Conflict of Interest

None declared.

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Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1549756

Baseline 18F FDG PET/CT imaging in NSCLC: Possible utility in predicting strong-positive PD-L1 expression

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Received: 14.09.2024
Accepted: 19.11.2024

ABSTRACT

Purpose: To assess whether 18F FDG PET/CT imaging can predict non-small cell lung cancer (NSCLC) patients with strong PD-L1 expression (≥50%).

Methods: This retrospective study analyzed 149 NSCLC patients who had undergone baseline 18F FDG PET/CT imaging from June 2021 to May 2024. We recorded age, sex, smoking history, histopathology, TNM stage, metastasis, and PD-L1 expression levels. PET/CT parameters such as SUVmax, SUVmean, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were recorded. Patients were dichotomized based on two PD-L1 expression thresholds, as measured by immunohistochemistry: higher or lower than 1% (<1%, n = 62 versus ≥1%, n = 87) and higher or lower than 50% (<50%, n = 100 versus ≥50%, n = 39).

Results: No significant results were found for the comparison of PD-L1 negative (<1%) and positive (≥1%) patients. The <50% and ≥50% groups were similar in terms of all examined characteristics and PET/CT parameters except for TLG, which was significantly higher among patients with strong PD-L1 expression. ROC analysis revealed an area under curve of 0.606 (95% CI: 0.508–0.705, p = 0.049) for the discrimination of patients with and without strong PD-L1 expression, yielding 89.7% sensitivity, 30% specificity, and 45.6% overall accuracy.

Conclusion: This study identified TLG as a potential predictor for NSCLC patients with strong PD-L1 expression (≥50%) based on 18F FDG PET/CT imaging, despite low accuracy. High sensitivity and negative predictive value suggest a role as a supportive tool in screening.

Keywords: 18F-fluorodeoxyglucose, positron emission tomography, programmed death-ligand-1, non-small cell lung cancer

ÖZET

Amaç: Çalışmamızın amacı, inisyal F-18 FDG PET/BT'nin güçlü programlı ölüm ligandı 1 (PD-L1) (≥%50) ekspresyonu gösteren küçük hücreli dışı akciğer kanseri (KHDAK) hastalarını öngörmedeki rolünün değerlendirilmesidir.

Yöntemler: Haziran 2021-Mayıs 2024 tarihlerinde F-18 FDG PET/BT görüntülemesi yapılan 149 KHDAK hastaları retrospektif değerlendirildi. Yaş, cinsiyet, sigara anamnezi, histopatoloji, TNM evresi, metastaz durumu ve PD-L1 ekspresyon seviyeleri kaydedildi. Akciğer lezyonlarının SUVmax, SUVmean, metabolik tümör hacmi (MTV) ve toplam lezyon glikolizi (TLG) PET/BT parametreleri kaydedildi. Hastalar, immünohistokimya ile belirlenen PD-L1 seviyelerine göre PD-L1 ekspresyonları %1'den düşük ve yüksek (<%1, n = 62'ye karşılık ≥%1, n = 87) olan hastalar ve PD-L1 ekspresyonları % 50'den düşük ve yüksek (< %50 , n = 100'e karşılık ≥%50, n = 39) olan hastalar şeklinde gruplandı.

Bulgular: PD-L1 <%1 ve ≥%1 hasta gruplarının PET parametreleri arasında anlamlı farklılık izlenmedi. PD-L1 <%50 ve ≥%50 gruplarının karşılaştırılmasında ise ≥%50 PDL ekspresyonu olan hastaların primer lezyonlarına ait TLG değerleri anlamlı derecede daha yüksek bulundu. ROC analizinde TLG'nin bu iki grup hastayı %89,7 duyarlılık, %30 özgüllük ve %45,6 doğruluk ile ayırt edebildiği gösterildi.(EAA: 0,606, %95 CI: 0,508-0,705, p = 0,049)

Sonuç: Bu çalışma, düşük doğruluk oranına rağmen, F-18 FDG PET/BT görüntülemeden elde edilen TLG değerinin güçlü PD-L1 ekspresyonu (≥%50) gösteren KHDAK hastaları için potansiyel bir belirleyici olduğunu göstermektedir. Yüksek duyarlılık ve negatif öngörü değeri, bu hasta grubunu ön görmede destekleyici bir araç olarak rol oynayabileceğini düşündürmektedir.

Anahtar Kelimeler: 18F-florodeoksiglukoz, pozitron emisyon tomografisi, programlanmış ölüm ligand-1, küçük hücreli dışı akciğer kanseri

Lung cancer is the leading cause of cancer-related death, accounting for 18.0% of total cancer deaths. Approximately 85% of all lung cancers are non-small cell lung cancer (NSCLC) (1), and until recently, the standard treatment of these malignancies involved cytotoxic chemotherapeutics (2). The (programmed death protein) PD-1 receptor is an immune checkpoint inhibitor (ICIs) expressed on activated B and T cells, which physiologically functions in the down-regulation of excessive immune responses. Binding of PD-1 to its programmed death ligands (PD-L1) on tumor cells suppresses T cell activity, allowing potentially immunogenic tumors to evade the immune responses (3). The administration of ICIs which target and block the binding of PD-1 and its ligand PD-L1 (referred to as PD-1/PD-L1 inhibitors) stimulates antitumor immune activity (4). Nowadays, targeted agents and immunotherapy have become the preferable options in the treatment of metastatic NSCLC since they achieve good treatment response and improve survival; however, treatment efficacy can vary significantly depending on various factors (5,6).

One such factor is accepted to be PD-L1 expression. Although the impact of PD-L1 expression on treatment response remains debatable, recent studies indicate superior response to PD-1/PD-L1 inhibitors in the presence of higher levels of PD-L1 expression (7). As such, the US Food and Drug Administration (FDA) has approved the use of multiple anti-PD-L1 agents, including pembrolizumab, Atezolizumab and Cemiplimab in advanced NSCLC with strong PD-L1 expression (≥50% of tumor cells) (8). In relation, NCCN guidelines recommend treatment with ICIs to be based primarily on the presence and expression levels of PD-L1, as determined by immunohistochemistry (IHC) (9). Identifying tumor PD-L1 expression by IHC requires high-quality tissue samples, which are obtained via invasive procedures. These procedures cause patient discomfort and the obtained material may be inadequate to evaluate PD-L1 due to several factors, such as limited cellularity (10). Therefore, new methods allowing the prediction of PD-L1 expression level could be crucial to improve or expedite management decisions.

18F fluorodeoxyglucose positron emission tomography/computed tomography (18F FDG PET/CT) is a non-invasive imaging modality that can portray the metabolic status of cancerous lesions. A relationship between PD-L1 expression and high glucose metabolism has already been described as a result of studies examining PET/CT results in patients with NSCLC (11,12). Therefore, the aim of this study was to investigate whether 18F FDG PET/CT imaging can be used to predict PD-L1 expression in NSCLC, especially with respect to identifying patients with strong PDL1 expression (≥50%).

Methods

Study Design

NSCLC patients who underwent baseline 18F FDG PET/CT imaging from June 2021 to May 2024 in the Department of Nuclear Medicine of our institution were analyzed retrospectively. Inclusion criteria were: pathologically-proven new-onset NSCLC, having complete data records for baseline 18F FDG PET/CT before operation or biopsy, and having undergone detection of PD-L1 expression levels by IHC. Exclusion criteria were being diagnosed with small cell lung cancer, previously receiving antitumor therapy or undergoing surgery before 18F FDG PET/CT, being diagnosed with NSCLC demonstrating epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or C-ROS oncogene 1 (ROS1) aberrations, and a history of any other malignancy.

Age, sex, smoking habit (pack/year), histopathology, TNM stage, clinical stage, primary tumor site, nodal involvement, metastasis, operation history, IHC result of PD-L1 expression levels, metabolic and volumetric parameters derived from 18F FDG PET/CT were recorded. Stage of cancer was determined according to 8th TNM classification for lung and pleural tumors (13).

Patients with PD-L1 expression <50% were determined as group 1, and patients with strong positive (≥50%) PD-L1 expression were determined as group 2 patients.

This study was approved by the University of Health Sciences Turkey, Cam and Sakura City Hospital Ethics Committee. (Decision no: E-96317027-514.10-241607520 date: 03.04.2024) All diagnostic and therapeutic procedures had been performed in accordance with the local national guidelines and the Declaration of Helsinki. All patients had received appropriate information and provided informed consent to undergo the procedures.

Pathological evaluation

Staining with the SP263 assay (Ventana Medical Systems) was performed on formalin-fixed paraffin-embedded tumor tissue sections. Tumors were scored in terms of the tumor proportion score (TPS), which represents the percentage of viable tumor cells showing partial or complete membranous PD-L1 staining. Tumor PD-L1 expression was defined by TPS cut-off values: PD-L1 negative (TPS < 1%), PD-L1 positive (TPS ≥ 1%) or PD-L1 strong positive (TPS ≥ 50%).

18F FDG PET/CT imaging procedure

Scans and image reconstructions were carried out based on EANM guidelines for tumor imaging (v2.015) (14), and images were acquired with an Ingenuity TF 64 scanner (Philips Medical Systems, OH, USA). In order to ensure a serum glucose level of <150 mg/dL prior to the administration of 18F FDG, patients were routinely instructed to fast for 6 hours before scheduled scanning. Patients were transferred to a secluded room after injection. Following the 50-minute rest, the patient was taken for imaging which started with a low-dose whole-body CT set at: 113 mAS, 120 kV and 4-mm section thickness, and obtained data were utilized in the correction of attenuation. The PET imaging began immediately in the caudocranial direction on the same field of view (transverse, 3 min per bed). Finally, maximum intensity projection and cross-sectional (transaxial, coronal, sagittal) projections were utilized to assess both corrected and non-corrected PET and CT images.

Imaging Assessment

Two nuclear medicine physicians blinded to clinical, radiologic, and pathological data assessed the images. To normalize the FDG uptake in the lung tumor, three spherical ROIs, each 3 cm in diameter, were placed in the right lobe of the liver, which demonstrated uniform FDG uptake, and the mean value (L SUVmean) was calculated. A volume of interest (VOI) was positioned around the primary lung tumor on attenuation-corrected FDG PET/CT images using automated contouring with manual adjustments to ensure the lesion was fully captured in the axial, sagittal, and coronal planes. The SUVmax, or maximum standardized uptake value, was determined as the highest SUV from a single voxel within the VOI, while the SUVmean represented the average SUV concentration within the VOI. Metabolic tumor volume (MTV), with a threshold of 40% of the SUVmax in the VOI, was recorded, and total lesion glycolysis (TLG) was calculated by multiplying MTV by SUVmean. Finally, the ratio of the tumor SUVmax to L SUVmean was calculated to produce the Normalized SUV.

Statistical Analysis

All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Analytical results showing $p < 0.05$ values were accepted as being statistically significant. For the normality check, the Shapiro-Wilk test was used. Descriptive statistics were presented with mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables, while frequency (percentage) values were used for categorical variables. Between-groups analysis of continuous variables was performed using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were analyzed with chi-square tests or the Fisher's exact test or its Freeman-Halton extension. The prediction performance of PET findings to determine PD-L1 expression was assessed using receiver operating characteristic (ROC) curve analysis. Optimal cut-off points were defined using the Youden index. Spearman correlation coefficients were calculated to evaluate directional relationship between continuous variables.

Results

We included 149 patients (127 males and 22 females) into the study, mean age was 63.93 ± 9.56 (range 37 - 87) years. PD-L1 expression was positive (≥1%) in 87 (58.39%) patients and was strongly positive (≥50%) in 39 (26.17%) patients. Patients were dichotomized based on being defined as PD-L1 negative (<1% expression, n = 62) or positive (>1% expression, n = 87), and also based on ≥50% PD-L1 expression, those with strong expression (n = 39) and without (n = 100).

When we compared PD-L1 negative (<1%) and positive groups (≥1%), we found that the groups were similar in terms of age, sex, pathology, smoking status, T stage, N stage, M stage, clinical stage, metastasis site, laterality (affected side), affected lobe, SUVmean, SUVmax, MTV, TLG, liver SUVmean and normalized SUV (**Table 1**). The only significant difference in this comparison was the smoking pack-years, which was lower in the positive group (p = 0.032).

Table 1: Summary of patient and tumor characteristics, PET findings with regard to PD-L1 expression positivity

		PD-L1 expression		p
	Total (n=149)	Negative, <1% (n=62)	Positive, ≥1% (n=87)	
Age	63.93 ± 9.56	64.45 ± 9.94	63.56 ± 9.32	0.578†
Sex				
Male	127 (85.23%)	55 (88.71%)	72 (82.76%)	0.438§
Female	22 (14.77%)	7 (11.29%)	15 (17.24%)	
Pathology				
Adenocarcinoma	94 (69.63%)	43 (74.14%)	51 (66.23%)	0.424§
SCC	41 (30.37%)	15 (25.86%)	26 (33.77%)	
Smoking	118 (86.13%)	53 (91.38%)	65 (82.28%)	0.203§
Pack year	40 (20 - 50)	40 (30 - 55)	30 (15 - 50)	**0.032‡**
T stage				
T1	11 (7.38%)	6 (9.68%)	5 (5.75%)	0.746§
T2	29 (19.46%)	11 (17.74%)	18 (20.69%)	
T3	47 (31.54%)	18 (29.03%)	29 (33.33%)	
T4	62 (41.61%)	27 (43.55%)	35 (40.23%)	
N stage				
N0	14 (9.40%)	8 (12.90%)	6 (6.90%)	0.190§
N1	22 (14.77%)	5 (8.06%)	17 (19.54%)	
N2	39 (26.17%)	17 (27.42%)	22 (25.29%)	
N3	74 (49.66%)	32 (51.61%)	42 (48.28%)	
M stage				
M0	59 (39.60%)	27 (43.55%)	32 (36.78%)	0.508§
M1	90 (60.40%)	35 (56.45%)	55 (63.22%)	
Clinical stage				
Stage I & II	8 (5.37%)	5 (8.06%)	3 (3.45%)	0.409¶
Stage III	51 (34.23%)	22 (35.48%)	29 (33.33%)	
Stage IV	90 (60.40%)	35 (56.45%)	55 (63.22%)	
Metastasis site (1)				
Other lung	9 (6.04%)	6 (9.68%)	3 (3.45%)	0.164#
Distant lymph node	32 (21.48%)	14 (22.58%)	18 (20.69%)	0.940§
Liver	14 (9.40%)	4 (6.45%)	10 (11.49%)	0.450§
Bone	45 (30.20%)	16 (25.81%)	29 (33.33%)	0.421§
Brain	27 (18.12%)	9 (14.52%)	18 (20.69%)	0.454§
Adrenal gland	25 (16.78%)	9 (14.52%)	16 (18.39%)	0.688§
Side				
Right	95 (63.76%)	40 (64.52%)	55 (63.22%)	1.000§
Left	54 (36.24%)	22 (35.48%)	32 (36.78%)	
Affected lobe (1)				
Superior	86 (57.72%)	34 (54.84%)	52 (59.77%)	0.665§
Middle	8 (5.37%)	4 (6.45%)	4 (4.60%)	0.719#
Inferior	58 (38.93%)	25 (40.32%)	33 (37.93%)	0.901§
SUVmean	6.6 (5.1 - 9.6)	6.45 (5.2 - 9.1)	7.0 (4.9 - 9.9)	0.439‡
SUVmax	11.6 (8.4 - 16.8)	11.2 (8.6 - 16.6)	12.4 (8.3 - 16.9)	0.492‡
MTV	42.8 (17.1 - 74.3)	43.2 (12.8 - 74.4)	42.4 (20.0 - 74.0)	0.831‡
TLG	325.22 (87.48 - 600.21)	332.61 (72.96 - 593.60)	325.22 (103.60 - 628.00)	0.641‡
Liver SUVmean	1.9 (1.6 - 2.2)	1.8 (1.6 - 2.2)	2.0 (1.7 - 2.2)	0.115‡
Normalized SUV	6.33 (4.47 - 8.80)	6.38 (4.22 - 9.42)	6.26 (4.48 - 8.80)	0.942‡

Descriptive statistics were presented with mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.
(1) Patients may have more than one of the defined categories.
† Student's t test, ‡ Mann Whitney U test, § Chi-square test, # Fisher's exact test, ¶ Fisher-Freeman-Halton test

The comparison of patients with and without strong PD-L1 expression (≥50%) revealed that the TLG values of the primary lesion were significantly higher among patients with strong PD-L1 expression (p = 0.049) (**Table 2**). A representative image from a patient is provide in **Figure 1**. There were no significant differences between these groups in terms of age, sex, pathology, smoking status, smoking pack year, T stage, N stage, M stage, clinical stage, metastasis locations, side, affected lobe, SUVmean, SUVmax, MTV, liver SUVmean, and normalized SUV (**Table 2**).

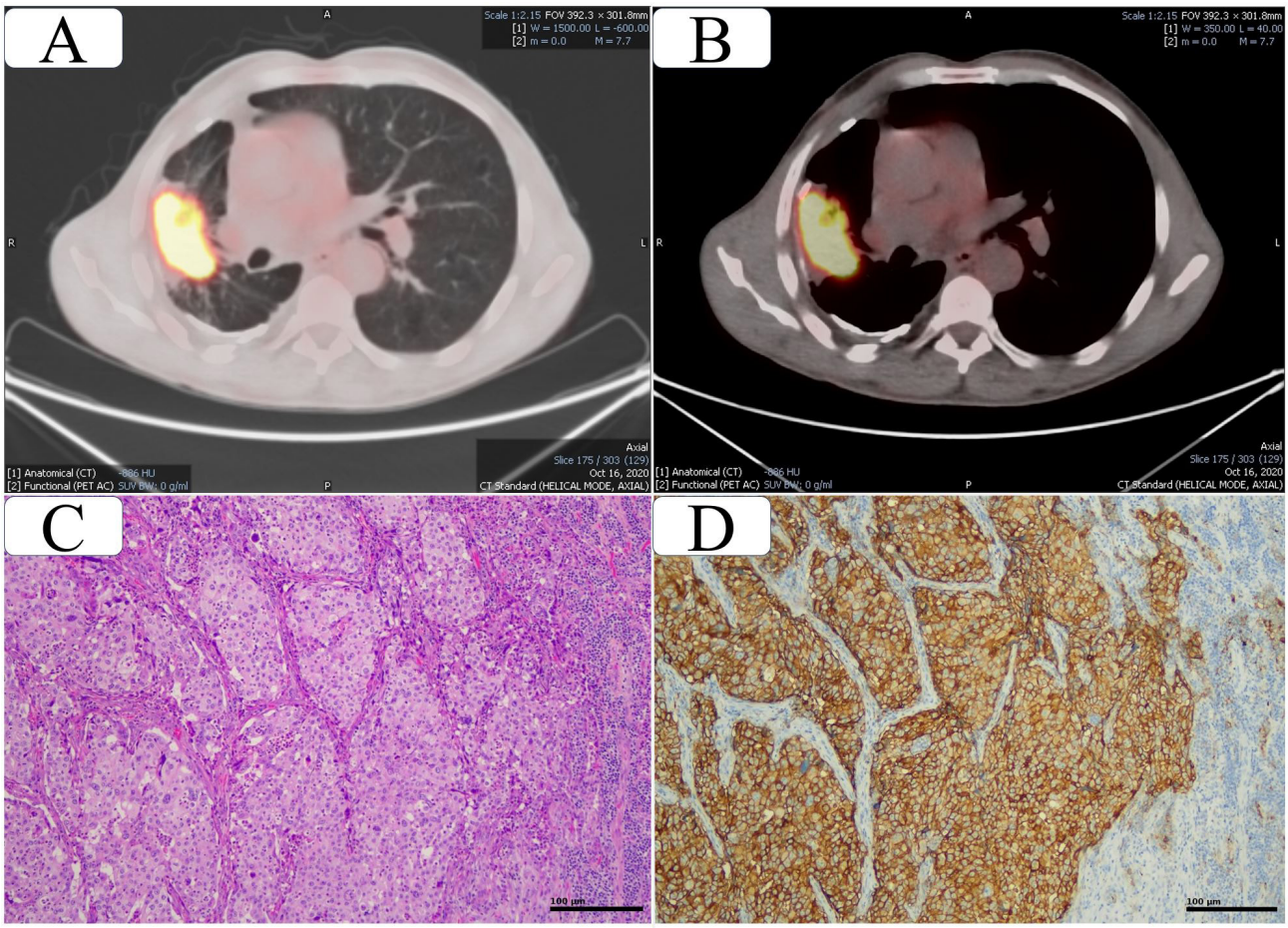

Figure 1: Representative images of 18F fluorodeoxyglucose positron emission tomography/computed tomography (18F FDG PET/CT) and immunohistochemical staining (IHC) of a non-small cell lung cancer (NSCLC) patient with high programmed death ligand-1 (PD-L1) expression (≥50%). (A, B) The axial fused pretreatment 18F FDG PET/CT images show values derived from the primary lung tumor: maximal standardized uptake value (SUVmax) of 15.9 g/ml, metabolic tumor volume (MTV) of 44.7 cm^3, and total lesion glycolysis (TLG) of 447. (C) Tumor infiltration areas showing strong PD-L1 positivity (H&E, x100). (D) Strong PD-L1 positivity observed in the tumor (x100).

Table 2: Summary of patient and tumor characteristics, PET findings with regard to strong (≥50%) PD-L1 expression

	PD-L1 expression		p
	<50% (n=110)	≥50% (n=39)	
Age	63.94 ± 9.83	63.92 ± 8.89	0.994†
Sex			
Male	93 (84.55%)	34 (87.18%)	0.892§
Female	17 (15.45%)	5 (12.82%)	
Pathology			
Adenocarcinoma	74 (71.84%)	20 (62.50%)	0.433§
SCC	29 (28.16%)	12 (37.50%)	
Smoking	83 (83.00%)	35 (94.59%)	0.143§
Pack year	35 (20 - 50)	40 (30 - 50)	0.323‡
T stage			
T1	11 (10.00%)	0 (0.00%)	0.150§
T2	23 (20.91%)	6 (15.38%)	
T3	33 (30.00%)	14 (35.90%)	
T4	43 (39.09%)	19 (48.72%)	
N stage			
N0	13 (11.82%)	1 (2.56%)	0.164§
N1	13 (11.82%)	9 (23.08%)	
N2	29 (26.36%)	10 (25.64%)	
N3	55 (50.00%)	19 (48.72%)	
M stage			
M0	45 (40.91%)	14 (35.90%)	0.719§
M1	65 (59.09%)	25 (64.10%)	
Clinical stage			
Stage I & II	7 (6.36%)	1 (2.56%)	0.636§
Stage III	38 (34.55%)	13 (33.33%)	
Stage IV	65 (59.09%)	25 (64.10%)	
Metastasis site (1)			
Other lung	8 (7.27%)	1 (2.56%)	0.447#
Distant lymph node	25 (22.73%)	7 (17.95%)	0.691§
Liver	9 (8.18%)	5 (12.82%)	0.523#
Bone	34 (30.91%)	11 (28.21%)	0.910§
Brain	18 (16.36%)	9 (23.08%)	0.488§
Adrenal gland	17 (15.45%)	8 (20.51%)	0.633§
Side			
Right	69 (62.73%)	26 (66.67%)	0.806§
Left	41 (37.27%)	13 (33.33%)	
Affected lobe (1)			
Superior	62 (56.36%)	24 (61.54%)	0.709§
Middle	5 (4.55%)	3 (7.69%)	0.432#
Inferior	45 (40.91%)	13 (33.33%)	0.520§
SUVmean	6.4 (4.9 - 9.1)	8.2 (5.3 - 10.8)	0.073‡
SUVmax	11.0 (8.2 - 16.2)	13.6 (9.4 - 19.4)	0.052‡
MTV	41.65 (12.8 - 73.2)	43.7 (25.0 - 105.3)	0.142‡
TLG	317.53 (79.05 - 592.90)	462.33 (182.32 - 838.32)	**0.049‡**
Liver SUVmean	1.9 (1.6 - 2.2)	2.0 (1.7 - 2.4)	0.336‡
Normalized SUV	6.09 (4.19 - 8.21)	7.39 (4.92 - 10.00)	0.082‡

Descriptive statistics were presented with mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.
(1) Patients may have more than one of the defined categories.
† Student's t test, ‡ Mann Whitney U test, § Chi-square test, # Fisher's exact test.

ROC analysis revealed that TLG had 89.74% sensitivity, 30.00% specificity, 31.25% positive predictive value and 89.19% negative predictive value (45.64% overall accuracy) in discriminating patients with and without strong (≥50%) PD-L1 expression. The area under the ROC curve of TLG was 0.606 (95% CI: 0.508 - 0.705, p = 0.049) (**Table 3, Figure 2**)

Table 3: Performance of PET findings to predict strong positive (≥50%) PD-L1 expression, ROC curve analysis

	Cut-off	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC (95% CI)	p
SUVmean	>7.9	53.85%	66.36%	63.09%	36.21%	80.22%	0.597 (0.491 - 0.703)	0.073
SUVmax	>13.2	53.85%	68.18%	64.43%	37.50%	80.65%	0.605 (0.501 - 0.708)	0.052
MTV	>18.1	89.74%	32.73%	47.65%	32.11%	90.00%	0.579 (0.481 - 0.678)	0.142
TLG	>87.0	89.74%	30.00%	45.64%	31.25%	89.19%	0.606 (0.508 - 0.705)	**0.049**
Normalized SUV	>8.4	41.03%	77.27%	67.79%	39.02%	78.70%	0.594 (0.493 - 0.695)	0.082

ROC: Receiver operating characteristic, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence interval

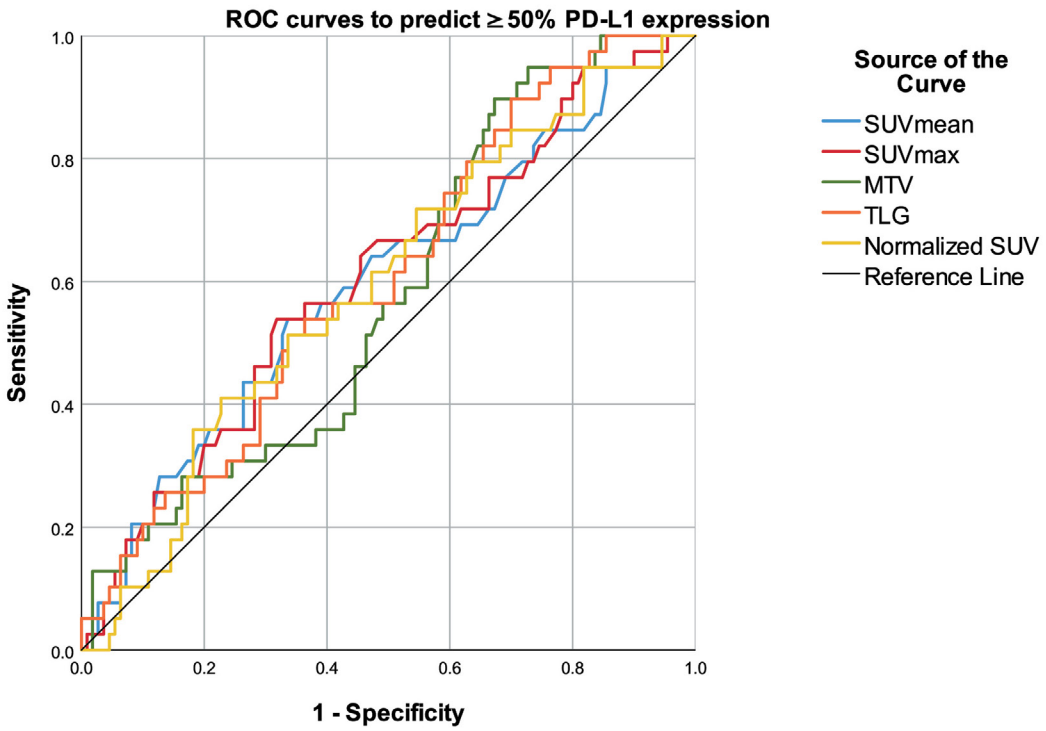

Figure 2: ROC curves of PET findings in the prediction of strong positive (≥50%) PD-L1 expression

Discussion

PD-1/PD-L1 inhibitors have become a crucial component of the treatment of advanced NSCLC without EGFR, ALK or ROS1 aberrations, either as a monotherapy or in combination with other immunotherapy/chemotherapies (15). Before initiating treatment, PD-L1 expression levels are assessed to predict which patients will respond to PD-1/PD-L1 inhibitors. Although the use of cut-off values to identify patients with high probability of therapeutic response is controversial, the FDA approved the use of multiple anti PD-L1 agents in a group of advanced NSCLC patients with strong PD-L1 expression (≥50%), suggesting that this threshold carries substantial clinical significance (7,8). Our analysis to assess the utility of 18F FDG PET/CT parameters in determining PD-L1 expression revealed that TLG was significantly higher among patients who were strongly positive for PD-L1 (as measured by IHC). Despite the very low overall accuracy (45.64%) determined by ROC analysis, the high sensitivity and negative predictive value show that elevated TLG values (defined as values greater than 87) might be utilized as supportive data in the identification of patients with ≥50% PD-L1 expression.

Many studies have shown that patients who failed first-line chemotherapy can benefit from PD-1/PD-L1 inhibitors, given that they have PD-L1 expression rates higher than 1% (16). The 50% cut-off value for PD-L1 expression was first identified in KEYNOTE-001, a phase 1 study of advanced NSCLC patients treated with pembrolizumab. In this study, PD-L1 expression in at least 50% of tumor cells was found to be associated with improved treatment response to pembrolizumab in advanced NSCLC patients (17). In another phase 3 trial including advanced NSCLC patients with a PD-L1 expression of ≥50%, pembrolizumab was associated with prolonged progression-free and overall survival as well as fewer adverse events compared to platinum-based chemotherapy (18), supporting the utility of quantifying PD-L1 expression. Similar results have also been reported with other PD-L1 inhibitors. For instance, Sezer et al. reported improved overall survival and progression-free survival with first-line cemiplimab monotherapy compared to platinum-double chemotherapy in patients with advanced NSCLC with a PDL of at least 50% (15). Other studies in advanced NSCLC patients with ≥50% PD-L1 expression have also demonstrated better clinical outcomes with first-line pembrolizumab (19,20). According to recent research, high PD-L1 expression is correlated with tumor angiogenesis, which may be an intracellular resistance mechanism for ICIs in patients with NSCLC. Researchers have proposed that this function has important consequences for the efficacy of ICIs, possibly demonstrating the need for the use of antiangiogenic drugs in conjunction with ICIs for first-line treatment of NSCLC patients exhibiting elevated PD-L1 expression, or as a second-line strategy when the tumor progresses (21). Data obtained from non-invasive 18F FDG PET/CT imaging might benefit the clinical management of the disease by potentially supporting the identification of individuals with a PD-L1 expression of ≥50%. Despite low discriminatory accuracy, the high negative predictive value particularly suggests that readily-obtained imaging data (shortly after diagnosis) can be useful to screen for candidates suitable (or unsuitable) for PD-1/PD-L1 inhibitor treatment.

The metabolic parameters acquired via 18F FDG PET/CT have been previously been associated with PD-L1 expression levels (11,12,22,23). However, there are remarkably limited investigations aiming to evaluate whether PD-L1 expression can be estimated with the radiomic features obtained from 18F FDG PET/CT (24). Xu et al examined patients with a PD-L1 expression of ≥50% (high expression) and reported that SUVmax and TLG values were significantly higher in patients with high expression (25), similar to our results. There are also several other studies that have described the possible use of radiomic data in the prediction of high PD-L1 expression (26,27). Li et al. reported convincing AUC scores for the prediction of PD-L1 expression (≥50%) with radiomic data, which were higher than the AUC for TLG values detected in our study (AUC: 0.606; 95% CI: 0.508 - 0.705). Of note, these differences between radiomic feature extraction and our results is not surprising since texture analysis can measure tumor heterogeneity of the entire tumor (27).

Prior research has established that patients with high TLG and high PD-L1 expression are recognized as having high risk, and these subjects have significantly worse overall survival. (28). Furthermore, it has been suggested that combining TLG and PD-L1 expression may produce a more accurate prognostic assessment for patients with NSCLC. (25) In our study, survival analysis could not be performed since these patients were not followed for a sufficiently long period.

Our comparison of PD-L1 negative (<1%) and positive (≥1%) groups did not reveal any notable differences between the groups and there were no relationships between PD-L1 expression and any of the 18F FDG PET/CT parameters. In contrast, several studies in the literature

have suggested that FDG uptake is significantly higher in PD-L1 positive patients relative to those defined to be negative (29,30). We believe that variations in patient characteristics and detection methods could explain these discrepancies in the literature.

This study has several limitations. First of all, this was a retrospective study and the sample size might be considered to be small, especially in terms of the distribution of patients with and without strong positivity for PD-L1. This difference in distribution is one of the factors that caused the exceedingly low accuracy detected for TLG despite very high sensitivity and negative predictive values. We believe future studies would benefit from including similar group sizes for patients with and without ≥50% PD-L1 expression, thereby improving the likelihood to clarify the utility of TLG measurements in this context. Secondly, since the follow-up period of the patients is short, survival analyses were not possible. Prospective studies with a larger number of patients are needed to determine the role of F 18 FDG PET/CT parameters in predicting PD-L1 expression levels among patients with NSCLC.

Conclusion

Our data shows that TLG, as measured by 18F FDG PET/CT, can predict NSCLC patients with strong positive (≥50%) PD-L1 expression owing to its high sensitivity. The high negative predictive value also suggests that TLG screening may be useful as a supportive tool in this context, despite the low overall accuracy which was caused by low specificity. Particularly since the use of multiple anti-PD-L1 agents has been approved for advanced NSCLC patients with ≥50% PD-L1 expression, there is a need for further research on this topic to improve the management and prognosis of the disease. Further studies on this subject with a larger patient population are needed to confirm our results.

Funding

The authors declare that the study received no funding..

Conflicts of interest

The authors declare no competing interests

Ethics approval

This study was approved by the University of Health Sciences Turkey, Cam and Sakura City Hospital Ethics Committee. (Decision no: E-96317027-514.10-241607520 date: 03.04.2024)

Availability of data and material

All data is available

Authors' contributions

ÖVT: Concept design, data collection, analysis, literature search, writing

EA: data collection

NB: data collection, writing

SB: data collection

BEA: writing

MK: writing

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