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

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Kapak resmi: Prof. Dr. Erkmen Böke (1939-2014):

İzmir'de 1939 yılında doğdu. 1962 yılında Ankara Üniversitesi Tıp Fakültesi'ni bitirdi. 1970 yılında Almanya Heidelberg Üniversitesi'nden Genel Cerrahi uzmanlığını aldı. Türkiye'ye döndükten sonra Hacettepe Üniversitesi'nde 1970 yılında Genel Cerrahi Uzmanı, 1973 yılında da Göğüs ve Kalp-Damar Cerrahisi Uzmanlığını aldı. Aynı üniversitede 1976 yılında Doçentliğe, 1982 yılında da Profesörlüğe atandı. 1982-1988 yılları arasında Hacettepe Üniversitesi Hastaneleri Başhekimliği görevinde bulundu. Almanca ve İngilizce bilen Prof. Dr. Böke, evli ve iki çocuk babasıdır.

Resim çalışmalarına 2003 yılından beri yoğun olarak devam etmiş olan Prof. Dr. Böke, ilk iki yağlıboya kişisel resim sergisini Hacettepe Üniversitesi Ahmet Göğüş Sanat Galerisi'nde 2005 ve 2007 yıllarında, üçüncü kişisel sergisini Arsuz İskender Sayek Evi'nde "Füsun'un Çiçekleri" adıyla ve dördüncü sergisini de 2011 yılında Ankara Elele Sanat Galerisi'nde açmıştır. Prof. Dr. Erkmen Böke, yedi karma sergiye katılmıştır.

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Cover image: Prof. Dr. Erkmen Böke (1939-2014):

He was born in Izmir in 1939. He graduated from Ankara University Faculty of Medicine in 1962. In 1970, he received his General Surgery specialty from Heidelberg University, Germany. After returning to Turkey, General Surgeon at Hacettepe University in 1970, also in 1973, took/finished the Thoracic and Cardiovascular Surgery Specialty. He was appointed Associate Professor in 1976 and Professor in 1982 at the same university. Between 1982-1988, he worked as the Chief Physician of Hacettepe University Hospitals. Speaking German and English, Prof. Dr. Böke is married and has two children.

Prof. Dr. Böke opened his first two personal oil painting exhibitions at Hacettepe University Ahmet GÖĞÜŞ Art Gallery in 2005 and 2007, the third one at the Arsuz İskender Sayek House under the name "Flowers of FÜSUN" and the fourth one at the Ankara Elele Art Gallery in 2011. Prof. Dr. Erkmen Böke participated in seven group exhibitions.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Medical Biochemistry / Tıbbi Biyokimya

Calculation of Measurement Uncertainty of 20 Clinical Chemistry Analytes According to the Practical ISO Approach

Abdulkadir Çat[1], Kamil Taha Uçar[2]

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ABSTRACT

Purpose: Measurement Uncertainty (MU) is a valuable tool for evaluating analytical performance and interpreting results in clinical laboratories. The International Organization for Standardization (ISO) has proposed a practical approach for MU calculation in its ISO/TS 20914:2019 guide. This study aimed to calculate the MU values of 20 clinical chemistry analyses per the ISO guideline and compare them with the Maximum expanded allowable measurement uncertainty (MAU) values.

Methods: The study was performed using long-term imprecision (uRw) obtained from 6-month internal quality control (IQC) values, and calibrator uncertainty (ucal) in line with the recommendations of the ISO/TS 20914:2019 guideline. The pooled MU value was calculated for 20 clinical chemistry tests on two identical devices, Roche Cobas 6000 c501 (Roche Diagnostics, Mannheim, Germany) analyzers. The calculated MU values for the tests were compared with the current MAU values in the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Biological Variation database (the current Clinical Laboratory Improvement Amendments/CLIA recommendation for Ethanol has been selected).

Results: MU values for Alanine aminotransferase, C-reactive Protein, Iron, Ethanol, Total Bilirubin, Triglyceride, and Blood urea nitrogen remained within the MAU limits. The MU values of the other 13 tests (excluding Aspartate aminotransferase, Glucose, and Potassium Level 2 IQC) exceeded the MAU values.

Conclusion: It was observed that the uRw value affected the MU value the most. Close monitoring and evaluation of uRw and thus IQC and implementation of corrective and preventive actions may reduce MU.

Keywords: Measurement uncertainty, internal quality control, quality management, laboratory medicine, clinical chemistry

Abdulkadir ÇAT
Kamil Taha UÇAR

20 Klinik Biyokimya Analitinin pratik ISO yaklaşımına göre ölçüm belirsizliği hesaplaması

ÖZET

Amaç: Ölçüm belirsizliği (MU), klinik laboratuvarlarda analitik performansın değerlendirilmesi ve sonuçların yorumlanması için değerli bir araçtır. The International Organization for Standardization (ISO), ISO/TS 20914:2019 kılavuzunda MU hesaplaması için pratik bir yaklaşım önermiştir. Bu çalışmada ISO kılavuzu doğrultusunda 20 klinik kimya analizinin MU değerlerinin hesaplanması ve İzin verilebilir genişletilmiş ölçüm belirsizliği değerleri (MAU) değerleriyle karşılaştırılması amaçlanmıştır.

Yöntemler: Çalışma ISO/TS 20914:2019 kılavuzu önerileri doğrultusunda, 6 aylık iç kalite kontrol (İKK) değerlerinden elde edilen uzun vadeli belirsizlik bileşeni (uRw) ve kalibratör belirsizliği (ucal) kullanılarak gerçekleştirilmiştir. İki özdeş cihaz olan Roche Cobas 6000 c501 (Roche Diagnostics, Mannheim, Almanya) analizörleri üzerinden 20 klinik kimya testi için ortak MU değeri hesaplanmıştır. Testler için hesaplanan MU değerleri The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Biyolojik Varyasyon veri tabanındaki güncel MAU değerleriyle (Etanol için güncel Clinical Laboratory Improvement Amendments/CLIA önerisi seçilmiştir) kıyaslanmıştır.

Sonuçlar: Alanin aminotransferaz, C-reaktif Protein, Demir, Etanol, Total Bilirubin, Trigliserid ve Kan üre nitrojeni için MU değerleri MAU sınırları içerisinde kalmıştır. Diğer 13 testin MU değerleri (Aspartat aminotransferaz, Glukoz ve Potasyum Level 2 IQC hariç) MAU değerlerini aşmıştır.

Sonuç: MU değerini en fazla uRw değerinin etkilediği görülmüştür. uRw'nin dolayısıyla İKK'nın yakın takibi, değerlendirilmesi ve düzeltici önleyici faaliyetlerin uygulanması MU'nun azaltılabilmesini sağlayabilir.

Anahtar kelimeler: Ölçüm belirsizliği, iç kalite kontrol, kalite yönetimi, laboratuvar tıbbı, klinik biyokimya

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Analysis results performed in clinical laboratories play a critical role in the patient's diagnosis, treatment, monitoring, and risk assessment. Therefore, there is a need for precise and accurate routine measurements that can ensure the reliability of the measurement result and the appropriate treatment for the patient (1). Total error (TE) is the first approach to evaluate measurement reliability and accuracy. TE consists of a combination of random and systematic errors and indicates the deviation of the measured value from the exact value (2). Based on these error components, Westgard et al. formulated the TE value as the absolute value of the measured bias plus 2 standard deviations (3). The TE concept requires knowing the exact value of the measurement results; otherwise, the TE cannot be calculated. Another approach to the assessment of measurement accuracy, the concept of measurement uncertainty (MU), is expressed as a non-negative parameter associated with the result of the measurement, which characterizes the distribution of values that can reasonably be attributed to the measurement (2). MU assumes that the exact value of the test results cannot be known, and the lack of a fully accurate value of the results is highlighted (1). MU indicates the range in which the measurable value is determined and that the measurement of values in this range can occur with the same probability for that analyte (4). As with the TE concept, the MU concept requires comparison with allowable analytical performance specifications (APS) to determine whether a result deviates significantly from accuracy (5). International accreditation bodies such as The International Organization for Standardization (ISO), Joint Committee for Guides in Metrology (JCGM), and The International Laboratory Accreditation Cooperation (ILAC) state that the MU values of test results should be evaluated appropriately in routine laboratory practices (6–8).

Many factors can contribute to the MU value, including matrix effects, interferences, environmental factors, uncertainties from reference materials, the uncertainty of commercial system calibrators, and measurement uncertainty methods and procedures (9). Literature data points to two models in the approaches that can be used to estimate measurement uncertainty. The first is the bottom-up model proposed by JCGM (6). In this model, all potential sources of uncertainty that significantly affect the outcome for a given measurement procedure (e.g., calibration, weighing, pipetting, temperature, and instrument fluctuations) are identified, and the uncertainty of each is considered. However, this model is unsuitable for use in routine laboratory medicine, as it is necessary to identify a large number of sources and use complex mathematical models (1). The other model is the top-down approach, where measurement uncertainty is calculated from internal and external quality control data or method verification data (10). A practical approach to MU calculation is proposed in conjunction with the ISO/TS 20914:2019 guide. According to this guideline, it is recommended to calculate the MU value mainly based on long-term imprecision (uR_w) and calibrator uncertainty (u_{cal}) and add the bias (u_{bias}) to the MU calculation only in cases where it creates a significant medical difference (9).

This study aimed to compare the MU values of the biochemistry parameters studied in two identical devices of the same brand and model in our laboratory, based on the ISO/TS 20914:2019 guideline, with the allowable analytical performance specifications and is to evaluate the impact of results on possible clinical decisions over clinical decision thresholds.

MATERIAL AND METHOD

This retrospective and single-center study was approved by the Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (Decree Date and No: 22 December 2021/393) and was conducted per the Declaration of Helsinki principles.

We calculated the MU values in line with the "Combined standard uncertainties and expanded uncertainties ISO/TS 20914:2019" guideline (9). We determined the definitions of the quantities for 20 clinical chemistry analytes from which MU values were to be calculated (Table 1). The analysis was carried out using two identical (A and B measurement systems) Roche Cobas 6000 c501 (Roche Diagnostics, Mannheim, Germany) biochemistry auto analyzer and the manufacturer's original reagents in the Medical Biochemistry Laboratory of Gaziosmanpaşa Training and Research Hospital.

Table 1. Measurands Definitions

Test (Abbreviations)	Method	Sample type
Albumin (Alb)	Bromocresol green colorimetric method	Serum
Alanine aminotransferase (ALT)	IFCC method without pyridoxal phosphate activation	Serum
Amylase (Amy)	IFCC method, enzymatic colorimetric	Serum
Aspartate aminotransferase (AST)	IFCC method without pyridoxal phosphate activation	Serum
C-reactive protein (CRP)	Immunoturbidimetric method with expanded particle surface	Serum
Iron (Fe)	Ferrozine colorimetric method	Serum
Ethanol (EtOH)	Enzymatic method with alcohol dehydrogenase	Serum
Glucose (Glu)	Enzymatic hexokinase, colorimetric method	Serum
HDL - Cholesterol (HDL-C)	Homogeneous enzymatic colorimetric method	Serum
Calcium (Ca)	Colorimetric method, o-cresolphthalein complex	Serum
Chloride (Cl)	Indirect method using ion-selective electrodes	Serum
Creatinine (Crea)	Jaffe kinetic colorimetric method	Serum
Potassium (K)	Indirect method using ion-selective electrodes	Serum
Sodium (Na)	Indirect method using ion-selective electrodes	Serum
Total Bilirubin (T.Bil)	Diazo method	Serum
Total Cholesterol (Cholesterol)	Enzymatic colorimetric method	Serum
Total Protein (TP)	Colorimetric	Serum
Triglyceride (TG)	Enzymatic colorimetric	Serum
Blood urea nitrogen (BUN)	Kinetic test with urease and glutamate dehydrogenase	Serum
LDL- Cholesterol (LDL-C)	Homogeneous enzymatic colorimetric method	Serum

Calculations

Standard deviation (SD), which measures the distribution of values obtained from precision studies under long-term precision conditions, is called standard uncertainty (u) in measurement uncertainty calculations (SD = u). To estimate the overall (combined) uncertainty of the result, it is necessary to combine values from different uncertainty sources. According to the ISO/TS 20914:2019 guideline, under long-term precision conditions, which contribute to uncertainty in the calculation of u(y) of the Y analyte measured in the laboratory, the uncertainty of the measurement procedure (uR_w), the uncertainty of the value assigned to the calibrator (u_{cal}) and the uncertainty (u_{bias}) of the bias from the specified value are combined (Formula 1). We calculated the uRw component of uncertainty based on the last six months' internal quality control (IQC) results of normal and pathological control materials studied in the auto analyzer (PreciControl ClinChem Multi 1 Lot no: 47572405, 46149001 and 49417305; PreciControl ClinChem Multi 2 Lot no: 46159701, 46160304 and 46160305, Roche Diagnostics, Mannheim, Germany). We included the ucal values in the calculations per the manufacturer's declaration. We did not add the ubias component to the uncertainty calculation as no medically significant bias was observed. Because the mean values of the different IQC lots differ from each other, we calculated the pooled average uRw over three different lots (Formula 2).

$$u(y)=\sqrt{(uR_w^2 + u_{cal}^2 + u_{bias}^2)} \text{ (Formula 1).}$$

$$\text{Pooled average } uR_w(\text{lot1, lot2, lot3}) = \frac{\sqrt{(u^2\text{-}1+u^2 2+u^2 3)}}{3} \text{ (Formula 2).}$$

Since it is not known in advance which measurement system the samples will be studied in laboratories with more than one identical device, it is recommended to calculate a single pooled average standard uncertainty [u(pooled)] that can be applied to two devices. We calculated the means $\dot{x}$(A), $\dot{x}$(B), $\dot{x}$(A, B) and variances uR_w^2(A), uR_w^2(B), uR_w^2(A, B) for each measurement system from the IQC data used on two identical instruments A and B in our laboratory. We then calculated the variance u^2(A, B) of the two mean values between the two measurement systems (Formula 3). For u(pooled) calculation, we combined u^2(A, B) and uR_w^2(A, B) (Formula 4). For a single u(y) value, the u(pooled) value could now be combined with u_{cal} and u_{bias} (in the case of a medically significant bias) (Formula 1).

$$\text{Variance } SD^2(A, B) = u^2(A, B) = [\sum \dot{x}\text{- } \dot{x}\ (A, B)]/(n\text{-}1) \text{ (Formula 3).}$$

$$u(\text{pooled}) = \sqrt{(u^2(A, B) + uR_w^2(A, B))} \text{ (Formula 4).}$$

We calculated the expanded uncertainty (U) by multiplying the calculated u(y) value for each analyte with k (coverage factor) and the percentage relative expanded uncertainty value ($\%U_{rel}$) according to the mean value (Formulas 5 and 6). We set the k value as 2 to represent the 95% confidence interval.

$U(y) = 2 \times u(y)$ (Formula 5).

$$\%U(y)\ \text{rel} = \frac{(U(y))}{\text{mean}} \times 100 \text{ (Formula 6).}$$

We obtained maximum expanded allowable measurement uncertainty (MAU) targets by selecting desirable targets from The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Biological Variation database for tests other than ethanol (11). We determined the MAU value for ethanol as 20%, which is the current acceptance limit of Clinical Laboratory Improvement Amendments (CLIA) (12). Microsoft Office 365 (Microsoft Excel Software, Microsoft Corporation, US) was used to perform the calculations and create the tables.

RESULTS

The $\%U_{rel}$ (pooled) values of two identical devices for ALT, CRP, Fe, EtOH, T. Bil, TG, and BUN remained within the MAU values. The $\%U_{rel}$ (pooled) values of the two identical devices for AST, Glu, and K remained within the MAU values only for Level 2 IQC. The $\%U_{rel}$ (pooled) values of two identical devices for the other ten tests exceeded the MAU values for both levels (Table 2). u^2 (A, B), u^2R_w (A, B), u^2cal, $u(y)$ (A, B), $\%U_{rel}$ (pooled), and MAU values calculated for two identical devices are presented in Table 2. The IQC control number (n), %CV, u^2R_w, u^2_{cal}, $u(y)$, and $\%U_{rel}$ values of all tests on both devices can be found in Supplemental Tables 1 and 2.

DISCUSSION

The present study revealed that the MU values calculated for only 7 of the 20 clinical biochemistry analytes (ALT, CRP, Fe, EtOH, T. Bil, TG, and BUN) remained within the MAU values. When we reviewed the MU components, we determined that the uRw values obtained from the internal quality control studies were the biggest contributors to the combined standard uncertainty. Similar to our study, uRw appears as a basic component in current MU approaches (9,13). Hence, it is of great importance to evaluate the IQC, follow up on inappropriate results, and take corrective and preventive actions.

Keeping MU values within as a narrow range as possible means producing quality and reliable test results suitable for patient care. Although it is not obligatory to present MU values in laboratory result reports, laboratories must have MU information about the tests to inform clinicians upon their request. For example, if the clinician has a request for MU for a patient with a glucose value of 120 mg/dl (U_{rel}=10%), the possible options for reporting MU would be 120±12 mg/dl, 120 mg/dl ±10% or 120 mg/dl (108 – 132 mg/dl) (k=2, 95% CI) (9,14).

The MU calculation we made for glucose in our study revealed the $\%U_{rel}$ (pooled) values, including identical A and B measurement systems in our laboratory, as 10.4% and 4.2% for IQC-1 and 2, respectively. We determined that the MU we calculated for the IQC-2 met the targeted quality specification (5%), but the MU value for the IQC-1 material exceeded the allowable targets. Measurement of blood glucose plays a central role in the diagnosis and follow-up of diabetes and the assessment of organ damage risks due to glucose metabolism disorders (15). Therefore, clinicians expect accurate and reliable glucose results to be provided with the highest level of consistency with the clinical condition. In this context, evaluating MU together with test results can help clinicians interpret patient results to understand whether a glucose test result measurably exceeds the medical decision limit.

The present study found the $\%U_{rel}$ (pooled) values for creatinine to be 11.9% and 7.6% for IQC-1 and 2, respectively. We determined that the MU values did not meet the allowable quality specification (4.5%). It was demonstrated that very small changes in serum creatinine concentrations, widely used for diagnosing and treating kidney diseases, are directly related to the severity of acute kidney injury (16,17). Therefore, knowing with what uncertainty the creatinine test result is measured will make valuable contributions to the proper management of acute kidney injury. Also, we saw that $\%U_{rel}$ (pooled) values for Na, K, and Cl remained outside the MAU (0.5%, 4.1%, and 1.1% for Na, K, and Cl, respectively). These ions are tightly controlled by metabolic and renal mechanisms (5). In particular, the K value may change due to the drugs used, and for this reason, close follow-up is recommended in terms of both its effect on the cardiac system and the evaluation of renal functions (15). Keeping the MU values of these tests within the allowable range may benefit clinicians in managing diseases.

Table 2. Within-laboratory precision, calibration uncertainty and percent relative expanded uncertainty values of two identical devices calculated according to ISO guideline

Test	Material	u^2(A,B)	u^2R_w(A,B)	u^2cal	U(y) (A,B)	U_{rel}% (pooled) (k=2)	MAU(%)
Alb	IQC-1 (A,B)	0,02	1,8939	0,0882	1,42	**8,65**	2,5
	IQC-2 (A,B)	0	3,0553	0,0882	1,77	**7,01**	
ALT	IQC-1 (A,B)	0,005	3,7445	0,1018	1,96	8,29	10,1
	IQC-2 (A,B)	0,08	15,2767	0,1018	3,93	6,36	
Amy	IQC-1 (A,B)	0,845	40,639	0,49	6,48	**16,15**	6,6
	IQC-2 (A,B)	0,5	84,013	0,49	9,22	**9,78**	
AST	IQC-1 (A,B)	0,02	4,9199	0,1845	2,26	**9,74**	9,6
	IQC-2 (A,B)	0,08	25,1047	0,1845	5,04	7,03	
CRP	IQC-1 (A,B)	0,005	0,1229	1,051	1,09	22,98	34,1
	IQC-2 (A,B)	0,002	5,5586	1,051	2,57	10,04	
Fe	IQC-1 (A,B)	64,98	3007	164,4	56,89	10,33	20,7
	IQC-2 (A,B)	320	8008,86	164,4	92,16	7,71	
EtOH	IQC-1 (A,B)	0,13	6,6218	1,452	2,86	11,3	20*
	IQC-2 (A,B)	0,18	23,231	1,452	4,99	6,7	
Glu	IQC-1 (A,B)	0,08	27,5749	0,637	5,32	**10,4**	5
	IQC-2 (A,B)	1,445	21,7093	0,637	4,88	4,2	
HDL-C	IQC-1 (A,B)	0,32	1,625	0,3399	1,51	**9,5**	5,8
	IQC-2 (A,B)	1,125	17,1055	0,3399	4,31	**14,2**	
Ca	IQC-1 (A,B)	0,02	0,0901	0,00188	0,34	**7,52**	1,8
	IQC-2 (A,B)	0,045	0,1093	0,00188	0,4	**5,83**	
Cl	IQC-1 (A,B)	0,245	6,9892	0,16	2,72	**6,41**	1,1
	IQC-2 (A,B)	0,125	5,1305	0,0625	2,31	**4,52**	
Crea	IQC-1 (A,B)	0,00005	0,0031	0,00083	0,06	**11,9**	4,5
	IQC-2 (A,B)	0,00005	0,0226	0,00083	0,15	**7,6**	
K	IQC-1 (A,B)	0	0,0111	0,000625	0,11	**6,02**	4,1
	IQC-2 (A,B)	0	0,0157	0,0001	0,13	3,7	
Na	IQC-1 (A,B)	0,02	7,5145	0,16	2,77	**4,92**	0,5
	IQC-2 (A,B)	0,005	5,7189	0,0625	2,401	**3,58**	
T.Bil	IQC-1 (A,B)	0,005	0,0049	0,000337	0,1	19,27	20
	IQC-2 (A,B)	0,02	0,0651	0,000337	0,29	15,8	
Cholesterol	IQC-1 (A,B)	4,81	10,6041	0,4563	3,98	**7,9**	5,3
	IQC-2 (A,B)	12	30,3426	0,4563	6,54	**7,8**	
TP	IQC-1 (A,B)	1,125	4,4217	0,0181	2,36	**9,7**	2,6
	IQC-2 (A,B)	2,645	8,1977	0,0181	3,3	**8,5**	
TG	IQC-1 (A,B)	0,72	12,8189	0,64	3,77	6,3	20
	IQC-2 (A,B)	1,28	34,3906	0,64	6,03	5,7	
BUN	IQC-1 (A,B)	0,5	1,825	0,194	1,59	8,06	13,9
	IQC-2 (A,B)	4,205	11,2289	0,194	3,95	6,9	
LDL-C	IQC-1 (A,B)	2,38	4,41	0,596	2,72	**8,9**	8,3
	IQC-2 (A,B)	3	41,37	0,596	6,71	**13,7**	

Alb – Albumin, ALT – Alanine aminotransferase, Amy – Amylase, AST – Aspartate aminotransferase, CRP – C-reactive protein, Fe – Iron, EtOH – Ethanol, Glu – Glucose, HDL-C – HDL Cholesterol, Ca – Calcium, Cl – Chloride, Crea – Creatinine, K – Potassium, Na – Sodium, T.Bil – Total Bilirubin, Cholesterol – Total Cholesterol, TP – Total Protein, TG – Triglyceride, BUN – Blood Urea Nitrogen, LDL-C – LDL Cholesterol.

Mean (A, B) – Mean of two measurement systems mean values, u^2 (A, B) – variance of two mean values between two measurement systems, u^2Rw (A, B) - standard uncertainty component for the long-term precision obtained from six months' internal quality control, u^2cal - uncertainty of calibrator values provided by manufacturer, U(y) - expanded uncertainty, %Urel (pooled) - percent relative expanded uncertainty, MAU - Maximum expanded allowable measurement uncertainty.

*%Urel (pooled) values exceeding the MAU are indicated in bold. All MAU values obtained from The EFLM Biological Variation Database (11), except EtOH. *The MAU value of EtOH obtained from updated CLIA (Clinical Laboratory Improvement Amendments) Proposed Acceptance Limits (12).*

Supplemental Table 1. MEASUREMENT UNCERTAINTY COMPONENTS OF CLINICAL CHEMISTRY ANALYTES IN ANALYZER A								
Analyte	Material	n	%CV	u^2R_w	u^2cal	u (y)	$\%U_{rel}$ (k=2)	MAU
Alb	IQC-1	177	3,61	1,42	0,0882	1,23	**7,48**	2,5
	IQC-2	175	2,6	1,74	0,0882	1,35	**5,35**	
ALT	IQC-1	175	4,01	3,69	0,1018	1,95	8,23	10,1
	IQC-2	175	3,37	17,81	0,1018	4,23	6,86	
Amy	IQC-1	169	6,83	31,25	0,49	5,63	**13,93**	6,6
	IQC-2	189	4,25	69,22	0,49	8,35	**8,83**	
AST	IQC-1	176	3,73	3,03	0,1845	1,79	7,73	9,6
	IQC-2	175	3,05	19,18	0,1845	4,4	6,15	
CRP	IQC-1	175	3,56	0,11	1,051	1,08	22,91	34,1
	IQC-2	174	4,22	4,67	1,051	2,39	9,32	
Fe	IQC-1	197	4,88	2917,08	164,4	55,5	10,02	20,7
	IQC-2	187	3,7	7896,1	164,4	89,8	7,47	
EtOH	IQC-1	173	5,03	6,55	1,452	2,83	11,1	20*
	IQC-2	175	3,03	2,37	1,452	1,96	2,6	
Glu	IQC-1	176	2,53	6,71	0,637	2,71	**5,3**	5
	IQC-2	175	1,85	18,32	0,637	4,35	3,8	
HDL - C	IQC-1	175	3,17	1	0,3399	1,16	**7,4**	5,8
	IQC-2	173	7,31	17,81	0,3399	4,26	**14,2**	
Ca	IQC-1	180	3,39	0,096	0,00188	0,31	**6,96**	1,8
	IQC-2	177	2,3	0,096	0,00188	0,31	**4,57**	
Cl	IQC-1	414	2,93	6,25	0,16	2,53	**5,94**	1,1
	IQC-2	407	2,2	5,06	0,0625	2,26	**4,42**	
Crea	IQC-1	187	4,52	0,0025	0,00083	0,058	**10,8**	4,5
	IQC-2	183	3,42	0,0196	0,00083	0,143	**7,1**	
K	IQC-1	430	3,18	0,0121	0,000625	0,113	**6,27**	4,1
	IQC-2	416	1,87	0,0169	0,0001	0,13	3,83	
Na	IQC-1	425	2,59	8,53	0,16	2,95	**5,22**	0,5
	IQC-2	411	1,91	6,55	0,0625	2,57	**3,83**	
T.Bil	IQC-1	193	6,46	0,005	0,000337	0,07	13,16	20
	IQC-2	189	6,9	0,068	0,000337	0,26	13,72	
Cholesterol	IQC-1	178	3,06	9,99	0,4563	3,23	**6,3**	5,3
	IQC-2	177	2,95	25,4	0,4563	5,09	**6**	
TP	IQC-1	177	3,09	2,34	0,0181	1,54	**6,22**	2,6
	IQC-2	176	2,63	4,29	0,0181	2,07	**5,27**	
TG	IQC-1	175	3,05	13,18	0,64	3,72	6,3	20
	IQC-2	173	2,56	29,59	0,64	5,5	5,2	
BUN	IQC-1	180	3,52	1,96	0,194	1,47	7,36	13,9
	IQC-2	177	2,96	11,77	0,194	3,46	5,96	
LDL-C	IQC-1	192	4,3	7,07	0,596	2,77	**9**	8,3
	IQC-2	195	5,25	27,23	0,596	5,28	**10,6**	

Supplemental Table-2: MEASUREMENT UNCERTAINTY COMPONENTS OF CLINICAL CHEMISTRY ANALYTES IN ANALYZER B								
Analyte	Material	n	%CV	u^2R_w	u^2cal	u (y)	$\%U_{rel}$ (k=2)	MAU
Alb	IQC-1	177	4,73	2,37	0,0882	1,57	**9,62**	2,5
	IQC-2	178	4,17	4,37	0,0882	2,117	**8,34**	
ALT	IQC-1	176	4,13	3,8	0,1018	1,98	8,34	10,1
	IQC-2	177	2,88	12,75	0,1018	3,58	5,79	
Amy	IQC-1	175	8,44	47,06	0,49	6,9	**17,33**	6,6
	IQC-2	182	5,25	98,8	0,49	9,97	**10,6**	
AST	IQC-1	177	5,52	6,81	0,1845	2,65	**11,35**	9,6
	IQC-2	178	3,85	31,03	0,1845	5,59	7,78	
CRP	IQC-1	178	3,81	0,14	1,051	1,09	22,94	34,1
	IQC-2	179	4,91	6,45	1,051	2,74	10,72	
Fe	IQC-1	211	5,08	3097	164,4	57,11	10,42	20,7
	IQC-2	208	3,79	8122	164,4	91,03	7,66	
EtOH	IQC-1	176	5,37	7,29	1,452	2,96	11,7	20*
	IQC-2	167	4,47	44,09	1,452	6,75	9,1	
Glu	IQC-1	177	6,99	48,44	0,637	7,01	**13,7**	5
	IQC-2	187	2,16	25,1	0,637	5,07	4,4	
HDL - C	IQC-1	174	4,63	2,25	0,3399	1,61	**10**	5,8
	IQC-2	176	6,55	16,4	0,3399	4,09	**13,3**	
Ca	IQC-1	178	3,31	0,08	0,00188	0,29	**6,66**	1,8
	IQC-2	178	2,63	0,12	0,00188	0,35	**5,26**	
Cl	IQC-1	392	3,3	7,73	0,16	2,81	**6,65**	1,1
	IQC-2	374	2,24	5,2	0,0625	2,29	**4,5**	
Crea	IQC-1	194	5,76	0,0036	0,00083	0,07	**12,6**	4,5
	IQC-2	190	4,04	0,0256	0,00083	0,16	**8,1**	
K	IQC-1	400	2,81	0,01	0,000625	0,1	**5,73**	4,1
	IQC-2	383	1,7	0,0144	0,0001	0,12	3,54	
Na	IQC-1	393	2,28	6,5	0,16	2,58	**4,58**	0,5
	IQC-2	379	1,64	4,88	0,0625	2,22	**3,31**	
T.Bil	IQC-1	193	7,3	0,0049	0,000337	0,07	14,47	20
	IQC-2	194	6,88	0,0625	0,000337	0,25	13,93	
Cholesterol	IQC-1	182	3,32	11,22	0,4563	3,42	**6,8**	5,3
	IQC-2	184	3,51	35,28	0,4563	5,98	**7,2**	
TP	IQC-1	189	5,28	6,5	0,0181	2,55	**10,66**	2,6
	IQC-2	190	4,52	12,11	0,0181	3,48	**9,12**	
TG	IQC-1	174	2,95	12,46	0,64	3,62	6,1	20*
	IQC-2	176	2,96	39,18	0,64	6,31	6	
BUN	IQC-1	177	3,34	1,69	0,194	1,37	7,06	13,9
	IQC-2	180	2,88	10,69	0,194	3,3	5,84	
LDL-C	IQC-1	194	2,22	1,752	0,596	1,53	5,1	8,3
	IQC-2	195	7,68	55,5	0,596	7,49	**15,4**	

Alb – Albumin, ALT – Alanine aminotransferase, Amy – Amylase, AST – Aspartate aminotransferase, CRP – C-reactive protein, Fe – Iron, EtOH – Ethanol, Glu – Glucose, HDL-C – HDL Cholesterol, Ca – Calcium, Cl – Chloride, Crea – Creatinine, K – Potassium, Na – Sodium, T.Bil – Total Bilirubin, Cholesterol – Total Cholesterol, TP – Total Protein, TG – Triglyceride, BUN – Blood Urea Nitrogen, LDL-C – LDL Cholesterol.

u^2Rw - standard uncertainty component for the long-term precision obtained from six months internal quality control, u^2cal - uncertainty of calibrator values provided by manufacturer, U(y) - expanded uncertainty, %Urel (y) - percent relative expanded uncertainty, MAU - Maximum expanded allowable measurement uncertainty.

*%Urel values exceeding the MAU are indicated in bold. All MAU values obtained from The EFLM Biological Variation Database, except EtOH. *The MAU value of EtOH obtained from updated CLIA (Clinical Laboratory Improvement Amendments) Proposed Acceptance Limits.*

Lipid metabolism disorders are independent risk factors for developing atherosclerotic cardiovascular diseases (18). Therefore, considering MU may change the way of diagnosis and treatment, especially if the patient's lipid profile is at medical decision levels. Our study found $\%U_{rel}$(pooled) values for LDL-C to be 8.9% and 13.7% for IQC-1 and 2, respectively. We determined $\%U_{rel}$ (pooled) values for HDL-C to be 9.5% and 14.2% for IQC-1 and 2, respectively, and $\%U_{rel}$ (pooled) values for triglyceride as 6.3% and 5.7% for IQC-1 and 2, respectively. We found the $\%U_{rel}$ (pooled) values for total cholesterol to be 7.9% and 7.8% for IQC-1 and 2, respectively. The MU values for triglyceride met the quality target (20%). However, none of the MU values for HDL-C, LDL-C, and Total cholesterol met the allowable quality targets (5.8%, 8.3%, and 5.3% for HDL-C, LDL-C, and Total cholesterol, respectively).

Ethanol analysis, which is one of the tests performed in the forensic toxicology laboratory, significantly affects the status of individuals in terms of clinical and forensic decisions (19). We determined the $\%U_{rel}$ (pooled) values for ethanol as 11.3% and 6.7% for IQC-1 and 2, respectively, and met the quality specification (20%). To ensure the accuracy and reliability of a result measured in a laboratory that measures ethanol, especially within the limits of medical and forensic decisions, giving the test result together with MU can change the shape of the decisions to be taken.

Different results can be obtained in clinical laboratories using different MU models for the same analyte. Using two separate MU calculation models for glucose, Chen et al. found 7.38% and 13.58% values (20). Therefore, laboratories should standardize their MU calculation methods. Recently, Coskun et al. reported that only *u* (SD) value could be used for MU calculation, which would be sufficient for routine clinical laboratory operations (13). This new model, named MU for practical use (MUPU), is a very facilitating tool for laboratories to calculate and evaluate MU. Besides, the authors think that the main component of MU is u value, as seen in our study. However, in this approach, ignoring the ucal value and using a single level (especially normal level) IQC material can be stated as aspects of the MUPU approach that need to be developed (21). Also, there are multiple APS options with which MU values can be compared (22). Recently, MAU values on a BV basis have been published by EFLM (11). Since the most recent recommended MAU values are in the EFLM BV database, we used these values in our study, except for the EtOH test. However, APS options may be different for each laboratory and analyte (23). Therefore, it is thought that laboratories can make APS selections by determining their priorities and considering Milan models (24).

In laboratories using more than one device, the MU values calculated for the same analyte in each device must not exceed the allowable APS values separately to keep the analytical difference between the devices within acceptable limits. However, it is known that the result obtained from the given laboratory can be obtained from different devices. Hence, it is considered that the *u* (pooled) calculation suggested by the ISO/TS 20914:2019 guide will be more useful in terms of evaluating the effect of MU on the reported results. However, the *u* (pooled) value will be higher or lower than the individual *u* values of the devices. This is one of the problems with reporting MU with results because the MU value calculated over u (pooled) will not fully reflect the analytical performance of the instruments. Since there are two identical devices in our laboratory in our study, we evaluated over *u* (pooled) per the recommendation of the ISO guideline, but it should not be overlooked that we calculated the *u* (pooled) value when evaluating the results of this study. For example, in our study, the MU value of the LDL-C test in the 1st device was calculated as 5.1% and in the 2nd device as 9%. The MU value of the two devices was calculated as 8.9%, and it was observed to exceed the MAU value of 8% (Supplemental Table 1-2). For all these reasons, we think that the MU and MAU evaluation can be used mainly to evaluate the analytical performance of the devices and that we are just at the beginning of the way in adding the MU values calculated from identical devices to the result reports.

CONCLUSION

The present study demonstrated that the component with the most significant effect on the MU value was the uR_w value. To solve this problem, it may be suggested to follow the IQC values of the relevant method more closely and to change the calibration frequency. With the help of MU, laboratories can reliably monitor their analytical performance. By knowing the MU concept, clinicians can accurately perceive the measurement result and provide reliable patient care. Therefore, we hypothesize that understanding the MU concept and adapting it to routine laboratories may increase the reliability of the results.

DECLARATIONS

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Conflicts of Interest: The authors declare no conflict of interest.

Ethics Approval: All protocols for this study were approved by the Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (Decree Date and No: 22 December 2021/393)

Availability of Data and Material: All data is available.

Authors' Contributions: Establishing the main idea and hypothesis of the study: A.Ç.; Developing the hypothesis and designing the materials and methods section: A.Ç. and K.T.U.; Evaluation of data: A.Ç. and K.T.U.; Writing the draft of the article: A.Ç. and K.T.U..; Assessing the final version of the article and making necessary corrections: A.Ç. and K.T.U.

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In Silico Studies and *In Vitro* Microsomal Metabolism of Potent Metap2 Inhibitor And *In Vivo* Tumor Suppressor for Prostate Cancer: A Thioether-Triazole Hybrid

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ABSTRACT

Background/aim: The *in vitro* microsomal metabolism of (*S*)-3-((2,4,6-trimethylphenyl)thio)-4-(4-fluorophenyl)-5-(1-(6-methoxynaphtalene-2-yl)ethyl)-4*H*-1,2,4-triazole (SGK636), an anticancer drug candidate was studied using pig microsomal preparations fortified with NADPH to identify the potential *S*-oxidation and *S*-dealkylation metabolites.

Materials and methods: In the present study, the sulfoxide metabolite was synthesized, purified and characterized by chromatographic and spectroscopic methods. SGK636, the *S*-oxidation and *S*-dealkylation metabolites were then separated by a reversed phase LC-MS, with UV detection and with an HP-TLC system. The results from the in-vitro microsomal metabolic experiments showed that SGK636 produced the corresponding *S*-oxidation metabolite (sulfoxide) which was observed by LC-MS, LC-MS/MS and HP-TLC with the identical Rt and Rfx100 values and UV/MS spectra in comparison with the authentic compounds, but no any *S*-dealkylation metabolite was detected.

Results: The present results were proved with molecular docking and molecular dynamic studies. Since sulfoxidation process can be reversible and it may partly explain the low amount of sulfoxide metabolite in our experiment, we also incubated the sulfoxide. No conversion back to the substrate (SGK636) was observed, but it produced the corresponding sulphone metabolite. In order to establish if SGK636 is autooxidized, the substrate was also incubated in buffer under standard incubation conditions, but no any autooxidation was observed into the corresponding sulfoxide. We also did a stability work for SGK636-SO (sulfoxide) in buffer to see any possible autooxidation to sulfone or reduction back to SGK636. No conversion was observed in either way. The substrate seems to be stable to metabolic reactions and to autooxidation which could be an advantage in terms of its pharmacological activity.

Conclusion: The present metabolic study indicates that SGK 636 underwent *S*-oxidation. In order to identify the responsible oxidative enzyme, molecular docking and molecular dynamic studies were performed. CYP3A4 was found to be responsible enzyme for *S*-oxidation.

Keywords: *S*-oxidation, *in vitro* metabolism, thioether, 1,2,4-triazole, Naproxen

Bir Tiyoeter-Triazol Hibriti: Güçlü MetAP2 Inhibitörü ve Prostat Kanseri için *In Vivo* Tümör Baskılayıcı Bileşiğin *In Silico* Çalışmaları ve *In Vitro* Mikrozomal Metabolizması

ÖZET

Arka plan/amaç: Antikanser bir ilaç adayı bileşik olan (*S*)-3-((2,4,6-trimetilfenil)tiyo)-4-(4-florofenil)-5-(1-(6-metoksinaftalen-2-)il) etil)-4*H*-1,2,4-triazol (SGK636), bileşiğinin in vitro mikrozomal metabolizması çalışılmış ve potansiyel *S*-oksidasyon ve *S*-dealkilasyon metabolitlerini belirlemek için NADPH ile güçlendirilmiş domuz mikrozomal preparatları kullanılarak incelenmiştir.

Gereç ve Yöntemler: Bu çalışmada, sülfoksit metaboliti kromatografik ve spektroskopik yöntemlerle sentezlenmiş, saflaştırılmış ve karakterize edilmiştir. SGK636, *S*-oksidasyon ve *S*-dealkilasyon metabolitleri daha sonra ters fazlı bir LC-MS, UV spektroskopisi ve bir HP-TLC sistemi ile ayrılmıştır. *In vitro* mikrozomal metabolik deneylerin sonuçları, SGK636'nın, aynı Rt ve Rfx100 değerleri ve UV/ ile LC-MS, LC-MS/MS ve HP-TLC tarafından gözlemlenen karşılık gelen *S*-oksidasyon metabolitini (sülfoksit) ürettiğini göstermiştir. Otantik bileşiklerle karşılaştırıldığında MS spektrumlarında, herhangi bir *S*-dealkilasyon metaboliti tespit edilmemiştir.

Bulgular: Mevcut sonuçlar moleküler doking ve moleküler dinamik çalışmalarla kanıtlanmıştır. Sülfoksidasyon işlemi tersine çevrilebilir olduğundan ve deneyimizdeki düşük miktarda sülfoksit metabolitini kısmen açıklayabildiğinden, sülfoksit bileşiği de inkübe edilmiştir. Substrata (SGK636) geri dönüşüm gözlenmemiş olup, karşılık gelen sülfon metabolitinin oluştuğu gözlenmiştir. SGK636'nın otooksidize olup olmadığını belirlemek için substrat ayrıca standart inkübasyon koşulları altında tampon içinde inkübe edilmiştir, ancak karşılık gelen sülfoksitte herhangi bir oto-oksidasyon gözlenmemiştir. Sülfona herhangi bir olası otooksidasyonu veya tekrar SGK636'ya indirgemeyi görmek için tampondaki SGK636-SO (sülfoksit) için bir stabilite çalışması da yapılmıştır. Her iki şekilde de dönüşüm gözlemlenmemiştir. Substrat, farmakolojik aktivitesi açısından bir avantaj olabilecek metabolik reaksiyonlara ve otooksidasyona karşı kararlı görünmektedir.

Sonuç: Mevcut metabolik çalışma, SGK 636'nın *S*-oksidasyonuna uğradığını göstermektedir. Sorumlu oksidatif enzimi belirlemek için moleküler yerleştirme ve moleküler dinamik çalışmalar yapılmıştır. CYP3A4'ün *S*-oksidasyonundan sorumlu enzim olduğu bulunmuştur.

Anahtar kelimeler: S-oksidasyon, *in vitro* metabolizma, tiyoeter, 1,2,4-triazol, Naproksen.

Sulphur containing molecules provide a wide range of place in medicinal chemistry. Many drug molecules carry sulphur atom and some of them show their pharmacological activities depending of sulphur structure. One of the most commonly known drugs in this area are organophosphates. As they show their activity by acetylation of acetyl co-esterases, the metabolic inactivation of these compounds mostly depends on *S*-oxidation or desulphuration (1). Thioethers (or sulfides) can be included in a variety of drugs and potential drug candidates are designed with this group as an isostere of ethers. Phase I reactions are *S*-oxygenation to sulfoxide and sulfones and *S*-dealkylation although the latter is a minor metabolic dealkylation reaction compared to the *N*- or *O*-analogues. Sulfoxide reduction back to the parent sulfide is also possible. The conversion of sulfide to sulfoxide is important in terms of potential pharmacological and toxicological changes in activity (2). Chlorpromazine sulfoxidation is catalyzed by P450 dependent monooxygenases whereas *S*-oxygenation of H2 receptor blockers cimetidine, albendazole, ranitidine, and sulindac is catayzed by flavin containing monooxygenases (3). Sulfoxidation is reported as minor metabolic pathway for the urinary rat metabolism of H2 receptor blockers cimetidine, ranitidine and nizatidine (4). Earlier studies on sulphur containing compounds were performed by using computational studies with density functional theory. The metabolic profile of dimethylsulfoxide (DMSO) and dimethylsulfide (DMS) was recorded accordingly. As the ability of oxidation and dealkylation reactions high in cytochrome P450 enzyme family, it many times depends on the compound's certain functional groups. The computitonal studies identify the most favorable reaction pathway in sulphur carrying model molecules. It was also observed that *S*-oxidation is more preferred than *S*-dealkylation by the experimental and computational studies on DMSO and DMS (5). Another study showed the metabolic profile of a sulindac derivative in different species both in mouse and human. It was observed that phospho-sulindac amide undergoes hydroxylation reaction to form di-hydroxyl-phospho-sulindac amide and mono-hydroxyl-phospho-sulindac amide. Further investigations with mouse and human liver microsomes showed that phospho-sulindac amide is oxidized or reduced. The oxidation and reduction reactions were observed with the formation of sulfone and sulfide derivatives of phospho-sulindac amide respectively (6). The metabolic pathway from sulfoxide to sulphide has been used on a common non-steroidal anti-inflammatory pro-drug, Sulindac. Sulindac has no cyclooxygenase I (COX-1) or cyclooxygenase II (COX-2) inhibitory activity. However, it undergoes a reversible reduction reaction via biotransformation. The active form of this drug is a thioether derivative (sulindac sulfide). Sulindac also undergoes *S*-oxidation resulting with the formation of a sulfone metabolite which has also no inhibitory activity against COX-1 and COX-2 isoenzymes (7). Limited studies are available related to thioether metabolism in the literature. In these studies, the enzymatic profile of sulphur containing compounds were mentioned. As cytochrome P450 enzyme family plays a vital role in human and animal metabolism, some studies hold flavin monooxyganase responsible for sulfoxide formation. Li and co-workers reported that Compound I (Cpd I) from iron–oxo porphyrin species is responsible for sulfoxide formation (8).

The synthesis and anticancer profile of some thioether containing drug candidate molecules were studied in our previous experiments. As prostate cancer is the second highest incidence of cancer among men, our previous study focused on (*S*)-Naproxen ((+) (*S*)-2-(6-methoxynapthalene-2-yl)propanoic acid) derivatives. It is an active substance that has been reported to have anticancer activities in recent years (9-13). In addition, researchers have reported anticancer activities of Naproxen derivatives in prostate and breast cancer (14-20). On the other hand, many studies have been conducted on compounds containing thioether structures, have anticonvulsant, antidepressant, antimalarial, antiviral, vasodilator, antimicrobial, antiurease and antitumoral activities (19, 21-33). In the light of this information, Birgül and co-workers studied the thioether derivative of Naproxen (16). SGK636 exhibited the best anticancer activity among the tested molecules. The compound showed no toxic profile on the healthy cells, it was found to be valuable to undergo further research in terms of metabolic profile. Our previous work indicated the *in vitro* metabolic profile of some active molecules (34-36). In-vitro and in-vivo metabolic studies are needed to identify the potential metabolites of thioether structures with potential pharmacological activity. In the present work, we therefore planned to study SGK636's in-vitro hepatic microsomal metabolism to observe if it is converted to any *S*-oxidation or dealkylated metabolites. We have performed the synthesis of authentic *S*-oxide metabolic standard of compound SGK636 and elucidated its structure by using spectroscopic methods. This paper also presents for the first time a rapid and simple method for the determination of metabolites using HP-TLC.

MATERIALS AND METHODS

SGK636 and authentic triazole metabolic standard (DT) were previously prepared (16). In the present study, SGK636-SO was synthesized as described later in the text. *m*-Chloroperoxybenzoic acid (*m*-CPBA) and all other chemicals were purchased from Sigma Aldrich and Merck. Melting point was recorded on a Stuart SMP50 Automatic Melting Point apparatus and uncorrected. The structure of SGK636-SO were confirmed by FT-IR, LC-MS, LC-MS/MS spectra and elemental analysis. FT-IR analysis were performed with Thermo Scientific Nicolet IS10 device. LC-MS separation of SGK636, DT and SGK636-SO (authentic standards) were performed by an Agilent 1260 Infinity II LC-MS chromatographic system comprised of a G7115A 1260DAD WR detector, a G7311B 1260 Quad Pump system, a G1328C 1260 Manual Injection unit and a G6125B LC/MSD detector. An ACE C18 column was used as a stationary phase. LC-MS/MS analysis for standards and test extracts were performed in an Agilent 1640 series HPLC system equipped with online degasser, a binary pump, an autosampler, and column oven and interfaced to an Agilent 6460A triple-quadrupole mass spectrometer equipped with an electrospray ionization source (Agilent Technologies, Santa Clara, USA). All raw data were acquired and analyzed using Agilent Masshunter data processing software. A Camag Automatic Developing Chamber (ADC-2) device was used for HP-TLC studies. Densitometric scanning was performed in fluorescence mode using Camag TLC Scanner IV and Vision CATS software after derivation.

Adult male Suffolk white pig was used in this study. ß-Nicotinamide dinucleotide phosphate (disodium salt, NADP) and glucose-6-phosphate (disodium salt, G-6-P) were purchased from Sigma. Glucose-6-phosphate dehydrogenase suspension (Reinheit grade II, 10 mg per 2 ml; G-6-PD) was obtained from Sigma Aldrich. Dichloromethane was obtained from Merck.

Experimental

Synthesis

S-oxide (SGK636-SO) ((*S*)-3-((2,4,6-trimethylphenyl) thioxo)-4-(4-fluorophenyl)-5-(1-(6-methoxynaphtalen-2-yl)ethyl)-4*H*-1,2,4-triazole): To synthesize the authentic *S*-oxide, the substrate (SGK636, 0.001 mol) was dissolved in ethanol (20 ml) and *m*-chloroperoxybenzoic acid (*m*-CPBA, 0.0012 mol) was added dropwise in an ice bath (0-5 °C). The mixture was stirred for 4 hours and the reaction was monitored by TLC. After the reaction completed, ethanol was evaporated under atmospheric pressure and the solid was extracted with dichloromethane/water mixture. The organic phase was evaporated. The solid product was further purified by column chromatography. M.p 168-170°C. FT-IR υmax (cm^{-1}): 3065 (C-H), 1605 (C=N), 1391 (S=O). MS (vAPCI): (M+1) 528.5; 520.6; 353.7; 342.9; 338.3; 327.3. Elemental analysis: $C_{31}H_{30}FN_3O_2S$ Calculated: 67.94 (C%); 5.98 (H%); 6.69 (N%); 5.01 (S%). Found: $C_{31}H_{30}FN_3O_2S$. C_2H_5OH 67.21 (C%); 6.15 (H%); 7.13 (N%); 5.44 (S%). LCMS: (M+1) 528.2

LC-MS Analysis

An acetonitrile (ACN)/water (70/30, v/v) mobile phase mixture was used. The substrate and metabolic standards were separated according to their mass/charge ratio and their molecular ion peaks were determined in the mass spectroscopy section and the retention times (Rt) of the substrate and metabolic standards were recorded. A DAD detector was also used to compare UV spectra of standard and metabolic products.

LC-MS/MS analysis

An acetonitrile (ACN) (100%) mobile phase was used. The substrate and the *S*-oxide metabolic standard were directly applied to triple-quad mass spectrometer. The substrate (SGK 636), *S*-oxide metabolic standard (SGK-636-SO) and incubation extract were analyzed according to their mass/charge ratio. Their molecular ions and fragmentations were recorded.

HP-TLC Analysis

The standard compounds (1mg/ml) were prepared in methanol. Each prepared solution was filtered through a 0.45 µm syringe filter except the incubates. The sample and standard solutions were applied in bands of 8 mm length on silica gel glass HP-TLC plates 60 F_{254} with Camag Automatic TLC Sampler IV. A constant application rate was performed, and the gaps between the tracks were 10 mm. The mobile phase was petroleum ether/dichlorometane/ethyl acetate (25:50:25 v/v/v) at 25°C. The chamber was saturated for 20 min, and the plate was pre-conditioned for 5 min before the development. The humidity is controlled by ADC-2 using $MgCl_2$ (33% RH) for 10 minutes. Densitometric scanning was performed in fluorescence mode using Camag TLC Scanner IV and Vision CATS software after derivation. The slit size was kept at 5×0.2 mm, the micro and scan speeds were set at 20 mm/s.

Biological Studies

The animals were deprived of food overnight prior to sacrifice, but were allowed water ad libitum. They were previously fed on a balanced diet. Hepatic washed pig microsomes were prepared as described by Schenkman and Cinti (37) and Ulgen (38).

Incubation and Extraction Procedures

Incubations were carried out in a shaking water bath at 37°C using a standard co-factor solution consisting of NADP (2 µmole), G-6-P (10 µmole), G-6-PD suspension (1 unit) and aqueous $MgCl_2$ (50% w/w) (20 µmole) in phosphate buffer (0.2M, pH 7.4, 2 ml) at pH 7.4. Co-factors were pre-incubated for 5 min to generate NADPH, before the addition of microsomes (1 ml equivalent to 0.5 g original liver) and substrate (5 µmole) in methanol (50 µl). Briefly, seven test tubes were prepared (3 for test, 4 for controls) and co-factors (2ml in each tube), microsomal fraction (1 ml for each tube) and substrate (50 µl for each tube) were added respectively. The incubation was continued for 30 min, terminated and extracted with dichloromethane (3x5 ml). The organic extracts were evaporated to dryness under a steream of nitrogen (3).The residues were reconstituted in methanol (200 µl) for LC-MS and LC-MS/MS. The reconstituted extracts were analysed using the reverse-phase LC-MS system described in the text. Test extracts were further investigated in LC/MSMS. For HPTLC studies, these samples (dissolved in 50 µl metanol per sample) were also analysed using HPTLC equipment.

Autooxidation Studies

Either the substrate (2 µM) (SGK636) or authentic *S*-oxide standard (SGK636-SO) (2 µM) was dissolved in methanol (50 µl). Then, phosphate buffer (0.2 M, pH 7.4) (3ml) was added in the same incubation conditions as test experiments. The incubation was continued for 30 min, terminated and extracted with dichloromethane (3x5 ml). The organic extracts were evaporated to dryness under a steream of nitrogen (3).The residues were reconstituted in methanol (200 µl) for LC-MS and LC-MS/MS. The reconstituted extracts were analyzed using the reverse-phase LC-MS system described in the text. Test extracts were further investigated in LC-MS/MS. For HP-TLC studies, these samples (dissolved in 50 µl methanol per sample) were also analyzed using HP-TLC equipment.

Denaturation of Microsomes

For control experiments, microsomes were denaturated using boiling water. The necessary amount of freshly defrosted microsomes were taken in a test tube and it was placed in boiling water for 5 mins. After the heat-denaturation, the denatureated microsomes were used for control experiments.

***In Silico* Studies**

Our study group aimed to observe how the compound binds to P450 CYP3A4 protein, which probably causes its *S*-oxidation, using *in silico* approaches in the light of experimentally obtained information. For this purpose, the X-RAY crystal structure of the protein (PDB ID: 4D7D) was retrieved from the Protein Data Bank server (www.pdb.org, accessed 08 September 2022). Schrödinger Maestro Schrödinger Release 2020-3, Maestro, Schrödinger, LLC, New York, NY, USA (2020) interface was used for the molecular docking study and the enzymes crystals were processed using the Protein Preparation Wizard protocol of the Schrödinger Suite 2020. Compounds were prepared using the LigPrep module Schrödinger Release. 2020-1: LigPrep 2020, Schrödinger, LLC, New York, NY, USA (2020) to correctly assign the protonation states (pH=7.4) as well as the atom types. Bond orders were assigned, and hydrogen atoms were added to the structures. The grid generation was formed using the Glide module Schrödinger Release 2020-3, Glide, Schrödinger, LLC, New York, NY, USA (2020), and docking runs were performed in standard precision docking mode (SP).

After determining the best pose for ligand-enzyme complex, we aimed to determine and clarify the changes in the interactions during the time and environmental changes using molecular dynamic simulation (MDS) technics. Thus, an MDS study was performed for 100 ns with the POPE transmembrane model system and 3 points (TIP3P) water model followed by energy minimization of the complex waters. The neutralization of the system was achieved using Na^+ and Cl^- ions and 150 mM NaCl was added. The molecular dynamic simulation was performed following the completion of the system setup. The radius of gyration (Rg), root mean square fluctuation (RMSF), and root mean square deviation (RMSD) values were calculated by the Desmond application Schrödinger Release 2020, Desmond, Schrödinger, LLC, New York, NY, USA (2020) and perused to previous literatures (39-40).

RESULTS AND DISCUSSION

The aim of this present study is first to observe and prove any qualitative *in vitro* microsomal metabolite formation of the anticancer drug candidate, SGK636. The formation of the metabolites was proved in LC-MS, LC-MS/MS and HP-TLC analyses. There are limited data available on HP-TLC and microsomal metabolism studies in the literature. This study is the first representative on this field in terms of HP-TLC usage in in vitro microsomal metabolism studies (41).

LC-MS, LC-MS/MS and HP-TLC

Several attempts were made in order to separate SGK636, DT and the corresponding *S*-oxide (SGK636-SO) with LC-MS and HPTLC. Acetonitrile/water (70:30, v/v) was found to be the best mobile phase for the LC-MS separation of substrate and its metabolites (Figure 1a) and the best mobile phase for HP-TLC was a mixture of petroleum ether (40-60°C)/dichloromethane/ethyl acetate (25:50:25 v/v/v) at 25 °C (Figure 4). The retention times and Rfx100 values of the compounds were recorded (Table 1).

Table 1 Chromatographic properties of the substrate and the potential metabolites (**SGK636, DT** and **SGK636-SO**).

Compound (abbreviation)	M.W. (g/mol)	Molecular ion peak (M+1) (m/z)	HPTLC Rfx100 values	LC-MS retention time (min)
Substrate (**SGK636**)	512.20	513	35.8	15.05
Dealkylated thiole (**DT**)	379.11	380	74.7	4.68
SGK636 S-oxide (**SGK636-SO**)	527.20	528	16.3	7.66
for HPTLC and LC-MS conditions see text				

Following the metabolic experiments using SGK636 as a substrate, no *S*-dealkylation product (DT) was detected by using pig liver microsomes following LC-MS (Figure 1b). After the incubation, the oxidative metabolite (SGK636-SO) was observed with LC-MS (Figure 1b) analyses. The control experiments with denaturated microsomes or in the absence of co-factors were also carried out to establish whether the *S*-oxidation reaction is enzymatic and co-factor dependent (Figure 1c, 1d). *S*-oxide metabolite was only formed in the presence of enzyme and co-factors but not in the control experiments (in the presence of denaturated microsomes and in the absence of co-factors) indicating that the reaction was enzymatic. In order to establish any autooxidation into the corresponding sulfoxide, the substrate SGK636 was also incubated in buffer under standard incubation conditions (but without enzyme and co-factors) and no autooxidation into the corresponding sulphone was observed. A stability work for SGK636-SO (sulfoxide) in buffer was also performed to see any possible autooxidation to sulphone or reduction back to SGK636. However, no conversion into SGK636 or the corresponding sulphone was observed in either way.

The authentic and metabolically formed SGK636-SO were compared with their retention times, UV and MS spectra and gave identical Rt and Rfx100 values on LC-MS and HP-TLC and identical spectra in both UV and MS (Figure 1, 2, 3, 4). LC-MS/MS analysis also confirmed the formation of sulfoxide (*S*-oxide metabolite). The fragmentations were recorded as their *m/z* values. Both substrate (SGK 636) and *S*-oxide metabolic standard (SGK 636-SO) were found to be stable in terms of fragmentation (Figure 5, 6, 7).

Further study was performed for the incubation of *S*-oxide metabolic standard compound, SGK636-SO. The result presented that the corresponding sulfoxide is further oxidized to sulfone derivative. The sulfone formation was proved in LC-MS analysis (Figures 8a and 8b).

The experiments were performed with test and control incubation systems. We have also included the autooxidation procedure for both substrate and the authentic metabolic standards (Figure 9). The control incubation procedures consisted of 'denaturated microsomes'. The denaturation of the microsomes was provided by placing the mixture into hot boiling bath for 5 mins. The 'heat inactivation' procedure was performed for providing denaturated microsomes. Although this study does not cover the enzymatic profile, some critical assumptions can be made in terms of enzymatic pathways. Sulphur oxidation is mainly provided by FMO enzymes rather than CYP enzymes. A few studies indicates the oxidation mechanism of sulphur containing molecules regarding biotransformation. A study showed the enzymatic participation of P450 and FMO in fenthion biotransformation. When recombinant P450s are used, CYP2C19 was found to be responsible for sulfoxide formation. CYP1A1, CYP3A4 and CYP3A7 was also found to have a significant role in sulfoxide formation (42). When human liver microsomes used at low concentration of fenthion, sulfoxidation is predominantly P450-mediated. At the high concentrations, FMO's get on the line (43). Rawden and co-workers studied the metabolic sulfoxidation profile of albendazole using human liver microsomes. *In vivo* studies mostly hold CYP enzymes responsible for sulfoxide formation. Recombinant CYP3A4, CYP1A2 and FMO3 produced more sulfoxide of albendazole than control microsomes. This study presented that the formation of sulfoxide depends on CYP activation, rather than FMO; primarily CYP3A4 was found to be most relatively involved in oxidation reaction (44). In our study male pig liver microsomes were used as consistent with the literature (45). Using this literature data, it may be assumed that the formation of sulfoxide mostly depends on CYP activation, as there was no metabolite formed in control experiments.

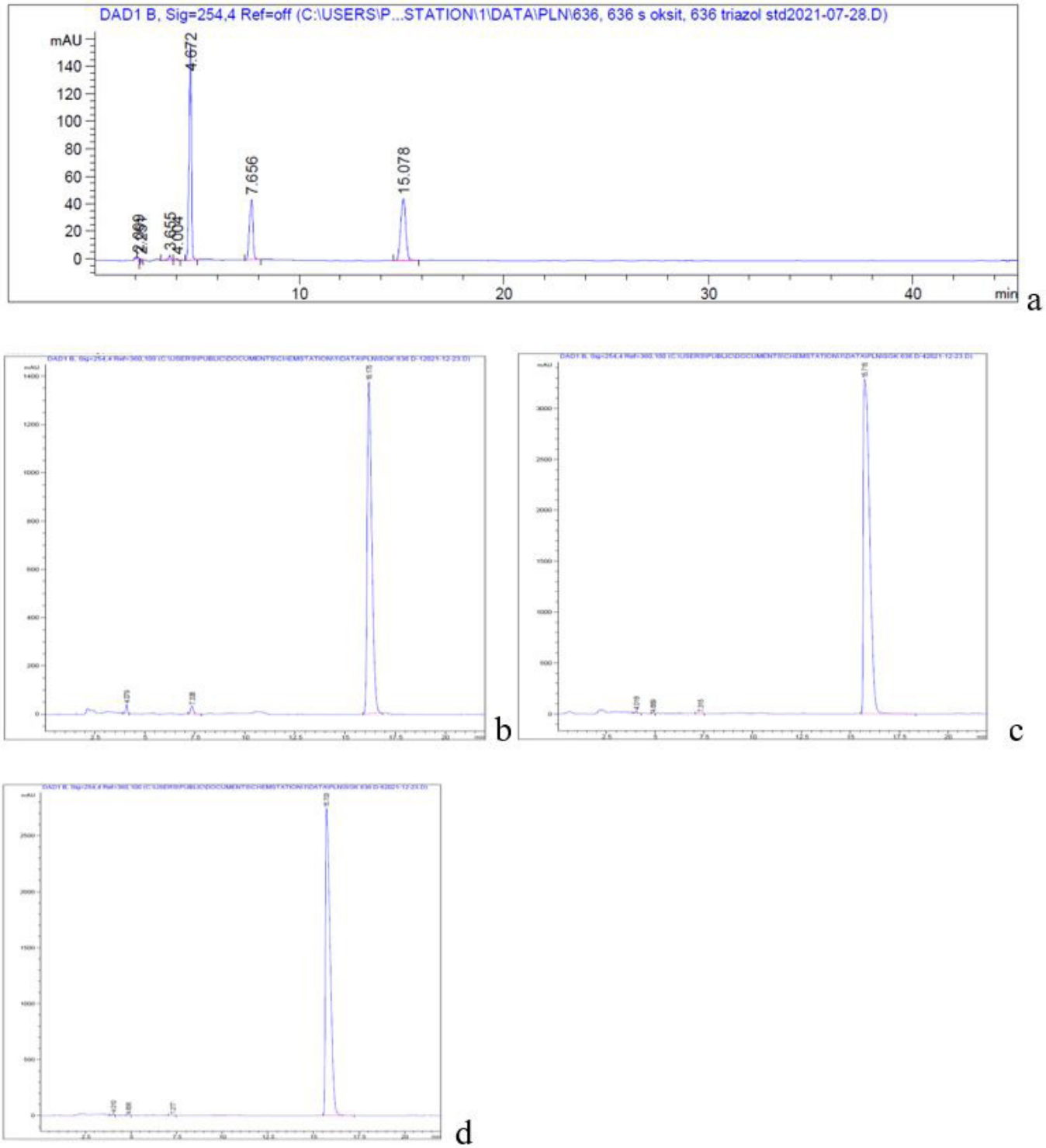

Figure 1. *(a), HPLC chromatogram of substrate (SGK636: 15.078) and its metabolic standarts (DT: 4.672 and SGK636-SO: 7.656) (b), HPLC chromatogram from SGK636 test mixture (c) HPLC chromatogram from SGK636 control experiment without microsomes (d) HPLC chromatogram from SGK636 control experiment without co-factors (see Table 1 for abbreviations)*

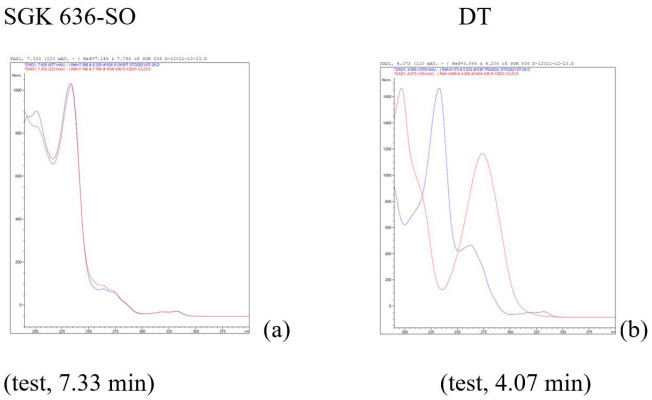

Figure 2. *(a) UV spectrum of standard and metabolic SGK636-SO; (b) standard DT and metabolically formed unknown metabolite (see text for abbreviations) (note: although the retention times were the same (4.07 min), their UV spectra were different indicating the metabolite is different from DT)*

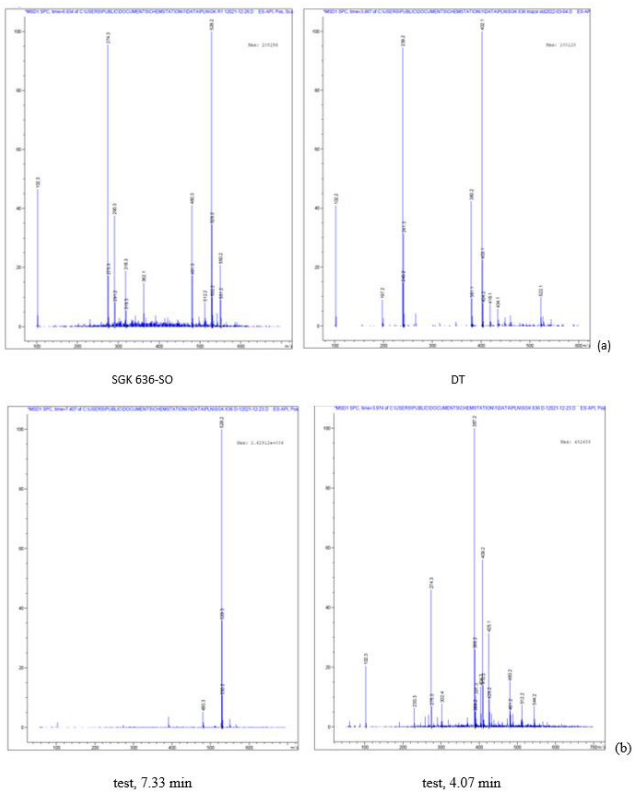

Figure 3. *(a) Mass spectrum of standard SGK636-SO and DT (b) Mass spectrum of SGK636-SO metabolite and unknown metabolite from SGK636 test mixture following incubation of SGK636 with pig liver microsomes fortified with NADPH*

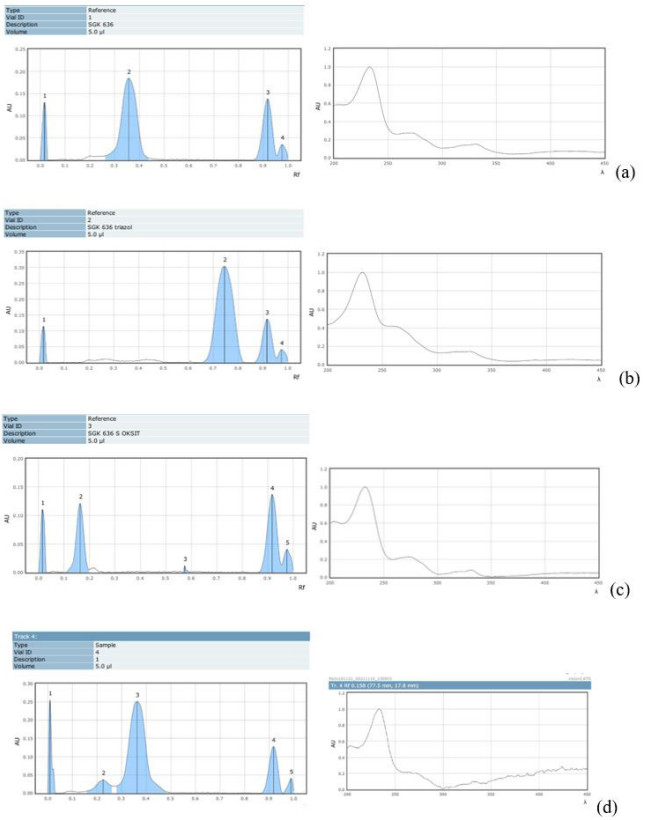

Figure 4. *HPTLC chromatogram and UV spectra of (a) SGK636, (b) DT, (c) SGK636-SO (peak 2: standard compounds, i.e. peak 2 for a is SGK636; peak 2 for b is DT; peak 2 for c is SGK636-SO. All other peaks are related to solvents used) and (d) in-vitro metabolic extract from SGK636 metabolism with pig liver microsomes fortified with NADPH (peak 2 for d is SGK636-SO; peak 3 for d is SGK636, all other peaks are related to solvents used) (see Table 1 for specific Rfx100 values).*

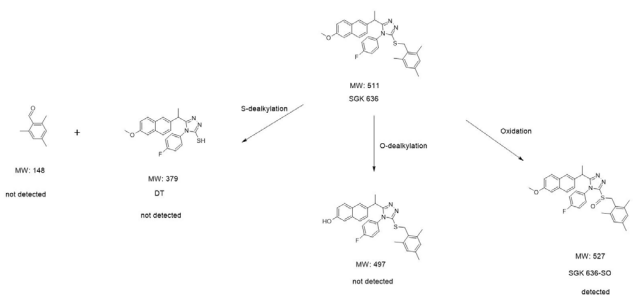

Figure 5. *Metabolic profile of **SGK636** and molecular weights of metabolites (see text for abbreviations)*

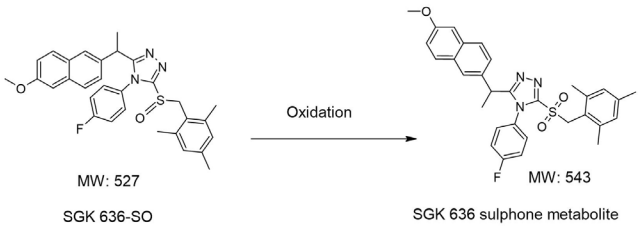

Figure 6. *S-oxidation profile of SGK 636-SO*

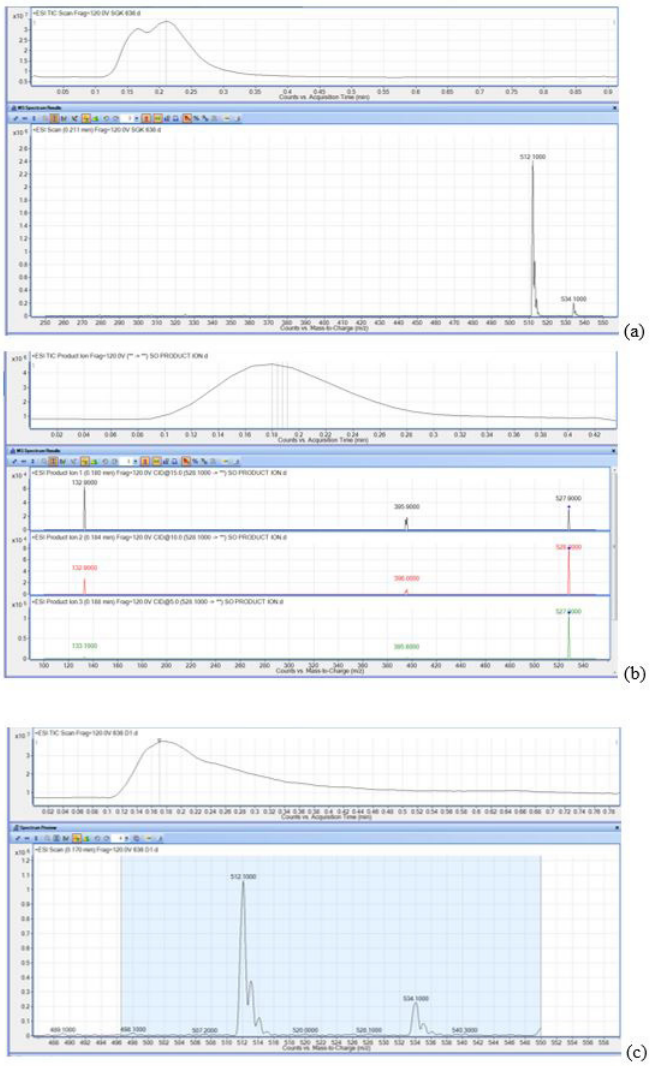

Figure 7. *LC-MS/MS results for SGK636, authentic S-oxide standard and test experiment: (a) LC-MS/MS analysis of standard substrate (SGK 636) (b) LC-MS/MS analysis of SGK 636-SO standard (c) SGK 636 Test (512 is substrate and 528 is S-oxide metabolite)*

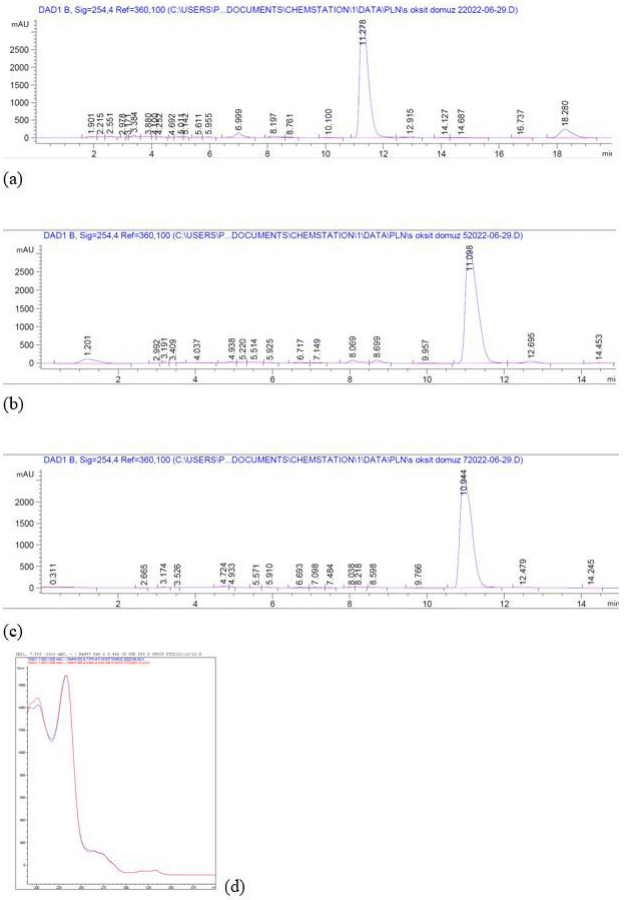

Figure 8a. *Authooxidation of SGK636 and SGK636-SO; (a) HPLC chromatogram of SGK 636-SO test incubation (b) HPLC chromatogram of SGK 636-SO control (with no microsomes) (c) HPLC chromatogram of SGK 636-SO control (with no co-factor) (d) UV comparison of SGK 636-SO and sulfone metabolite*

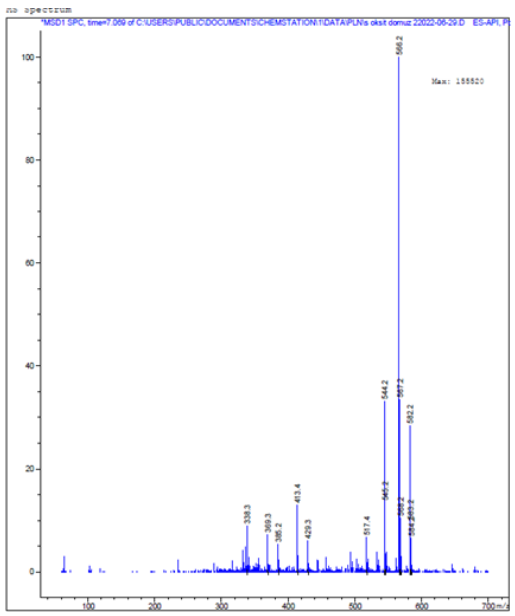

Figure 8b. *Authooxidation of SGK636 and SGK636-SO; Mass spectrum of SGK 636-SO sulphone metabolite in 6.99 min (544 resulted from sulfone metabolite)*

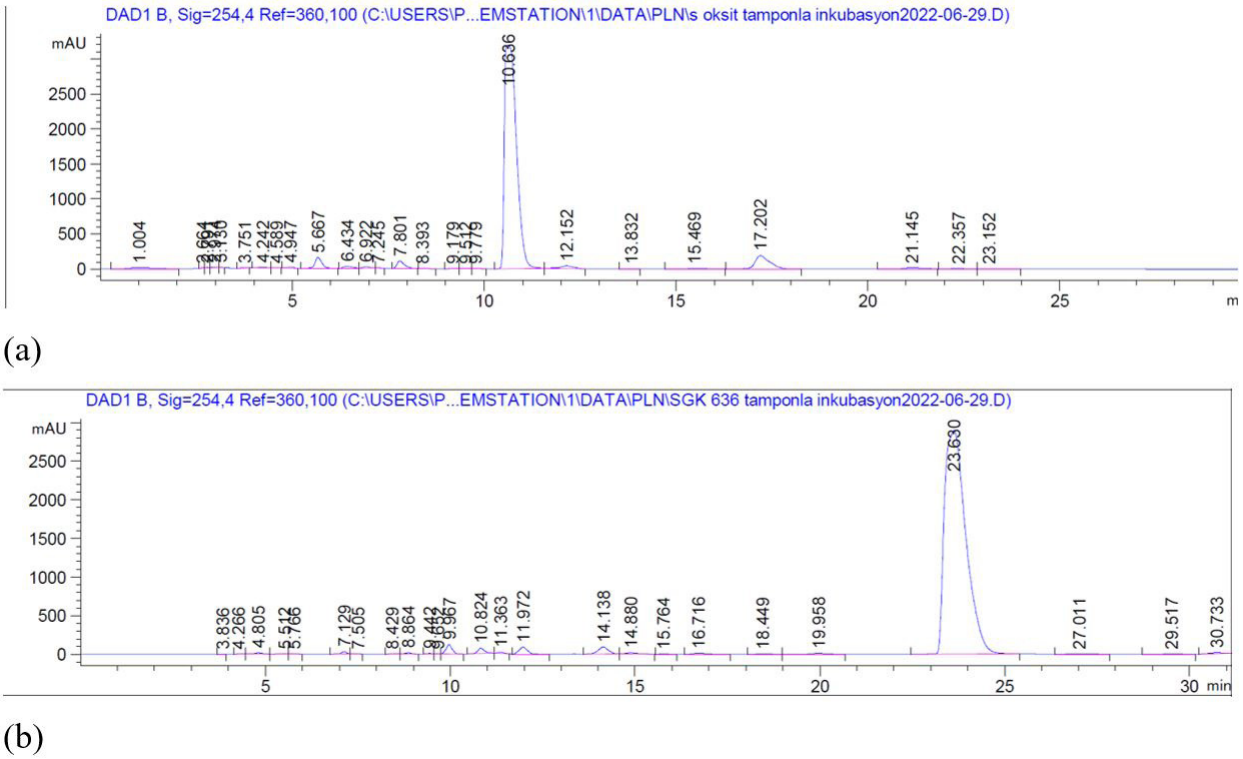

Figure 9. *Autooxidation study of SGK636 and SGK636-SO standard; (a) HPLC chromatogram of SGK 636-SO incubation with buffer (b) HPLC chromatogram of SGK636 incubation with buffer*

An unknown metabolite was also observed only in the test tubes at 4.07 min (Figure 1b). That peak could not belong to the *S*-dealkylated metabolite (DT) since its UV and MS spectrum were not identical with the authentic standard (Figure 2 and 3). It can not be O-dealkylation metabolite either (Figure 2 and 3) as this unknown product has a different molecular weight (MW: 387) compared to the calculated value for *O*-dealkylation metabolite (MW: 497) (Figure 5).

HP-TLC results also indicated the formation of SGK636-SO (Figure 4) (see Table 1 for Rfx100 values). The existence of this sulfoxide metabolite was confirmed by the identical Rfx100 values and UV spectra of authentic and metabolically formed SGK636-SO (Figure 4).

According to the previous study (46), the possible biotransformation site (SOM) of the ligands in the ligand-CYP3A4 enzyme complex can be determined if it is within 6.0 Å from the iron atom of heme. In fact, the methodology behind the determination of possible SOMs is applicated using the extra-precision (XP) or induced-fit (IF) docking methods because the CYP3A4 is very flexible enzyme.

But in this case, since we have a known metabolite obtained from experimental study and thus not searching for possible metabolites, we used the standard precision (SP) docking method. The docking result (Figure 10) revealed that SGK636 ligated to the substrate region of the enzyme and contacted the iron atom of the HEM protein. This was observed as π-cation interaction. Also, there was an aromatic H-bond between H3 of 4-fluorophenyl and Ser119 amino acid. These two interactions pointed out that the ligand and the complex adapted to each other, thus, it is also suggested that one of the possible biotransformation mechanisms is probably catalyzed by Cyp3A4. Additionally, Ser119 amino acid is described as a key residue to stabilize the complex (47).

According to the docking study, there were three possible sites on SGK636 to oxidate, one is a sulfur atom, one is methyl group of 2,4,6-trimethylphenyl and the other one is a methyl group of ethyl bridge. To clarify this issue and understand the binding mode versus conformational changes by time-dependent and environmental changes, we also performed a molecular dynamics simulation study. The MDS data was shared in Figure 11.

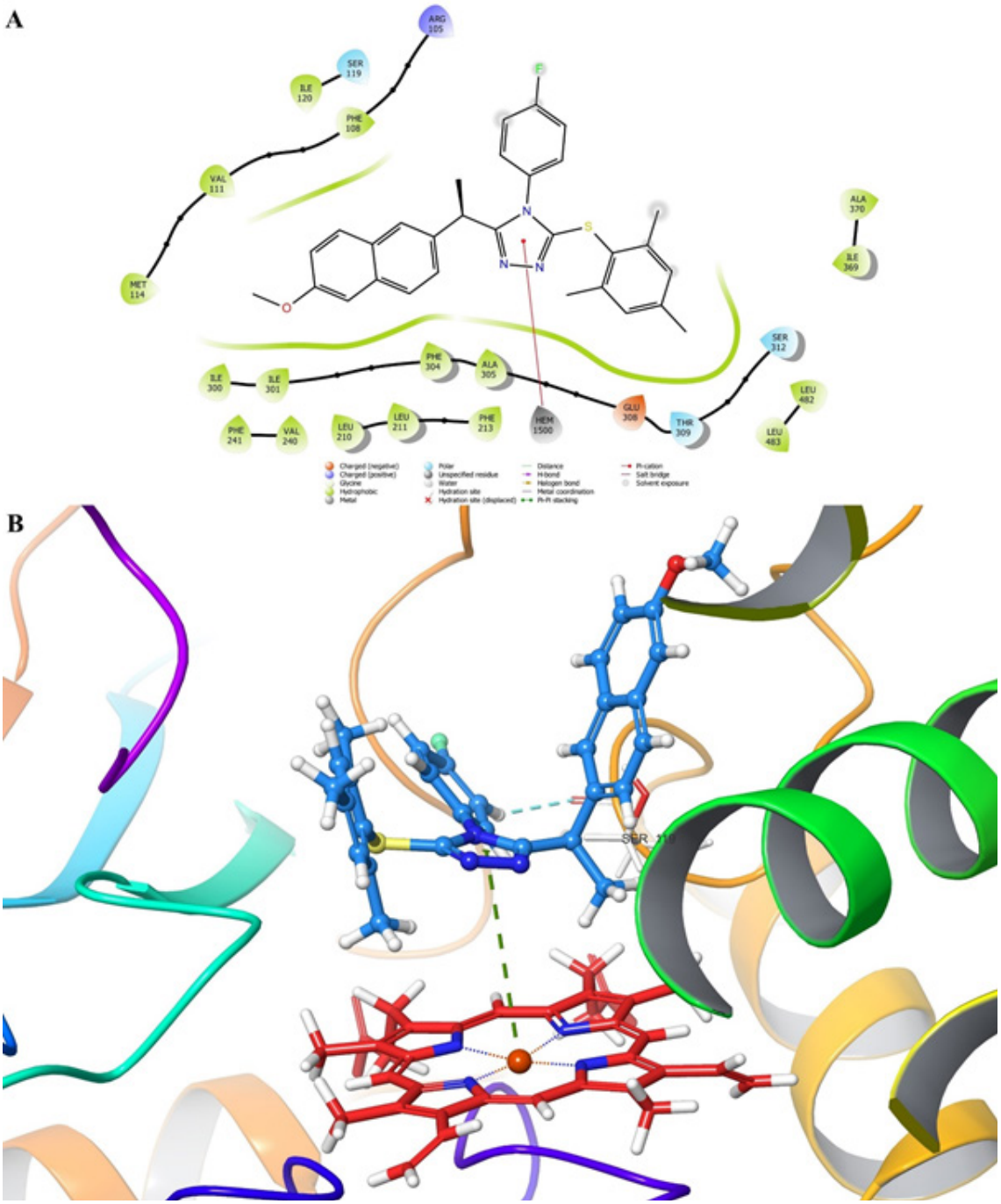

Figure 10. *2D (**A**) and 3D (**B**) representations of the compound at Cyp3A4 substrate pocket (PDBID: 4D7D). The Green dashed lines are used for π-cation and the cyan dashed lines are used for the aromatic hydrogen bond.*

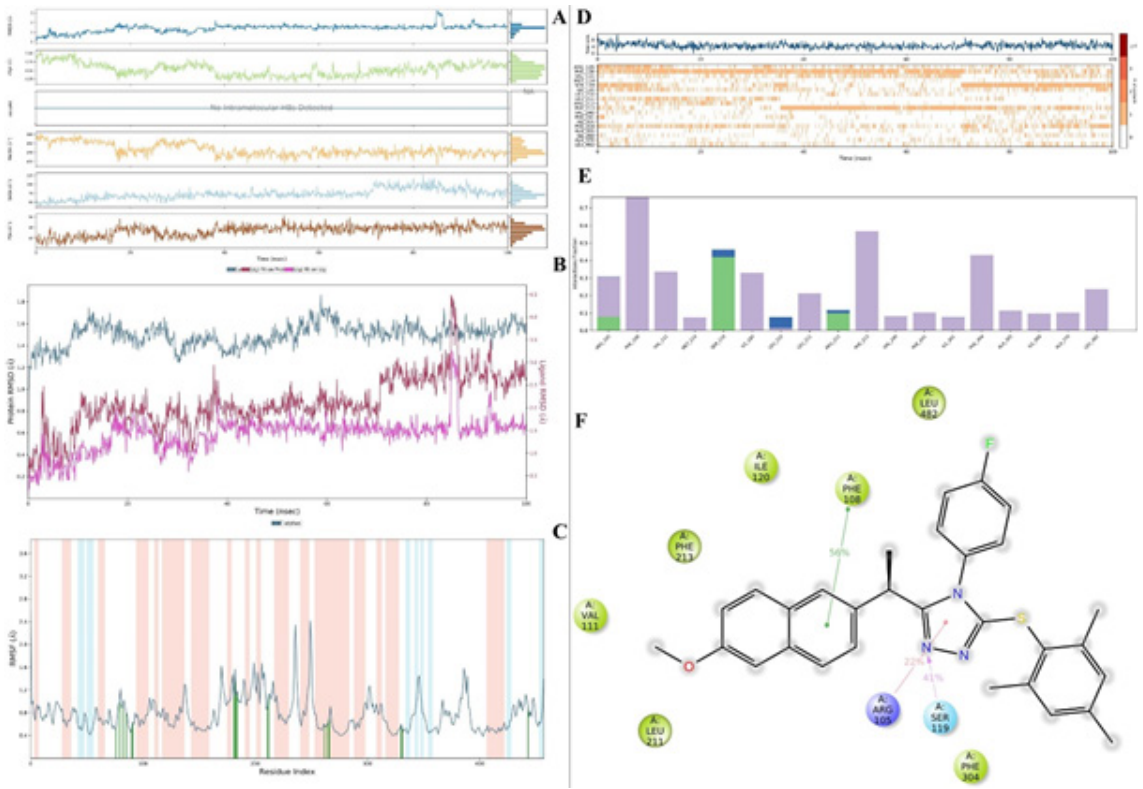

Figure 11. *MDS results for the compound and CYP3A4 protein complex.* ***A-C:*** *The stability properties of the complex.* ***A:*** *Physicochemical properties of the ligand;* ***B:*** *RMSD plot of the protein, the ligand versus protein and the ligand versus ligand;* ***C:*** *RMSF plot of the complex.* ***D-E:*** *The contacts properties of the complex.* ***D:*** *Number of interactions and interaction types versus time plot;* ***E:*** *Plot of interaction fractions versus residues with their interaction types during the time;* ***F:*** *2D diagram for contact strength (cutoff = 20%).*

The stability criteria (48-49) were found in acceptable ranges. Rg values decreased around 0.5 Å from 0 to 36.60 ns, after that, their changes were observed between 0.25 Å. RMSD values of protein were observed between 1.00-1.86 Å (RMSDmax was observed at 58.80 ns). RMSD values of ligand were observed between 0.36-3.26 Å and 0.92-4.48 Å, according to itself and the protein, respectively. And the RMSF values were observed as expected, for the rigid structures (helixes and strands), they were observed under 1.2 Å, and if there was a contact, then these values were under 0.8 Å. Besides that, the RMSF values of interacted flexible structures (loops) were observed under 1.2 Å. Specifically, the RMSF value of Ser119 was determined as 0.54 Å. As a result, all these criteria guaranteed that the MDS results are reliable. So, the interactions and their properties could be evaluated to understand the behavior of the complex. Direct H-bonds were observed with Arg105, Ser119, and Arg212 amino acids. Aromatic H-bonds formed with Ser119, Leu210, Arg212, Phe241, Ala370, and HEM1500 residues, and water-mediated H-bonds were with Ser119, Leu210 and Arg212 amino acids. The hydrophobic interactions were with Arg105, Phe108, Val111, Met114, Ile120, Leu211, Phe213, Val240, Phe241, Ile301, Phe304, Ala305, Ile369, Ala370, and Leu482 amino acids. Furthermore, especially, the interactions with Phe118, Ser119, and Arg105 had a pivotal role in ligating to CYP3A4 enzyme by SGK636, were noted.

The histograms of the distance values frequency were shared in Figure 12 (AH and BH). Also, in MDS video, the purple dashed line and its number represent the distance between the iron of Hem and the sulfur atom or methyl group of SGK636. The distance changes during the time (ps) were also plotted in Figure 12 (AP and BP). As seen, while the methyl group of 2,4,6-trimethylphenyl digressed from HEM, the sulfur atom was getting closer to iron of HEM. Therefore, it's clearly said that this methyl group is not a favorable candidate for SOM. Moreover, as seen in the MDS video, the methyl group of ethyl localized outside to do not contact with the HEM (>10 Å). As mentioned, if the maximal distance between SOM and iron of HEM is 6 Å, the CYP enzymes can catalyze the xenobiotic. In this MDS study, the mean value (distance between iron and S atom) was calculated as 5.248±0826 Å during the entire simulation. (As the mean value (for between iron and CH3 of the 2,4,6-trimethylphenyl group) was meaningless, it was not calculated).

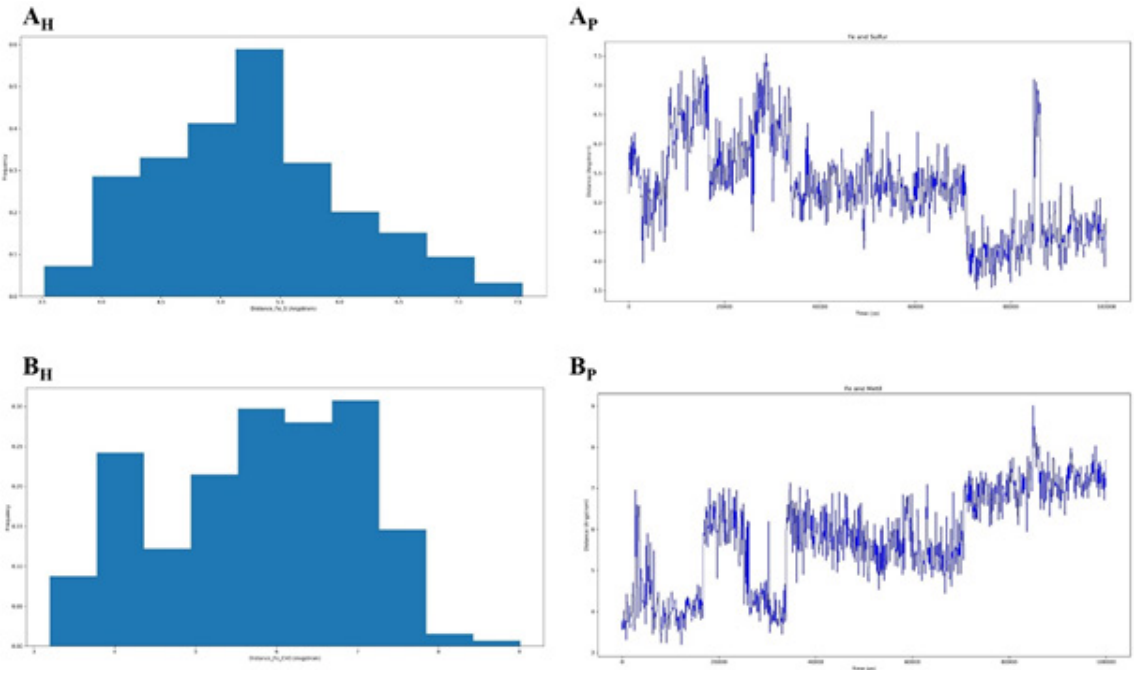

Figure 12. *The fractions of the distances between the iron of HEME and (**A**) sulfur atom or (**B**) methyl group.* $_H$ *for histogram of frequency versus distances,* $_P$ *for plot of distance versus time.*

As a result, this MDS study revealed that there is only one possibility, and this possible SOM of SGK636 is upon *S*-oxidation. Since our experimental study also proved the obtained metabolite was *S*-oxide-SGK636, *in vitro* and *in silico* studies are in harmony.

CONCLUSION

The present metabolic study indicates that an anticancer drug candidate, SGK 636 converted to the corresponding *S*-oxide metabolite following its *in vitro* microsomal metabolism by pig liver microsomes but no any dealkylated metabolite was observed. The *in silico* studies also proved the *S*-oxidation via CYP3A4 enzyme. Since sulfoxidation process can be reversible and it may partly explain the low amount of sulfoxide metabolite, SGK636-SO (sulfoxide) was also incubated but no metabolic or chemical conversion into the SGK636 was observed. However, it produced the corresponding sulfone metabolite. This was established by LC-MS. The findings also indicate that this substrate is very stable to metabolic *S*- or *O*-dealkylation reactions which could be an advantage in terms of its pharmacological activity. The *S*-oxide metabolite was detected and confirmed by comparison with retention times, Rfx100 values, UV and MS spectra of authentic and metabolic product using LC-MS, LC-MS/MS and HP-TLC techniques. Further study was performed for the incubation of *S*-oxide metabolic standard compound, SGK636-SO. The result presented that the corresponding sulfoxide is further oxidized to sulfone derivative. The sulfone formation was proved in LC-MS analysis. An unknown product was also observed following metabolic experiment which did not correspond to the molecular weight of any dealkylation metabolite or of any possible metabolic conversion product. In order to establish if the *S*-oxidation reaction is enzymatic and/or requires co-factors, control experiments were carried out using denaturated microsomes, buffer instead of co-factors. In additon, the substrate was also incubated with buffer under standard incubation conditions (but without any enzyme and/or co-factors) to find out any autooxidation into corresponding sulfoxide and no autooxidation was observed.

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Ethics Approval And Consent To Participate

The pig livers were donated by Acibadem University, Animal Laboratory Centre from the Project by Dr. Mehmet Emin Aksoy; laparoscopic and robotic surgery, with the 2021-01 ethical approval number. At the end of the training, liver tissue was obtained from the euthanized pig.

Human And Animal Rights

No humans were used in this study. All animal research procedures were followed in accordance with the standards set forth in the eighth edition of Guide for the Care and Use of Laboratory Animals (published by the National Academy of Sciences, The National Academies Press, Washington, D.C.).

Conflict of Interest

The authors declare no conflicts of interest, financial or otherwise.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Neurology / Nöroloji

A Comparison of Auto Train Brain Neurofeedback Rewarding Interfaces in Terms of Efficacy

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ABSTRACT

Background/aim: Auto Train Brain is a mobile app that was specifically developed for dyslexic children to increase their reading speed and reading comprehension. In the original mobile app, only one unique neurofeedback user interface provided visually and audibly rewarding feedback to the subject with a red-green colored arrow on the screen. Later, new modules are added to the app with the end-users requests. These are the "youtube" video-based interface and "Spotify" auditory-based interface. In this research, we have compared the efficacy of the neurofeedback rewarding interfaces.

Materials and methods: The experiment group consists of 20 dyslexic children aged 7-to 10 (15 males, 5 females) who were randomly assigned to one rewarding interface and used it at home for more than six months.

Results: The result indicates that though the "youtube" interface is liked most by the participants, the arrow-based simple neurofeedback interface reduces theta brain waves more than other rewarding schemes. On the other hand, "youtube" and "Spotify" based interfaces increase Beta band powers more than the arrow interfaces in the cortex. The "Spotify" user interface improves the fast brain waves more on the temporal lobes (T7 and T8) as the feedback given was only auditory.

Conclusion: The results indicate that the relevant neurofeedback rewarding interface should be chosen based on the dyslexic child's specific condition.

Keywords: Neurofeedback, multimodality, QEEG, Auto Train Brain.

Auto Train Brain nörogeribildirim ödüllendirme arayüzlerinin etkinlik açısından karşılaştırılması

ÖZET

Arka plan/amaç: Auto Train Brain, disleksili çocukların okuma hızını ve anlama düzeyini artırmak için özel olarak geliştirilmiş bir mobil uygulamadır. Orijinal mobil uygulamada, yalnızca bir benzersiz nörogeribildirim kullanıcı arayüzü, ekranın kırmızı-yeşil renkli bir oku ile konuya görsel ve işitsel olarak ödüllendirici geri bildirimi sağlıyordu. Daha sonra, kullanıcı talepleriyle uygulamaya yeni modüller eklendi. Bunlar "youtube" video tabanlı arayüz ve "Spotify" işitsel tabanlı arayüzdür. Bu araştırmada, nörogeribildirim ödüllendirme arayüzlerinin etkinliğini karşılaştırdık.

Malzemeler ve yöntemler: Deney grubu, 6 ay ve üzeri süreyle evde bir ödüllendirme arayüzü kullanan ve 7 ila 10 yaş arasında (15 erkek, 5 kadın) disleksili çocuktan oluşmaktadır.

Sonuçlar: Sonuçlar, "youtube" arayüzünün katılımcılar tarafından en çok beğenilmesine rağmen, ok şeklindeki basit nörogeribildirim arayüzüne göre daha az theta beyin dalgaları azalttığını göstermektedir. Diğer yandan, "youtube" ve "Spotify" tabanlı arayüzler, kortekste ok arayüzlerinden daha fazla beta bant güçlerini artırmaktadır. "Spotify" kullanıcı arayüzü, sadece işitsel olarak verilen geri bildirim nedeniyle temporal loblarda (T7 ve T8) hızlı beyin dalgalarını daha da iyileştirir.

Çalışmanın özeti: Sonuçlar, disleksili çocuğun özel durumuna göre ilgili nörogeribildirim ödüllendirme arayüzünün seçilmesi gerektiğini göstermektedir.

Anahtar kelimeler: Nörogeribildirim, çoklu duyusal, QEEG, Auto Train Brain.

Even if their IQ is normal or above average, some children may struggle to learn to read quickly in the early years of school. According to DSM-V criteria, dyslexia is a subtype of a distinct learning disability that affects children for at least 6 months and cannot be related to neurological or motor disorders, developmental disorders, or intellectual disabilities(1).

In dyslexia, neurologically, there is a temporal disruption and a disconnection between the left anterior and the left posterior regions of the brain (2). This situation affects the learning of letters and words and phonemic awareness. The increased slow brain waves in the left temporal region can be tracked in QEEG (3). The main affected brain region due to this disconnection syndrome might be the Wernicke region (4).

Neurofeedback has been shown to help with dyslexia's disconnection syndrome. Neurofeedback is beneficial in improving spelling, reading speed, and reading comprehension in studies (5,6,7,8). Neurofeedback employs the brain's plasticity and operant conditioning to teach the user how to gain greater control over central nervous system activity. The user receives direct neurofeedback regarding their actual brain activation pattern, allowing them to learn to control QEEG signals voluntarily (9). Real-time feedback of QEEG signals to oneself is a technique that allows individuals to obtain immediate feedback on their neural activity as reflected in visual and aural stimuli. It is a well-known reality that the neurons that fire together wire together (10).

Nazari used neurofeedback to decrease slow brain waves, such as delta and theta, at T3 and F7, while increasing beta-1 at T3 and F7(10). The treatment lowered the amount of time spent reading and the number of errors made while reading. Walker and Norman (5) used various neurofeedback protocols to reduce slow brain waves, such as delta and theta at Cz, enhance beta-1 at T3, and decrease coherence in the delta and theta range, and their findings revealed at least two levels of improvement in dyslexic reading levels. Applying neurofeedback to dyslexia (delta down at T3-T4, beta down at F7 and C3, coherence training in the delta, alpha, and beta regions) was shown to be beneficial for spelling but not reading (6). The latest research found that neurofeedback improves reading comprehension and reading speed (8).

Auto Train Brain is a mobile software that combines neurofeedback, multi-sensory learning, and special education principles (11,12,13). Machine learning algorithms exist for diagnosing dyslexia and recommending individualized treatment plans.

In Auto Train Brain's original user interface, there was a colored arrow to give neurofeedback to the child with a visual and auditory cue. Although it was simple and unique, this user interface was proven to be beneficial to children with dyslexia to improve their condition. During its product lifecycle, new features are added to Auto Train Brain. The neurofeedback interface is also developed more. In the latest version of Auto Train Brain, it is possible to choose the user's preferred video and start neurofeedback by providing multimodal -namely visually and audibly rewarding neurofeedback. When the subject focuses more on the video, he can see the screen more and can hear the sound of the video more. In another auditory rewarding scheme, the user starts a podcast or a storyteller on Spotify and runs in the background, while neurofeedback rewards the user by increasing or decreasing the volume of the sound.

In this research, we have collected QEEG data from children with dyslexia during neurofeedback sessions and determined which user interface decreased Theta brain waves more (5).

Materials and Methods

Subjects & Experimental Data

The neurofeedback data of 20 dyslexic children for 6 months are studied in this study. The children's ages range from seven to ten (15 males, 5 females). All participants gave their informed consent before the experiment after the experimental technique was explained to them according to research ethics committee requirements. The EMOTIV EPOC-X headset is used throughout the studies. The headset's internal sampling rate is 2048 samples per second per channel. The data is filtered to remove major artifacts before being downsampled to 128 samples per second per channel.

There are 14 EEG channels and two reference channels in total. Before the studies, the EMOTIV Headset is calibrated on the subjects' scalps using the EMOTIV APP, and each electrode is checked for high-quality EEG data transmission. The EEG electrode placements are AF3, F3, F7, FC5, T7, P7, O1, O2, P8, T8, FC6, F8, F4, and AF4.

The participants were randomly assigned the neurofeedback rewarding interfaces at the start of the experiment. The randomly assigned experiment groups were age-matched. Each group has only used the assigned rewarding interface. One group utilized a simple neurofeedback interface based on arrows. Their goal was to change the red arrow into a green arrow while avoiding hearing any beeps. The second group used the "youtube" interface, and the subject was told that if he focused more on the video, he would be able to view it better. The third group used the Spotify user interface. They listened to podcasts and when they give attention more, they can hear it better. The subjects were not given any extra information regarding the experimental technique.

Study Design

Each participant has used Auto Train for 6 months, has their brain waves read using the EMOTIV EPOC-X from 14 channels, and has received 30 minutes of visual and audio neurofeedback. The user interfaces for each group were different, but the neurofeedback algorithms were the same.

A recording of their QEEG is made and stored in a database. All 14-channel QEEG data is acquired during the tests in the Theta (4-8 Hz), Alpha (8-12 Hz), Beta-1 (12-16 Hz), Beta-2 (1625 Hz), and Gamma (25-45 Hz) bands for all analyses in this work. We evaluated the Theta band power values for 14 channels after collecting, averaging, and cleaning data from an EMOTIV EPOC-X headset.

Results

It was measured that the simple "arrow" based neurofeedback interface, which rewards visually and audibly, decreases theta band power more than that of the other neurofeedback interfaces ($p<.001$).

It was also measured that "youtube" and "Spotify" based neurofeedback rewarding interfaces improve Beta-1 and Beta-2 brain waves more than the arrow neurofeedback rewarding interface ($p<0.001$). There is no comparison between the improvements in reading comprehension / reading speed and neurofeedback interfaces.

Discussion

We have designed an experiment to test the new user interfaces of Auto Train Brain. The first neurofeedback interface is related to the "arrow" neurofeedback interface which is simply turning a red arrow into a green arrow. The second neurofeedback interface is related to "youtube" videos and neurofeedback during watching these videos. The third neurofeedback interface was based on Spotify (storyteller), an auditory interface. The users of Auto Train Brain prefer the "youtube" videos more than the "arrow" interface in real life as they think it is more amusing and attractive. The results of this experiment have shown that the original "arrow" interface which is easier to control and learn was more beneficial to children with dyslexia to reduce the slow brain waves. The reason would be to control the "arrow" much easier than the "youtube videos" with the brain, or the content of the "youtube" videos were distracting the children to focus.

Participants used the "youtube" interface to pay more attention to cartoon movies and therefore their fast brain waves increased more. The "Spotify" user interface improves the fast brain waves more on the temporal lobes (T7 and T8) as the feedback given was only auditory. The results indicate that the relevant neurofeedback rewarding interface should be chosen based on the child's specific condition. Some dyslexic people have general slowing or focal slowing of the cortex. Some dyslexic people have left temporal disruption. If the aim is to reduce the slow brain waves in the cortex or the theta brain waves should be trained, then the arrow-based interface should be chosen. If the aim is to increase the Beta brain waves in the cortex, "youtube" and/or "Spotify" based neurofeedback interfaces should be chosen. If the aim is to train phonemic awareness or auditory comprehension, a "Spotify" based user interface should be chosen. There may be a placebo effect and maturation effect in the experiments.

Extreme qEEG readings have been shown to be more likely to return to normal readings following Live z-score neurofeedback, especially in those who had normal alpha peak frequencies prior to the trial (12). EEG-based BCI systems have the potential to improve many people's lives because they are so powerful (13). According to the study, games are primarily top-down designed with kids in mind. They are typically motivated by causes outside of neurodivergent interests and tend to concentrate on educational and medical contexts. The majority of current work adopts a medical paradigm of impairment, which fails to promote neurodivergent players' autonomy and limits their options for immersion (14).

Simple observation of particular items has the ability to activate motor neurons. Neural responses to objects can vary significantly depending on their characteristics, and there are currently no standards for designing brain-computer interfaces (15). Our research offers fresh perspectives that will soon improve BCI design.

Figure -1 *Auto Train Brain "arrow" interface*

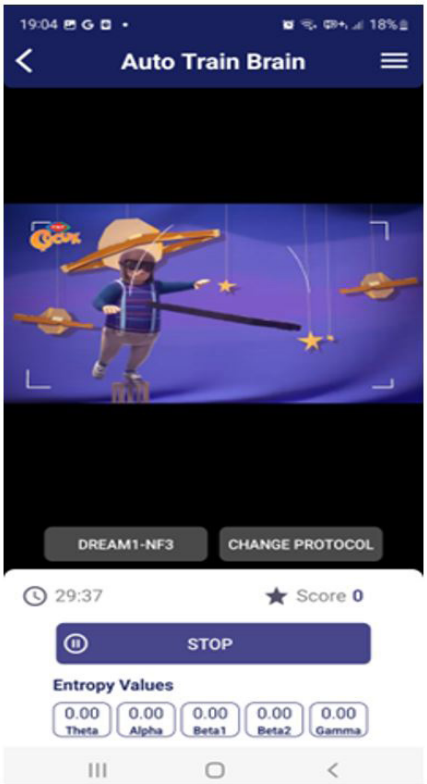

Figure -2 *Auto Train Brain "youtube" interface*

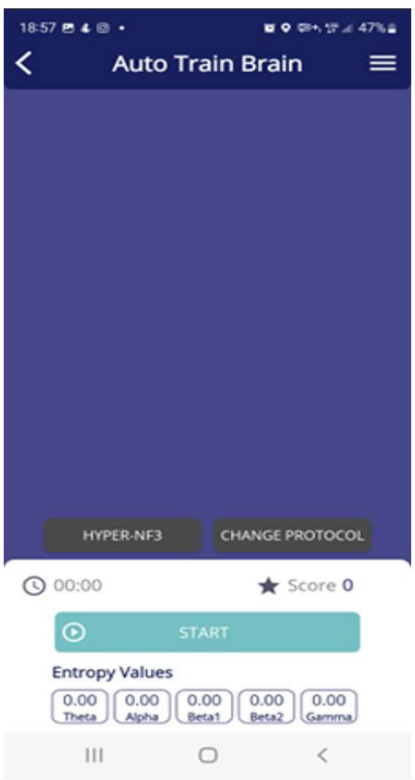

Figure -3 *Auto Train Brain "Spotify" interface*

Table 1. qEEG Band Power values per channel for each neurofeedback rewarding interface				
Variable	Youtube N = 382	Arrow N = 169	Spotify N = 104	p-Value
THETA_AF3	4.05 (± 2.96) 95% CI: [3.75 ; 4.35] Range: (0.0 ; 13.38) N = 382	3.73 (± 1.51) 95% CI: [3.5 ; 3.96] Range: (0.0 ; 8.73) N = 169	5.12 (± 2.97) 95% CI: [4.54 ; 5.69] Range: (0.0 ; 14.17) N = 104	<0.001
THETA_F3	4.61 (± 3.02) 95% CI: [4.3 ; 4.91] Range: (0.0 ; 13.84) N = 382	3.25 (± 1.3) 95% CI: [3.05 ; 3.44] Range: (0.0 ; 7.46) N = 169	5.26 (± 2.54) 95% CI: [4.76 ; 5.75] Range: (0.0 ; 13.41) N = 104	<0.001
THETA_F7	4.26 (± 2.4) 95% CI: [4.02 ; 4.5] Range: (0.0 ; 11.14) N = 382	3.47 (± 1.54) 95% CI: [3.23 ; 3.7] Range: (0.0 ; 9.1) N = 169	5.11 (± 1.9) 95% CI: [4.74 ; 5.48] Range: (0.165 ; 12.21) N = 104	<0.001
THETA_FC5	4.15 (± 2.11) 95% CI: [3.94 ; 4.36] Range: (0.0 ; 11.73) N = 382	2.93 (± 1.27) 95% CI: [2.74 ; 3.12] Range: (0.0 ; 6.87) N = 169	4.88 (± 2.34) 95% CI: [4.43 ; 5.34] Range: (0.0 ; 13.89) N = 104	<0.001
THETA_T7	3.05 (± 2.41) 95% CI: [2.81 ; 3.29] Range: (0.0 ; 12.75) N = 382	2.14 (± 1.28) 95% CI: [1.95 ; 2.34] Range: (0.0 ; 8.34) N = 169	3.23 (± 2.06) 95% CI: [2.83 ; 3.62] Range: (0.0264 ; 11.28) N = 104	<0.001
THETA_P7	2.52 (± 1.94) 95% CI: [2.33 ; 2.72] Range: (0.0 ; 14.06) N = 382	1.79 (± 1.14) 95% CI: [1.62 ; 1.96] Range: (0.00917 ; 6.72) N = 169	3.03 (± 1.92) 95% CI: [2.66 ; 3.4] Range: (0.149 ; 11.06) N = 104	<0.001
THETA_O1	3.72 (± 2.61) 95% CI: [3.46 ; 3.98] Range: (0.0 ; 14.51) N = 382	2.28 (± 1.07) 95% CI: [2.12 ; 2.45] Range: (0.0 ; 6.27) N = 169	4.4 (± 2.16) 95% CI: [3.98 ; 4.82] Range: (0.173 ; 13.39) N = 104	<0.001
THETA_O2	3.71 (± 2.22) 95% CI: [3.49 ; 3.94] Range: (0.0 ; 11.49) N = 382	2.58 (± 1.33) 95% CI: [2.38 ; 2.78] Range: (0.0 ; 7.27) N = 169	4.92 (± 2.5) 95% CI: [4.44 ; 5.41] Range: (0.198 ; 12.23) N = 104	<0.001
THETA_P8	3.17 (± 2.32) 95% CI: [2.93 ; 3.4] Range: (0.0 ; 11.59) N = 382	2.48 (± 1.72) 95% CI: [2.22 ; 2.74] Range: (0.0 ; 11.13) N = 169	3.94 (± 2.73) 95% CI: [3.41 ; 4.47] Range: (0.0 ; 11.77) N = 104	<0.001
THETA_T8	3.9 (± 2.22) 95% CI: [3.68 ; 4.12] Range: (0.0 ; 12.95) N = 382	3.03 (± 1.75) 95% CI: [2.77 ; 3.3] Range: (0.0 ; 8.39) N = 169	4.91 (± 2.49) 95% CI: [4.42 ; 5.39] Range: (0.14 ; 12.43) N = 104	<0.001
THETA_FC6	4.91 (± 2.92) 95% CI: [4.61 ; 5.2] Range: (0.0 ; 14.85) N = 382	4.16 (± 2.05) 95% CI: [3.85 ; 4.47] Range: (0.0 ; 13.16) N = 169	5.87 (± 2.79) 95% CI: [5.33 ; 6.41] Range: (0.0 ; 13.01) N = 104	<0.001
THETA_F8	5.34 (± 3.28) 95% CI: [5.01 ; 5.67] Range: (0.0 ; 14.36) N = 382	4.09 (± 1.86) 95% CI: [3.81 ; 4.37] Range: (0.0 ; 12.24) N = 169	5.92 (± 2.81) 95% CI: [5.37 ; 6.47] Range: (0.0 ; 12.79) N = 104	<0.001
THETA_F4	4.72 (± 2.8) 95% CI: [4.44 ; 5.0] Range: (0.0 ; 14.4) N = 382	4.18 (± 1.86) 95% CI: [3.9 ; 4.47] Range: (0.0 ; 10.34) N = 169	5.79 (± 2.13) 95% CI: [5.38 ; 6.2] Range: (0.0775 ; 12.48) N = 104	<0.001
THETA_AF4	5.02 (± 2.83) 95% CI: [4.74 ; 5.31] Range: (0.0 ; 12.5) N = 382	4.19 (± 1.86) 95% CI: [3.91 ; 4.47] Range: (0.0 ; 10.47) N = 169	5.58 (± 2.54) 95% CI: [5.08 ; 6.07] Range: (0.0 ; 12.8) N = 104	<0.001

ALPHA_AF3	2.6 (± 2.08) 95% CI: [2.39 ; 2.81] Range: (0.0 ; 8.47) N = 382	2.19 (± 1.68) 95% CI: [1.93 ; 2.44] Range: (0.0 ; 14.99) N = 169	3.69 (± 3.36) 95% CI: [3.04 ; 4.34] Range: (0.0 ; 15.64) N = 104	0.004
ALPHA_F3	3.67 (± 2.84) 95% CI: [3.38 ; 3.95] Range: (0.0 ; 12.84) N = 382	2.04 (± 1.51) 95% CI: [1.81 ; 2.27] Range: (0.0 ; 13.91) N = 169	4.71 (± 3.82) 95% CI: [3.96 ; 5.45] Range: (0.0 ; 15.38) N = 104	<0.001
ALPHA_F7	2.48 (± 1.6) 95% CI: [2.32 ; 2.64] Range: (0.0 ; 7.85) N = 382	1.88 (± 1.26) 95% CI: [1.69 ; 2.07] Range: (0.0 ; 9.8) N = 169	3.37 (± 2.09) 95% CI: [2.96 ; 3.78] Range: (0.142 ; 11.33) N = 104	<0.001
ALPHA_FC5	2.84 (± 1.69) 95% CI: [2.67 ; 3.01] Range: (0.0 ; 9.21) N = 382	1.74 (± 1.27) 95% CI: [1.55 ; 1.93] Range: (0.0 ; 10.17) N = 169	3.81 (± 2.79) 95% CI: [3.27 ; 4.36] Range: (0.0 ; 14.73) N = 104	<0.001
ALPHA_T7	2.05 (± 1.71) 95% CI: [1.88 ; 2.22] Range: (0.0 ; 12.12) N = 382	1.23 (± 0.887) 95% CI: [1.09 ; 1.36] Range: (0.0 ; 6.51) N = 169	2.3 (± 1.74) 95% CI: [1.96 ; 2.64] Range: (0.0188 ; 9.53) N = 104	<0.001
ALPHA_P7	1.83 (± 1.46) 95% CI: [1.68 ; 1.97] Range: (0.0 ; 13.93) N = 382	1.38 (± 1.26) 95% CI: [1.19 ; 1.57] Range: (0.0136 ; 12.74) N = 169	2.77 (± 2.6) 95% CI: [2.27 ; 3.28] Range: (0.175 ; 18.65) N = 104	<0.001
ALPHA_O1	3.39 (± 2.17) 95% CI: [3.17 ; 3.61] Range: (0.0 ; 15.62) N = 382	2.86 (± 2.81) 95% CI: [2.44 ; 3.29] Range: (0.0 ; 20.38) N = 169	5.79 (± 3.76) 95% CI: [5.06 ; 6.52] Range: (0.24 ; 18.5) N = 104	<0.001
ALPHA_O2	3.54 (± 2.4) 95% CI: [3.3 ; 3.78] Range: (0.0 ; 10.38) N = 382	2.71 (± 1.81) 95% CI: [2.43 ; 2.98] Range: (0.0 ; 8.27) N = 169	5.73 (± 3.65) 95% CI: [5.02 ; 6.44] Range: (0.247 ; 17.39) N = 104	<0.001
ALPHA_P8	2.86 (± 2.36) 95% CI: [2.62 ; 3.1] Range: (0.0 ; 10.12) N = 382	2.11 (± 1.54) 95% CI: [1.88 ; 2.34] Range: (0.0 ; 7.75) N = 169	3.9 (± 3.41) 95% CI: [3.24 ; 4.57] Range: (0.0 ; 14.29) N = 104	<0.001
ALPHA_T8	3.6 (± 2.41) 95% CI: [3.36 ; 3.84] Range: (0.0 ; 10.69) N = 382	2.32 (± 1.78) 95% CI: [2.05 ; 2.59] Range: (0.0 ; 8.75) N = 169	4.74 (± 3.64) 95% CI: [4.03 ; 5.45] Range: (0.18 ; 16.75) N = 104	<0.001
ALPHA_FC6	4.15 (± 2.91) 95% CI: [3.86 ; 4.44] Range: (0.0 ; 12.21) N = 382	2.95 (± 2.49) 95% CI: [2.57 ; 3.33] Range: (0.0 ; 24.05) N = 169	5.64 (± 4.46) 95% CI: [4.77 ; 6.5] Range: (0.0 ; 17.0) N = 104	<0.001
ALPHA_F8	4.41 (± 3.19) 95% CI: [4.09 ; 4.74] Range: (0.0 ; 13.12) N = 382	3.05 (± 2.98) 95% CI: [2.6 ; 3.5] Range: (0.0 ; 29.34) N = 169	6.08 (± 4.9) 95% CI: [5.13 ; 7.04] Range: (0.0 ; 21.75) N = 104	<0.001
ALPHA_F4	3.34 (± 2.3) 95% CI: [3.11 ; 3.57] Range: (0.0 ; 9.81) N = 382	2.64 (± 1.93) 95% CI: [2.34 ; 2.93] Range: (0.0 ; 12.82) N = 169	4.7 (± 3.15) 95% CI: [4.09 ; 5.32] Range: (0.0808 ; 13.99) N = 104	<0.001
ALPHA_AF4	3.74 (± 2.44) 95% CI: [3.49 ; 3.98] Range: (0.0 ; 10.34) N = 382	2.71 (± 2.26) 95% CI: [2.36 ; 3.05] Range: (0.0 ; 18.22) N = 169	4.58 (± 3.48) 95% CI: [3.9 ; 5.26] Range: (0.0 ; 15.24) N = 104	<0.001
BETA1_AF3	1.68 (± 1.5) 95% CI: [1.53 ; 1.83] Range: (0.0 ; 11.56) N = 382	1.36 (± 0.92) 95% CI: [1.22 ; 1.5] Range: (0.0 ; 7.19) N = 169	2.08 (± 1.86) 95% CI: [1.72 ; 2.44] Range: (0.0 ; 9.31) N = 104	0.04

BETA1_F3	2.28 (± 1.88) 95% CI: [2.09 ; 2.47] Range: (0.0 ; 11.83) N = 382	1.28 (± 0.862) 95% CI: [1.15 ; 1.42] Range: (0.0 ; 6.84) N = 169	2.67 (± 2.02) 95% CI: [2.28 ; 3.07] Range: (0.0 ; 8.92) N = 104	<0.001
BETA1_F7	1.54 (± 1.11) 95% CI: [1.43 ; 1.65] Range: (0.0 ; 6.77) N = 382	1.2 (± 0.853) 95% CI: [1.07 ; 1.33] Range: (0.0 ; 7.29) N = 169	1.88 (± 1.31) 95% CI: [1.63 ; 2.14] Range: (0.0787 ; 7.93) N = 104	<0.001
BETA1_FC5	1.85 (± 1.22) 95% CI: [1.73 ; 1.97] Range: (0.0 ; 7.35) N = 382	1.2 (± 0.805) 95% CI: [1.08 ; 1.32] Range: (0.0 ; 7.19) N = 169	2.21 (± 1.54) 95% CI: [1.91 ; 2.51] Range: (0.0 ; 8.44) N = 104	<0.001
BETA1_T7	1.75 (± 1.58) 95% CI: [1.59 ; 1.91] Range: (0.0 ; 13.06) N = 382	0.947 (± 0.725) 95% CI: [0.837 ; 1.06] Range: (0.0 ; 5.12) N = 169	1.56 (± 1.23) 95% CI: [1.32 ; 1.8] Range: (0.0138 ; 6.57) N = 104	<0.001
BETA1_P7	1.41 (± 1.29) 95% CI: [1.28 ; 1.54] Range: (0.0 ; 12.61) N = 382	1.2 (± 1.24) 95% CI: [1.01 ; 1.39] Range: (0.0109 ; 12.45) N = 169	2.1 (± 2.63) 95% CI: [1.59 ; 2.61] Range: (0.107 ; 19.19) N = 104	<0.001
BETA1_O1	2.22 (± 1.7) 95% CI: [2.05 ; 2.39] Range: (0.0 ; 13.41) N = 382	2.38 (± 2.66) 95% CI: [1.97 ; 2.78] Range: (0.0 ; 14.25) N = 169	3.49 (± 2.73) 95% CI: [2.95 ; 4.02] Range: (0.0965 ; 16.92) N = 104	<0.001
BETA1_O2	2.09 (± 1.59) 95% CI: [1.93 ; 2.25] Range: (0.0 ; 10.17) N = 382	2.08 (± 2.23) 95% CI: [1.74 ; 2.42] Range: (0.0 ; 23.75) N = 169	3.37 (± 2.21) 95% CI: [2.94 ; 3.8] Range: (0.131 ; 13.95) N = 104	<0.001
BETA1_P8	1.84 (± 1.53) 95% CI: [1.69 ; 2.0] Range: (0.0 ; 10.06) N = 382	1.68 (± 1.47) 95% CI: [1.46 ; 1.91] Range: (0.0 ; 14.14) N = 169	2.34 (± 1.63) 95% CI: [2.02 ; 2.66] Range: (0.0 ; 6.76) N = 104	0.002
BETA1_T8	2.52 (± 1.82) 95% CI: [2.34 ; 2.7] Range: (0.0 ; 12.11) N = 382	1.74 (± 1.28) 95% CI: [1.55 ; 1.94] Range: (0.0 ; 8.1) N = 169	2.92 (± 2.09) 95% CI: [2.51 ; 3.32] Range: (0.1 ; 9.58) N = 104	<0.001
BETA1_FC6	2.74 (± 2.01) 95% CI: [2.54 ; 2.95] Range: (0.0 ; 12.12) N = 382	2.04 (± 1.47) 95% CI: [1.81 ; 2.26] Range: (0.0 ; 10.86) N = 169	3.26 (± 2.2) 95% CI: [2.84 ; 3.69] Range: (0.0 ; 11.28) N = 104	<0.001
BETA1_F8	3.05 (± 2.4) 95% CI: [2.81 ; 3.29] Range: (0.0 ; 13.71) N = 382	2.07 (± 1.59) 95% CI: [1.83 ; 2.31] Range: (0.0 ; 11.13) N = 169	3.61 (± 2.49) 95% CI: [3.12 ; 4.09] Range: (0.0 ; 11.97) N = 104	<0.001
BETA1_F4	2.15 (± 1.63) 95% CI: [1.99 ; 2.31] Range: (0.0 ; 9.61) N = 382	1.69 (± 1.21) 95% CI: [1.5 ; 1.87] Range: (0.0 ; 9.66) N = 169	2.59 (± 1.65) 95% CI: [2.27 ; 2.91] Range: (0.0446 ; 10.28) N = 104	<0.001
BETA1_AF4	2.55 (± 1.87) 95% CI: [2.36 ; 2.74] Range: (0.0 ; 13.6) N = 382	1.73 (± 1.23) 95% CI: [1.54 ; 1.91] Range: (0.0 ; 8.68) N = 169	2.71 (± 1.89) 95% CI: [2.35 ; 3.08] Range: (0.0 ; 10.78) N = 104	<0.001
BETA2_AF3	1.02 (± 1.15) 95% CI: [0.902 ; 1.13] Range: (0.0 ; 12.01) N = 382	0.906 (± 1.01) 95% CI: [0.753 ; 1.06] Range: (0.0 ; 8.61) N = 169	1.17 (± 1.45) 95% CI: [0.887 ; 1.45] Range: (0.0 ; 12.91) N = 104	0.167
BETA2_F3	1.03 (± 0.924) 95% CI: [0.932 ; 1.12] Range: (0.0 ; 6.92) N = 382	0.82 (± 0.911) 95% CI: [0.681 ; 0.958] Range: (0.0 ; 7.63) N = 169	1.19 (± 1.32) 95% CI: [0.936 ; 1.45] Range: (0.0 ; 12.44) N = 104	<0.001

BETA2_F7	1.0 (± 0.861) 95% CI: [0.915 ; 1.09] Range: (0.0 ; 5.77) N = 382	0.848 (± 1.08) 95% CI: [0.684 ; 1.01] Range: (0.0 ; 9.74) N = 169	1.16 (± 1.15) 95% CI: [0.939 ; 1.39] Range: (0.0426 ; 10.94) N = 104	<0.001
BETA2_FC5	1.24 (± 0.967) 95% CI: [1.15 ; 1.34] Range: (0.0 ; 6.53) N = 382	0.884 (± 1.04) 95% CI: [0.726 ; 1.04] Range: (0.0 ; 9.09) N = 169	1.36 (± 1.32) 95% CI: [1.11 ; 1.62] Range: (0.0 ; 12.24) N = 104	<0.001
BETA2_T7	1.96 (± 2.8) 95% CI: [1.68 ; 2.24] Range: (0.0 ; 34.69) N = 382	0.783 (± 1.0) 95% CI: [0.631 ; 0.935] Range: (0.0 ; 9.13) N = 169	1.15 (± 1.15) 95% CI: [0.932 ; 1.38] Range: (0.0101 ; 9.36) N = 104	<0.001
BETA2_P7	1.15 (± 2.14) 95% CI: [0.937 ; 1.37] Range: (0.0 ; 35.47) N = 382	0.996 (± 1.31) 95% CI: [0.798 ; 1.19] Range: (0.00794 ; 9.63) N = 169	1.37 (± 1.45) 95% CI: [1.09 ; 1.65] Range: (0.0487 ; 9.88) N = 104	<0.001
BETA2_O1	1.17 (± 1.03) 95% CI: [1.06 ; 1.27] Range: (0.0 ; 7.0) N = 382	1.41 (± 1.53) 95% CI: [1.18 ; 1.65] Range: (0.0 ; 9.19) N = 169	1.86 (± 1.58) 95% CI: [1.55 ; 2.17] Range: (0.0373 ; 8.92) N = 104	<0.001
BETA2_O2	1.11 (± 1.04) 95% CI: [1.0 ; 1.21] Range: (0.0 ; 8.06) N = 382	1.14 (± 1.0) 95% CI: [0.984 ; 1.29] Range: (0.0 ; 7.92) N = 169	1.74 (± 1.23) 95% CI: [1.5 ; 1.98] Range: (0.0525 ; 8.42) N = 104	<0.001
BETA2_P8	1.12 (± 1.14) 95% CI: [1.01 ; 1.24] Range: (0.0 ; 9.33) N = 382	1.15 (± 1.12) 95% CI: [0.98 ; 1.32] Range: (0.0 ; 7.74) N = 169	1.43 (± 1.03) 95% CI: [1.23 ; 1.63] Range: (0.0 ; 4.78) N = 104	0.002
BETA2_T8	2.13 (± 3.08) 95% CI: [1.82 ; 2.44] Range: (0.0 ; 32.41) N = 382	1.17 (± 1.14) 95% CI: [1.0 ; 1.35] Range: (0.0 ; 9.06) N = 169	2.07 (± 1.99) 95% CI: [1.69 ; 2.46] Range: (0.0387 ; 12.37) N = 104	<0.001
BETA2_FC6	1.56 (± 1.43) 95% CI: [1.41 ; 1.7] Range: (0.0 ; 9.61) N = 382	2.67 (± 12.02) 95% CI: [0.846 ; 4.5] Range: (0.0 ; 139.5) N = 169	1.82 (± 1.72) 95% CI: [1.48 ; 2.15] Range: (0.0 ; 16.0) N = 104	0.002
BETA2_F8	1.38 (± 1.34) 95% CI: [1.25 ; 1.52] Range: (0.0 ; 11.04) N = 382	2.47 (± 12.53) 95% CI: [0.572 ; 4.38] Range: (0.0 ; 148.74) N = 169	1.69 (± 1.78) 95% CI: [1.34 ; 2.03] Range: (0.0 ; 16.89) N = 104	0.004
BETA2_F4	1.27 (± 1.14) 95% CI: [1.16 ; 1.39] Range: (0.0 ; 7.96) N = 382	1.22 (± 1.83) 95% CI: [0.944 ; 1.5] Range: (0.0 ; 19.05) N = 169	1.55 (± 1.55) 95% CI: [1.25 ; 1.85] Range: (0.0226 ; 14.88) N = 104	<0.001
BETA2_AF4	1.39 (± 1.77) 95% CI: [1.21 ; 1.57] Range: (0.0 ; 20.79) N = 382	1.37 (± 3.02) 95% CI: [0.908 ; 1.83] Range: (0.0 ; 34.27) N = 169	1.43 (± 1.56) 95% CI: [1.12 ; 1.73] Range: (0.0 ; 15.05) N = 10	0.006
GAMMA_AF3	0.868 (± 1.46) 95% CI: [0.721 ; 1.01] Range: (0.0 ; 20.52) N = 382	0.774 (± 1.31) 95% CI: [0.576 ; 0.973] Range: (0.0 ; 11.27) N = 169	1.08 (± 2.21) 95% CI: [0.646 ; 1.5] Range: (0.0 ; 21.7) N = 104	0.097
GAMMA_F3	0.724 (± 0.892) 95% CI: [0.634 ; 0.814] Range: (0.0 ; 7.56) N = 382	0.727 (± 1.49) 95% CI: [0.501 ; 0.953] Range: (0.0 ; 13.5) N = 169	0.992 (± 2.09) 95% CI: [0.586 ; 1.4] Range: (0.0 ; 21.18) N = 104	0.002
GAMMA_F7	0.774 (± 0.851) 95% CI: [0.689 ; 0.86] Range: (0.0 ; 7.73) N = 382	0.745 (± 1.36) 95% CI: [0.538 ; 0.952] Range: (0.0 ; 12.52) N = 169	1.06 (± 1.78) 95% CI: [0.715 ; 1.41] Range: (0.0224 ; 17.83) N = 104	<0.001

GAMMA_FC5	0.966 (± 0.941) 95% CI: [0.872 ; 1.06] Range: (0.0 ; 7.33) N = 382	0.815 (± 1.46) 95% CI: [0.593 ; 1.04] Range: (0.0 ; 12.9) N = 169	1.22 (± 2.06) 95% CI: [0.816 ; 1.62] Range: (0.0 ; 20.67) N = 104	<0.001
GAMMA_T7	1.61 (± 2.97) 95% CI: [1.32 ; 1.91] Range: (0.0 ; 41.77) N = 382	0.746 (± 1.2) 95% CI: [0.565 ; 0.928] Range: (0.0 ; 10.02) N = 169	1.14 (± 1.75) 95% CI: [0.799 ; 1.48] Range: (0.00463 ; 16.1) N = 104	<0.001
GAMMA_P7	0.882 (± 1.11) 95% CI: [0.771 ; 0.994] Range: (0.0 ; 9.39) N = 382	0.923 (± 1.3) 95% CI: [0.726 ; 1.12] Range: (0.00246 ; 9.77) N = 169	1.26 (± 1.55) 95% CI: [0.958 ; 1.56] Range: (0.0284 ; 9.33) N = 104	<0.001
GAMMA_O1	0.923 (± 1.05) 95% CI: [0.817 ; 1.03] Range: (0.0 ; 7.28) N = 382	1.52 (± 3.48) 95% CI: [0.992 ; 2.05] Range: (0.0 ; 41.68) N = 169	1.66 (± 1.94) 95% CI: [1.28 ; 2.04] Range: (0.0175 ; 15.62) N = 104	<0.001
GAMMA_O2	0.851 (± 1.04) 95% CI: [0.746 ; 0.956] Range: (0.0 ; 9.69) N = 382	1.02 (± 1.31) 95% CI: [0.826 ; 1.22] Range: (0.0 ; 11.78) N = 169	1.51 (± 1.69) 95% CI: [1.19 ; 1.84] Range: (0.0244 ; 15.03) N = 104	<0.001
GAMMA_P8	0.852 (± 1.07) 95% CI: [0.744 ; 0.96] Range: (0.0 ; 10.96) N = 382	1.11 (± 1.5) 95% CI: [0.879 ; 1.34] Range: (0.0 ; 11.11) N = 169	1.24 (± 1.21) 95% CI: [1.01 ; 1.48] Range: (0.0 ; 8.97) N = 104	<0.001
GAMMA_T8	1.6 (± 2.35) 95% CI: [1.36 ; 1.83] Range: (0.0 ; 26.29) N = 382	1.52 (± 6.7) 95% CI: [0.498 ; 2.53] Range: (0.0 ; 86.04) N = 169	2.01 (± 2.69) 95% CI: [1.48 ; 2.53] Range: (0.0167 ; 20.99) N = 104	<0.001
GAMMA_FC6	1.19 (± 1.47) 95% CI: [1.04 ; 1.33] Range: (0.0 ; 13.17) N = 382	1.46 (± 3.42) 95% CI: [0.942 ; 1.98] Range: (0.0 ; 37.29) N = 169	1.61 (± 2.86) 95% CI: [1.06 ; 2.17] Range: (0.0 ; 28.77) N = 104	<0.001
GAMMA_F8	1.0 (± 1.4) 95% CI: [0.86 ; 1.14] Range: (0.0 ; 14.62) N = 382	3.23 (± 23.79) 95% CI: [-0.386 ; 6.84] Range: (0.0 ; 303.08) N = 169	1.44 (± 2.91) 95% CI: [0.876 ; 2.01] Range: (0.0 ; 29.42) N = 104	0.003
GAMMA_F4	0.974 (± 1.22) 95% CI: [0.851 ; 1.1] Range: (0.0 ; 10.98) N = 382	1.27 (± 3.73) 95% CI: [0.703 ; 1.84] Range: (0.0 ; 36.68) N = 169	1.41 (± 2.53) 95% CI: [0.922 ; 1.91] Range: (0.00952 ; 25.11) N = 104	<0.001
GAMMA_AF4	1.03 (± 1.48) 95% CI: [0.881 ; 1.18] Range: (0.0 ; 13.61) N = 382	1.59 (± 6.76) 95% CI: [0.565 ; 2.62] Range: (0.0 ; 79.33) N = 169	1.27 (± 2.57) 95% CI: [0.766 ; 1.77] Range: (0.0 ; 25.54) N = 104	0.015

DECLARATIONS

Acknowledgment/Disclaimers/Conflict of Interest: We are especially grateful to the families who participated in this study; without their dedication and support, we may not have completed it.

Informed Consent: All the participants gave their informed consent after the experimental procedure was explained to them by guidelines set by the research ethics committee of Sabancı University, the protocol of the study was approved by the Ethics Committee of Yeditepe University and the clinical trial was registered to the Turkey Pharmaceuticals and Medical Devices Agency (Nbr: 71146310-511.06,2.11.2018).

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Orthopedics / Ortopedi

Social Media and Rotator Cuff Surgery : An Instagram Based Patient Analysis

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ABSTRACT

Purpose: The purpose of this observational study is to investigate the content of social media posts shared with the hashtags [#rotatorcuffsurgery], [#rotatorcuff repair] and [#rotatorcuff]. In particular, we analyzed the contents of posts for timing and perspective, tone, patient's satisfaction and content.

Methods: Posts shared in the Instagram database with the [#rotatorcuffsurgery], [#rotatorcuff repair], and [#rotatorcuff] hashtags from September 1, 2019, to September 1, 2020, were analyzed and categorized by three separate reviewers. Of all 1785 posts, 142 were excluded since they were not related to orthopedic surgery and 12 were excluded due to inter-reviewer disagreements. Finally, 1631 posts shared by patients and surgeons were identified for final analysis in terms of perspective, timing, tone and the content of the posts.

Results: Of the 1631 posts included in the study, 1140 were shared by patients and their acquaintances, whereas 491 posts were shared by orthopedic surgeons. Posts shared by patients and their acquaintances mainly focused on rehabilitation (66%), daily activities (12%) and surgical site (10%), whereas, posts shared by surgeons mainly focused on intraoperative images (52%) and postoperative patient images (29%).

Conlusions: Patients were found to share their surgical experiences in a positive tone and they particularly focused on the rehabilitation process. Whereas orthopedic surgeons commonly shared intraoperative images, probably to better market themselves. Our findings show that the social media posts of patients who undergo rotator cuff surgery may provide important data in the understanding of patients' expectations from rotator cuff surgery.

Keywords: Social media, Instagram, Rotator Cuff Surgery, Shoulder, Rehabilitation

Çağdaş PAMUK

Sosyal Medya ve Rotator Manşet Cerrahisi : Instagram Tabanlı Bir Hasta Analizi

ÖZET

Amaç: Bu gözlemsel çalışmanın amacı, [#rotatorcuffsurgery], [#rotatorcuff onarım] ve [#rotatorcuff] hashtag'leriyle paylaşılan sosyal medya paylaşımlarının içeriğini araştırmaktır. Özellikle gönderilerin içeriklerini zamanlama ve bakış açısı, ton, hasta memnuniyeti ve içerik açısından analiz ettik.

Gereç ve Yöntem: 1 Eylül 2019'den 1 Eylül 20120'e kadar Instagram veri tabanında [#rotatorcuffsurgery], [#rotatorcuff Repair] ve [#rotatorcuff] hashtag'leriyle paylaşılan gönderiler, üç ayrı yorumcu tarafından analiz edildi ve kategorilere ayrıldı. 1785 gönderiden 142'si ortopedik cerrahi ile ilgili olmadığı için ve 12'si hakemler arası anlaşmazlıklar nedeniyle hariç tutulmuştur. Son olarak, hastalar ve cerrahlar tarafından paylaşılan 1631 gönderi, perspektif, zamanlama, ton ve gönderilerin içeriği açısından nihai analiz için belirlendi.

Bulgular: Çalışmaya dahil edilen 1631 gönderiden 1140'ı hastalar ve tanıdıkları tarafından, 491'i ise ortopedi cerrahları tarafından paylaşılmışdı. Hastalar ve tanıdıkları tarafından paylaşılan gönderiler ağırlıklı olarak rehabilitasyon (%66), günlük aktiviteler (%12) ve cerrahi bölgeye (%10) odaklanırken, cerrahlar tarafından paylaşılan gönderiler ağırlıklı olarak intraoperatif görüntülere (%52) ve postoperatif hasta görüntülerine odaklanmıştı (%29).

Sonuç: Hastaların cerrahi deneyimlerini olumlu bir dille paylaştığı ve özellikle rehabilitasyon sürecine odaklandıkları görüldü. Ortopedik cerrahların ise muhtemelen kendi reklamları için genellikle ameliyat sırasındaki görüntüleri paylaştıkları görüldü. Bulgularımız rotator manşet ameliyatı geçiren hastaların sosyal medya paylaşımlarının hastaların rotator manşet ameliyatından beklentilerinin anlaşılmasında önemli veriler sağlayabileceğini göstermektedir.

Anahtar Kelimeler : Sosyal medya, Instagram, Rotator Manşet Cerrahisi, Omuz, Rehabilitasyon

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The widespread use and easy access to mobile devices globally led to the introduction of many social media platforms such as Facebook, Twitter, and Instagram in recent years. These platforms hold a large reach at relatively low cost, representing a distinct advantage over face-to-face approaches. From this point of view, Instagram (San Francisco, CA), one of the largest social media networks with the highest number of active users, is unique in providing a platform for users to share a variety of photo and/or video media content which are called 'posts'. Moreover, in Instagram, as in many of the social media platforms, individuals might also operate hashtags (#) to search and discover similar media produced by other users (1). According to 2020 data, more than 4.6 billion people worldwide use the internet and 4.1 billion people use social media daily (2).Due to its widespread use, social media platforms have an important place in patient education today (3). It has been shown that almost half of the people who use social media when making decisions about their health, do research on social media to choose a hospital and specialist, and those who already go to the specialist to get another opinion (4). It has been shown that the use of social media in health institutions and various specialties is an important factor in increasing the popularity and reputation of the health institution (5). Unavoidably, patients and healthcare professionals are also involved in social media interactions, of which Instagram plays an important part. Patients and healthcare professionals share their expectations and satisfaction regarding the care they have received and most importantly, procedures that they have undergone. However, current data regarding the integration of social media in scientific research in the area of orthopedic surgery is limited. As such, there are only a few studies investigating the social media posts of patients who have undergone shoulder and elbow surgeries and total joint arthroplasty (6,7).

Parallel to the increasing age of the population, the number of patients being subject to rotator cuff tears is also growing. Surgical repair is the definite treatment strategy in rotator cuff tears particularly when conservative strategies fail (8). Thus, obtaining information from patients in regard to their understanding of the operation, postoperative rehabilitation and expectations from the surgical procedure is of great importance to improve the quality of the medical care provided (9).

The purpose of this observational study was to obtain information reflecting patients' and surgeons' experiences regarding rotator cuff surgery from Instagram posts which were shared with the following hashtags: [#rotatorcuffsurgery], [#rotatorcuff repair], and [#rotatorcuff].

We hypothesized that most patients would post photographs and comments comprised of their experience with surgery and their healing process. In regard to the surgeons' posts, we expected to see posts aimed at conveying their clinical success which would arguably be the best form of advertisement.

Method

The public domains of Instagram were searched for posts shared with the following hashtags [#rotatorcuffsurgery], [#rotatorcuff repair] and [#rotatorcuff] on September 2, 2020 to include posts shared during the past 1 year, from September 1, 2019 to September 1, 2020. A total of 1785 posts shared with the aforementioned hashtags were assessed by three separate reviewers that who were orthopaedic surgeons, independently. The reviewers consisted of orthopedic surgeons experienced in rotator cuff surgery. All posts relevant to the above hashtags which featured human subjects were included in this observational study. Inter-reviewer consensus was required to consider a post to be related with these hashtags. In the case of any disagreements, for example, if another reviewer gives a different opinion on a post that one reviewer says has a good opinion the post in question was excluded. Of all 1785 posts, 142 were excluded since they were not related to orthopedic surgery and 12 were excluded due to inter-reviewer disagreement (Figure 1). A final total of 1631 posts shared by patients and surgeons were identified for analysis. The following characteristics of posts were evaluated: the user's perspective, timing, tone and the content of the posts (Table 1).

Table 1. Variables used to categorize the posts

Media format	Photo or video
Perspective of the user's	Patient, friend , family, surgeon
Timing	Preoperative , Postoperative, Peroperative
Tone	Positive or negative
Outcome	Satisfied or dissatisfied
Content	
Return to Work	Presence or Absence
Daily Activities	Presence or Absence
Rehabilitation	Presence or Absence
Surgical Site	Presence or Absence
X-rays	Presence or Absence

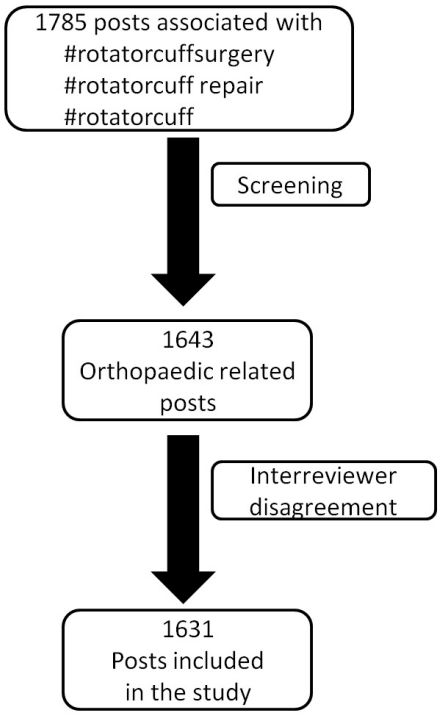

Figure 1. *Flow diagram depicting the selection of patient posts*

One of the evaluation criteria, tone was a criterion that varies according to the person. We have identified positive tone as a smiling expression, thanking the surgeon, telling you that surgery is better than before, recommending it to others, stating that you are satisfied. We defined negative tone as having a bad and anxious facial expression, words stating regret, reporting that it was worse than before, reporting that you did not recommend it to anyone. If all three rewievers made the same comment, positive or negative for a post, we accepted it as it is. However, when even one of the rewievers expressed a different opinion, three reviewers evaluated the post together and when a consensus was reached, the post was included. When there was no consensus, it was excluded from the study. The same method was used to evaluate patient satisfaction. Reasons for satisfactionor dissatisfaction, each entry was analyzed and interpreted for example, if a patient said, "I cannot move my arm or my pain continues," this was considered as dissatisfaction. When evaluating whether the patient was satisfied with the process, it was included in case of consensus among the reviewers. Post was excluded in the absence of consensus among reviewers.

Statistical Analysis

All data analysis was performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington). The study protocol was approved by the Institutional Ethical Committee. The primary outcome for the posts shared by patients was the content of the posts which were categorized as follows: return to work, daily activities, rehabilitation, surgical site, and X-ray images. The surgical site was defined as the incision site in the respective surgery. The content of posts was also the primary outcome for posts shared by the surgeons. The content of the posts shared by surgeons were categorized as follows: postoperative image of the patients, intraoperative images, X-ray images, patient education posts and advertisements.

Results

Of the 1631 posts included in the study, 1140 were shared by patients and their acquaintances, whereas 491 posts were shared by orthopedic surgeons. 1516 posts included photographic media (93%) while the remaining 115 were in the form of videos (7%).

Detailed descriptions of the posts shared by patients and their acquaintances are presented in Table 2. These posts were mostly photos (95%) and were frequently shared by the patients themselves (90%). A large majority of posts were shared postoperatively (91%) and the tone of the posts shared by patients was positive in 90% of all posts. Satisfaction related to the surgery was expressed in only 36 of the posts; however, only 2 posts expressed dissatisfaction. The content of the posts shared by patients and their acquaintances were focused on rehabilitation in 66%, on postoperative daily activities in 12%, on surgical site in 10%, and on X-rays and return to work in 8% and 4%, respectively (Figure 2).

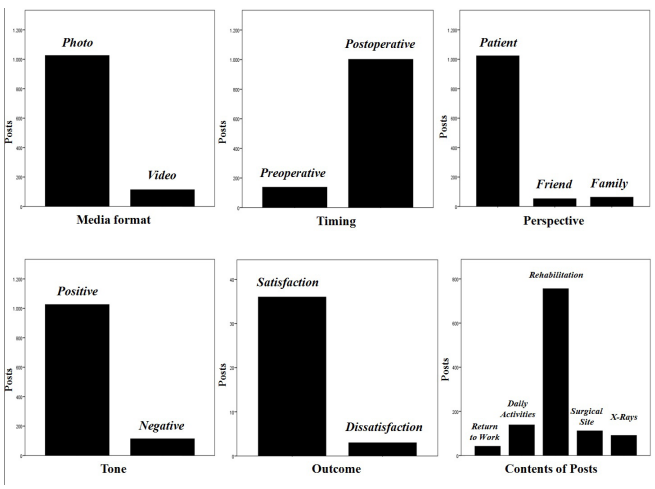

Figure 2. *Analyses of posts shared by patients and their acquaintances*

Table 2. Summary of the posts shared by patients and their acquaintances	
	Total posts (1140)
Media format	
Photo	1083 (95%)
Video	57 (5%)
Perspective	
Patient	1024 (90%)
Friend	51 (4%)
Family	65 (6%)
Timing	
Preoperative	102 (9%)
Postoperative	1038 (91%)
Tone	
Positive	1026 (90%)
Negative	114 (10%)
Outcome	
Satisfied	36
Dissatisfied	2
Content	
Rerturn to Work	42 (4%)
Daily Activities	139 (12%)
Rehabilitation	756 (66%)
Surgical Site	112 (10%)
X-rays	91 (8%)

Detailed descriptions of the posts shared by orthopedic surgeons are given in Table 3. These were mainly focused on intraoperative images of the surgical site (52%) and postoperative images of patients (29%). However, posts associated with patient education were quite low (Figure 3).

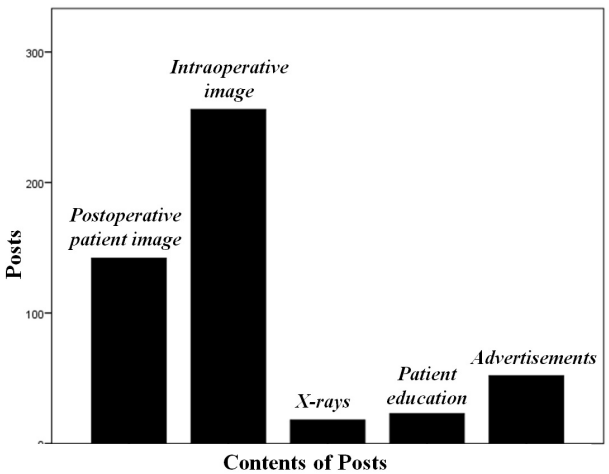

Figure 3. *The content of posts shared by orthopedic surgeons*

Table 3. Summary of the posts shared by orthopedic surgeons	
	Total posts (491)
Media format	
Photo	433 (88%)
Video	58 (12%)
Content	
Postoperative patient image	142 (29%)
Intraoperative image	256 (52%)
X-rays	18 (4%)
Patient education	23 (5%)
Advertisements	52 (10%)

Discussion

As healthcare approach has shifted towards patient-centric care models in recent years, understanding how patients perceive their health and medical procedures has received increased attention since this can provide valuable insight and first-hand feedback to healthcare providers. Several patient-reported outcomes and patient satisfaction surveys are currently in use for this purpose (10,11). However, these surveys and questionnaires are usually categorical and mostly concentrate on the subject determined by the professionals which have prepared the surveys and therefore do not always reflect patients' own perceptions and evaluations (12).

Conversely, social media platforms, for instance, Instagram, provide a wide area for their users to express their perspective without any limitation, allowing medical service providers to gain insight concerning the care they offer (13,14).

Rotator cuff pathologies have been shown to cause a significant burden to healthcare resources globally as a result of the increase in the aging population (15). It is one of the most frequently encountered and surgically addressed diseases of the upper extremity. Among people older than 60 years, the prevalence of rotator cuff tears has been estimated to be at least 10% (16) .In these patients, arthroscopic rotator cuff repair continues to provide a high success rate in terms of functional results when conservative management strategies fail (17). Based on this information, comprehension of patients' expectations, attitude and perspective regarding rotator cuff surgery is crucial to improve the quality of the healthcare provided. Therefore, in the present study, we used Instagram posts shared by patients, their acquaintances and orthopedic surgeons to analyze the perspectives of several specific populations

in terms of their perspectives on rotator cuff surgery. Our results indicate that Instagram, a popular social media platform is frequently used by the patients, their acquaintances and orthopedic surgeons. Patients usually share contents in a positive tone, giving rise to the thought that these patients are highly satisfied with the surgical procedure they have undergone, even though the number of patients reporting their surgical satisfaction was quite low. Previous studies conducted by Ramkumar and colleagues reported similar results regarding the tone of the posts shared by patients undergoing total joint arthroplasty (7). It could be difficult to conclude that patients are highly satisfied with surgery based on a positive tone in a post. Also, a positive tone a week after surgery is different than three months after surgery.

We also found that patients mainly shared posts concerning the rehabilitation process and daily activities, suggesting that these aspects of rotator cuff surgery are of higher importance to the patients and their acquaintances. Additionally, the long rehabilitation process after surgery may also be a contributor to the high number of posts shared in this context (18). This finding is also consistent with the results of Ramkumar et al. in which they enrolled patients undergoing total joint arthroplasty and found that 34% of the posts were associated with the rehabilitation process.

About 10% of the posts included videos or images of the surgical site. Patients may have shared media of the surgical site for the purpose of comparing their wound healing process with others who have undergone similar surgical procedures. The frequency of such posts in the current study was found to be similar to the findings of a similar study focused on total knee arthroplasty, whereas the frequency of similar images in total hip arthroplasty was lower. This result may be explained by the fact that patients do not prefer to share images of their hip which may be considered a more intimate part of the body compared to the knee and shoulder.

Only a minority of posts directly shared their satisfaction with the procedure. However, most of these posts were expressing satisfaction (94%) and only a minority of the posts reported dissatisfaction. The reason for this is unclear but it may have something to do with the fact that people tend to share positive aspects of their private life in social media (19,20).

In terms of surgeons, the large majority was found to share posts with intraoperative images and postoperative images of the patients. It is rather possible that these results are associated with surgeons' attempts at demonstrating their surgical practices and results for commercial purposes (21). It is interesting to note that, sharing intraoperative media might constitute an ethical issue if the images are shared without directly obtaining the patient's permission. The lack of patient privacy challenges patient safety and might deteriorate the patient-doctor relationship. Thus, it is important to remind physicians that sharing patient images in any form requires outright written permission from the patients (22).

The results of our study suggest that analyzing the content of social media posts might provide valuable data for further patient education, could increase the quality of tailored healthcare, and may empower the patient and also the physician in today's patient-centric health care model.

The present study has some limitations to be mentioned. We only included data from Instagram, as it is focused on images and is one of the most actively used social media platforms worldwide; however, this may have caused a bias towards patients who were willing to share images and thus chose to post on Instagram, which may have caused the omission of patients who did not wish to share images and thus primarily chose other social media to share their experiences. Instagram was chosen because it provides a more objective assessment due to the search parameters and media format (picture or video with text caption). However, additional search in Twitter and Facebook might have provided more comprehensive data as a result of the increased sample size. An additional concern from this analysis arises from the fact that individuals may tend only to share positive outcomes, which may positively distort our results. Conclusion

Patients who shared their surgical experiences in Instagram were found to employ a positive tone and they focused on the rehabilitation process in their posts. Orthopedic surgeons were found to primarily share intraoperative images, probably to better market themselves. We suggest that this study provides critical first-hand data in the understanding of patients' expectations after rotator cuff surgery, which can be used to improve the quality of health care.

DECLARATIONS

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Orthopedics / Ortopedi

Cortical Window Reconstruction With Cement Augmented Screw Fixation After Intralesional Curettage Of Low-Grade Chondrosarcomas: A Simple Method With Clinical Results

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ABSTRACT

Purpose: Intralesional curettage with a local adjuvant is a reliable surgical method in the treatment of low-grade chondrosarcomas (LGC). In order to maintain stability, some authors recommend osteosynthesis following intralesional treatment. However, larger osteosynthesis materials may increase complications as well as disturbing postoperative MRI evaluation. In this study, we describe a simple method of cortical window reconstruction with cement-augmented screw fixation.

Methods: 22 patients with LGC were enrolled in this retrospective study who underwent surgical intervention between 2011-2021. All patients were treated in the same manner by intralesional curettage, cement augmentation and fixation with titanium screws embedded in the cement. The clinical outcome was assessed, using the MSTS Score.

Results: The mean age at diagnosis was 44,5 and the mean follow up duration was 56,2 months. The mean long dimension of the cortical window was 4,8 cm for reconstructions with one screw and 6,2 cm for reconstructions with two screws. All of the patients showed excellent clinical outcomes with a mean MSTS score percentage of 91,3. We did not encounter any major complications postoperatively. On MRI evaluations, the image distortion due to thin titanium screw was minimal and cement bone interface was clearly visible without any disturbance.

Conclusion: The convenient use of cement-augmented screw fixation may be a good tool for the reconstruction of cortical window in the treatment of intramedullary tumours of long bones and give a potential chance of obtaining better MRI images without any disturbances postoperatively.

Keywords: Low grade chondrosarcomas, cement augmented screw fixation, intralesional curettage and cementation

Düşük Gradlı Kondrosarkomların İntralezyonel Küretajından Sonra Kortikal Pencerenin Çimento Destekli Vida İle Rekonstrüksiyonu: Basit Bir Yöntem Ve Klinik Sonuçları

ÖZET

Amaç: Lokal bir adjuvan ile intralezyonel küretaj, düşük dereceli kondrosarkomların (LGC) tedavisinde güvenilir bir cerrahi yöntemdir. Bazı yazarlar stabiliteyi korumak için intralezyonel tedaviyi takiben osteosentez önermektedir. Ancak büyük osteosentez materyalleri komplikasyonları arttırabileceği gibi postoperatif MRG değerlendirmesini de rahatsız edebilir. Bu çalışmanın amacı LGC tedavisinde uygulanan intralezyonel küretaj cerrahisi sonrasında kortikal pencerenin çimento ile güçlendirilmiş vida fiksasyonu ile basit bir şekilde rekonstrüksiyonu yöntemini açıklamak ve sonuçlarımızı paylaşmaktır.

Method: Bu retrospektif çalışmaya 2011-2021 yılları arasında cerrahi girişim uygulanan 22 LGC'li hasta alındı. Tüm hastalar aynı şekilde lezyon içi küretaj, sement augmentasyonu ve sement içerisine gömülü titanyum vidalarla fiksasyon ile tedavi edildi. Klinik sonuç, MSTS Skoru kullanılarak değerlendirildi.

Bulgular: Tanı sırasındaki ortalama yaş 44,5, ortalama takip süresi 56,2 ay idi. Kortikal pencerenin ortalama uzun boyutu tek vida ile yapılan rekonstrüksiyonlarda 4,8 cm, iki vidalı rekonstrüksiyonlarda 6,2 cm idi. Hastaların tümü, tedavi sonrasında ortalama MSTS skor yüzdesi 91,3 ile mükemmel klinik sonuçlar gösterdi. Ameliyat sonrası önemli bir komplikasyonla karşılaşmadık. MRI değerlendirmelerinde, ince titanyum vidaya bağlı görüntü bozulması minimum düzeydeydi ve çimento kemik ara yüzü herhangi bir bozulma olmadan net bir şekilde görülebiliyordu.

Sonuç: Çimento destekli vida fiksasyonunun uygun kullanımı, uzun kemiklerin intramedüller tümörlerinin tedavisinde kortikal pencerenin rekonstrüksiyonu için iyi bir araç olabilir ve postoperatif herhangi bir rahatsızlık olmadan daha iyi MRG görüntüleri elde etme şansı verebilir.

Anahtar Kelimeler: Düşük gradlı kondrosarkomlar, çimento destekli vida fiksasyonu, lezyon içi küretaj ve sementasyon

Chondrosarcomas are one of the most common primary malignant bone tumours with variable survival rates and clinical outcomes (1). They are resistant to chemotherapy and irradiation in most cases, therefore surgery is the preferred treatment method (2). High-grade chondrosarcomas are aggressive tumours with an increased risk of metastasis and they are generally treated with wide excision (3). However, there has been a debate about the surgical treatment method for low-grade chondrosarcomas (LGC), since they are less aggressive and rarely metastasize (4-6). Intralesional treatment with or without a local adjuvant therapy is a widely preferred surgical method with a low rate of complications and recurrence (5-11). Although there are different types of local adjuvants, polymethylmethacrylate (PMMA) bone cement is one of the most common local adjuvants used after intralesional curettage (1, 8). PMMA is also useful in providing stability for screw fixations, especially in osteopenic or osteoporotic bones of spinal surgeries (12-14).

Meticulous excision of tumour content requires sufficient visualization of the tumour mass inside the bone. The necessity and type of internal fixation after curettage are controversial in the literature. While some authors believe that internal fixation should be considered in order to avoid pathological fracture risk, others found no difference between an additional osteosynthesis and the lack of it. Besides, there have recently been a number of reports related to the disadvantages of internal fixation with plate and screws (8, 10, 11).

Histopathological diagnosis of LGC poses yet another dilemma. The distinction between benign cartilaginous tumours and LGC has always been a concern for musculoskeletal histopathologists (7). For this reason, the diagnosis is primarily based on the combination of clinical, radiological and histological features. Radiological evaluation in the postoperative period is as important as it is for the diagnosis. Magnetic resonance imaging (MRI) is mandatory for the detection of local recurrences postoperatively. Even though there are modern softwares available, it is generally accepted that internal fixation devices may cause problems with the interpretation of MRI due to distortion (15, 16). Reconstruction of the cortical window with thin titanium screws embedded in the bone cement mass might be a solution for this problem.

In our study, we described a simple method of cortical window reconstruction with cement augmented screw fixation after intralesional curettage of LGC in the long bones and we aimed to investigate the results and complications of this technique.

MATERIAL AND METHODS

We retrospectively evaluated 22 patients (10 male, 12 female) who underwent surgical intervention with intralesional curettage, bone cement augmentation and fixation of cortical window with screws embedded in the cement (Table 1). All patients were referred to our institution's musculoskeletal oncology department between the years 2011-2021 and diagnosed with low-grade chondrosarcomas with the approval of our institution's tumour council, consisting of orthopaedic surgeons, histopathologists, radiologists and medical oncologists. Patients with suspicion of high-grade chondrosarcomas and who had open biopsies or surgeries prior to surgical intervention were excluded. We also excluded patients with local recurrence or metastasis prior to the surgery and tumours located in the axial skeleton.

Pain was the most common presenting symptom (68%). All patients had preoperative AP and lateral radiographs, computed tomography (CT) of the chest, radionuclide bone scintigraphy and gadolinium-enhanced MRI of the lesion (Figure 1 and 2). The exact localization and dimension of the lesions were evaluated on preoperative MRIs and marked on the patients with a surgical skin marker prior to surgery, according to the distance between the lesion and anatomical landmarks (patella for the femur, acromion for the humerus, tibial tuberosity for the tibia and Lister's tubercle for the radius). The localizations were confirmed preoperatively under the fluoroscopic view. All surgeries were performed by the same senior orthopedic surgeon who had been a specialist in musculoskeletal oncology for many years. Under general anesthesia, skin incisions were made in accordance with the center of the tumour. After exposing soft tissues, small drill-holes were made on the cortex and combined with an osteotome to complete the rectangle-shaped cortical window. The dimensions of the cortical window were decided according to the preoperative imaging, being either equal to the size of the lesion in most cases, or having a sufficient visualization of the tumoural mass in the remaining ones. All patients had intraoperative frozen-section biopsies, all of which were identified as low-grade cartilaginous tumours. After biopsy, intralesional curettage was performed through the window and microscopic residual tumoural tissues were debrided with high speed burr both intramedullarily and on the inner layer of cortical window. Intralesional curettage was ended with high

pressure lavaging of the intramedullary region with saline. One or two micro (2,5 mm), headless, self-tapping and self-drilling, cannulated and fully-threaded compression screws (Acutruck®, Acumed, Oregon, USA) according to the length of the cortical window were used after drilling. Meanwhile, a polymethylmethacrylate (PMMA) bone cement (Versabond®, Smith & Nephew, UK) was prepared and the tumour cavity was filled with the cement. The cortical window with titanium screw was then embedded on the cement, anchoring the screw into the cement mass (Figure 3). Special attention was given to the continuity of the cortex on at least three host window edges. The procedure was finalized after irrigation and bleeding control. The tumoural tissues obtained from the cavity were sent to the histology department for the permanent diagnosis. All specimens were evaluated by the same histopathologist who had nearly 20 years of experience in musculoskeletal histopathology. Specimens were evaluated and staged according to the Enneking MSTS staging system (17).

Immediate range of motion exercises began in all patients on the second postoperative day. Patients who were operated for the lower extremity were allowed for partial weight-bearing with crutches for 3 to 4 weeks and patients who were operated for the upper extremity used either a sling (humerus patients) or a static wrist splint (distal radius patient) for 3 weeks.

All patients were followed with 3-monthly plain radiographs and 6-monthly MRIs during the postoperative first year and 6-monthly radiographs and MRIs during the postoperative second year (Figure 4 and 5). After two years, the patients were examined once a year with radiographs and MRIs until the final follow-up. The clinical outcome was assessed at every examination, using the Musculoskeletal Tumour Society (MSTS) scoring system (18). Local or systemic complications such as infection, loss in the range of motion, pathologic fracture, local recurrence or metastasis were recorded.

Table 1. Summary of patient data.

Case	Sex and Age, y	Side	Location	Follow-up Duration, mo	Number of screws embedded	MSTS	Oncologic
1	M, 62	L	Proximal humerus	84	1	26	A
2	F, 55	L	Distal femur	66	1	29	A
3	F, 56	R	Proximal humerus	78	1	28	A
4	M, 44	R	Distal femur	69	1	30	A
5	F, 48	L	Femur diaphysis	62	1	30	A
6	F, 45	L	Humerus diaphysis	64	2	23	A
7	F, 54	R	Distal femur	42	1	27	A
8	M, 24	R	Distal radius	40	1	27	A
9	F, 45	R	Humerus diaphysis	31	1	28	A
10	M, 34	L	Tibia diaphysis	27	1	28	A
11	F, 39	L	Femur diaphysis	38	2	29	A
12	F, 46	R	Proximal humerus	64	1	29	A
13	F, 38	R	Tibia diaphysis	60	1	27	A
14	M, 52	L	Proximal humerus	66	1	28	A
15	M, 39	R	Distal femur	48	1	28	A
16	M, 40	L	Distal femur	102	1	24	A
17	M, 43	R	Distal femur	40	2	27	A
18	F, 34	L	Distal femur	44	1	26	A
19	F, 40	L	Femur diaphysis	42	2	28	A
20	F, 44	L	Humerus diaphysis	60	2	26	A
21	M, 50	R	Distal femur	56	2	26	A
22	M, 47	R	Humerus diaphysis	54	2	29	A

y: year; mo: month; MSTS: Musculoskeletal Tumor Society Scoring System; M: male; F: female; L: left; R: right; A: alive and free of disease

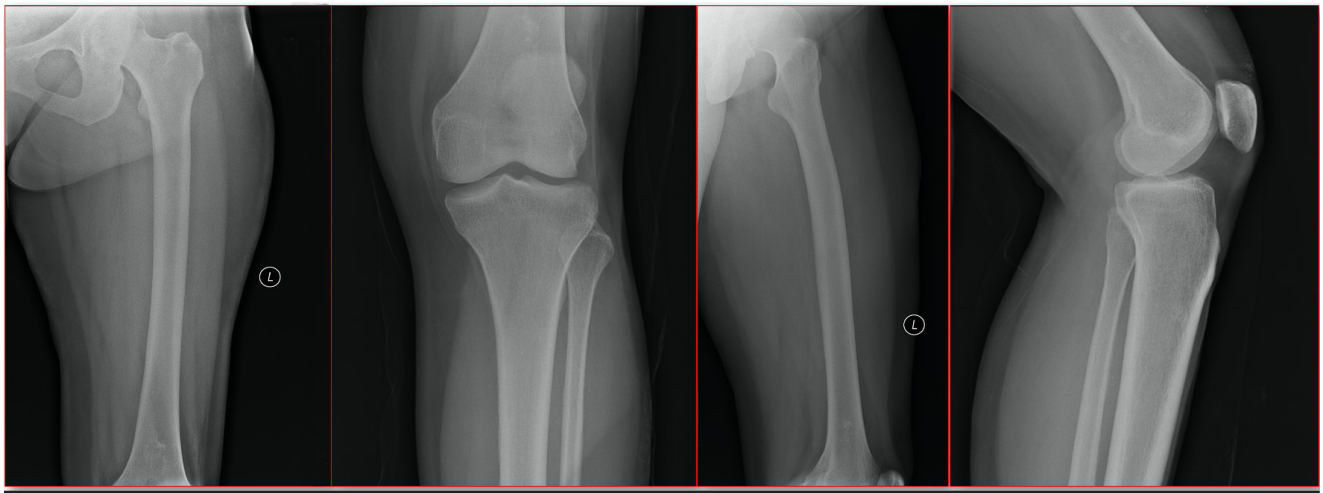

Figure 1. *Preoperative AP and lateral x-rays of the patient with LGC in left distal femur*

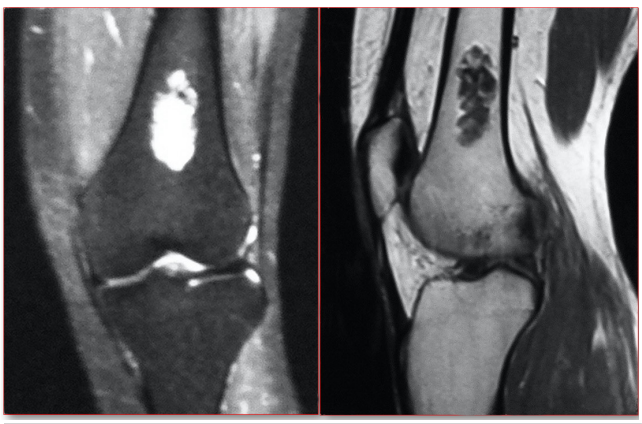

Figure 2. *Preoperative coronal and sagittal MRI views of the lesion*

Statistical analysis was performed using SPSS (version 25 .0 for Mac; SPSS, Chicago, IL). Descriptive statistics were stated as mean, minimum, maximum range for numerical variables and percentages for categorical variables. Mann-Whitney U test was used for the comparison of numerical variables in independent groups. A p value of <0.05 was accepted as statistically significant.

RESULTS

The mean age at diagnosis was 44,5 (24-62) and the mean follow up duration was 56,2 months (27-102). Anatomical localizations of the tumour were 8 distal femoral metaphysis, 3 femur diaphysis, 4 proximal humeral metaphysis, 4 humerus diaphysis, 2 tibia diaphysis and 1 distal radius. All patients had grade IA tumours according to the MSTS staging system and all of the final specimens were identified as low-grade chondrosarcomas. The mean length of intramedullary tumour extension was 6,4 cm (4-8). The mean long dimension of the cortical window was 5,3 cm (2-8). One thin titanium screw was used for the reconstruction of the cortical window in 15 patients, while two screws were used in 7 patients. The mean long dimension of the cortical window was 4,8 cm (4-6,2) for reconstructions with one screw and 6,2 cm (5,8-7,2) for reconstructions with two screws. None of the patients had local persisting pain during the postoperative sixth month and all of them returned to daily activities with full range of motion by the end of the third month. They all achieved excellent clinical outcomes during the first postoperative year control with a mean MSTS score of 27,4 (range between 23-30) (91,3%). There was no statistically significant difference between lower and upper extremity MSTS scores. Scores also did not show significant difference between patients with reconstruction of the cortical windows with either one or two screws.

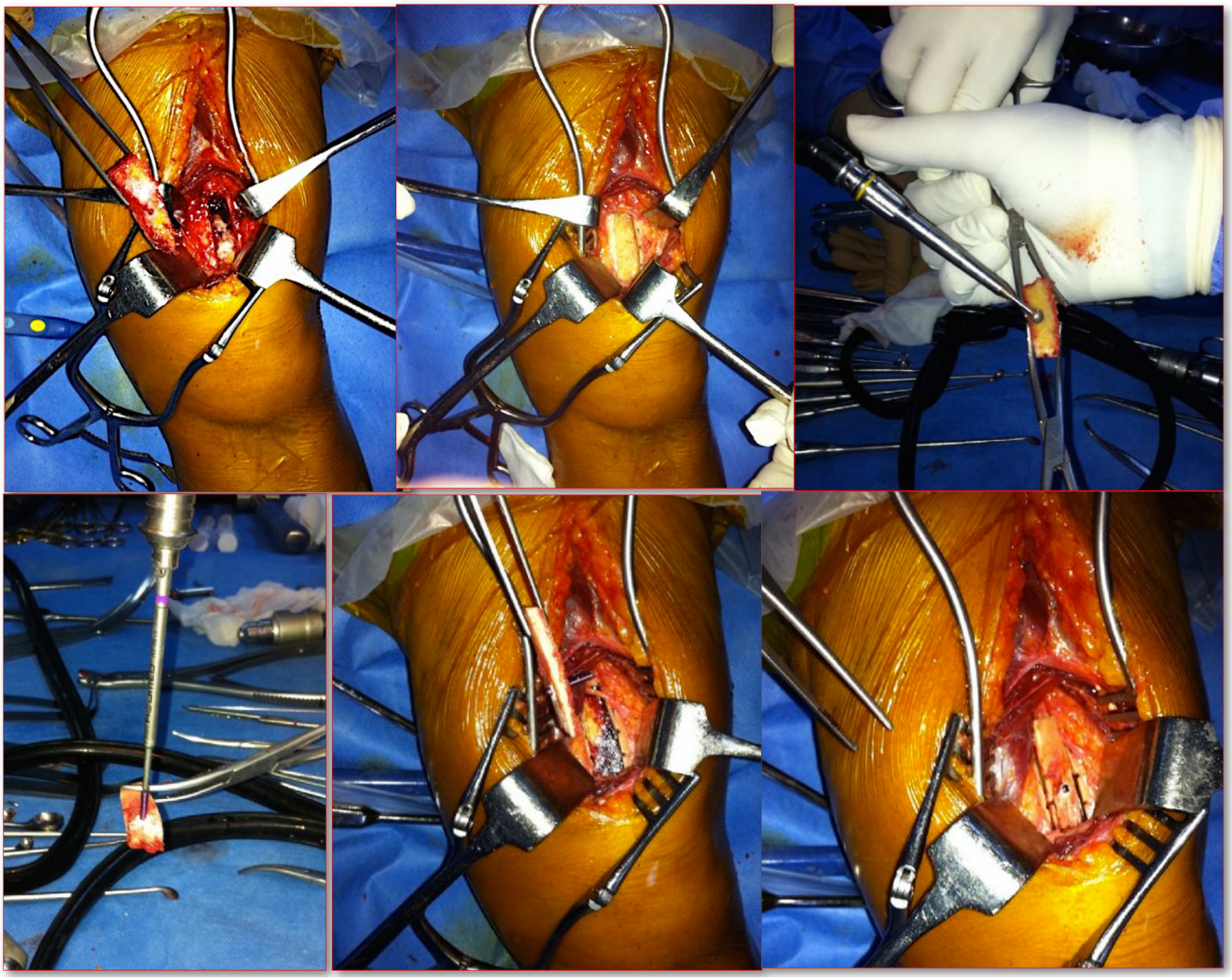

Figure 3. *Opening and extraction of the cortical window. Shaving of the cortical window with high-speed burr. Application of the mini titanium screw onto the cortical window. Closure of the cortical window and augmentation of the screw to the bone cement. View of the titanium screw embedded in the bone cement and cortical window*

In one of the patients, superficial skin infection had developed during the early postoperative period, but treated well with oral antibiotics. We did not observe any other infection, hematoma, delayed healing, nerve palsy, pseudoarthrosis or other complications postoperatively. None of the patients needed a revision surgery or removal of the screw due to an irritation. All cortices were united by the end of the third month postoperatively and no pathological fracture was observed in the follow-up period. No patients developed any local recurrence or distant metastasis and all of them were alive without disease until the final examination. On radiographic evaluations during the postoperative period, the cortical windows were stable without any displacements. On MRI evaluations, the image distortion due to thin titanium screw was minimal and cement bone interface was clearly visible without any disturbance.

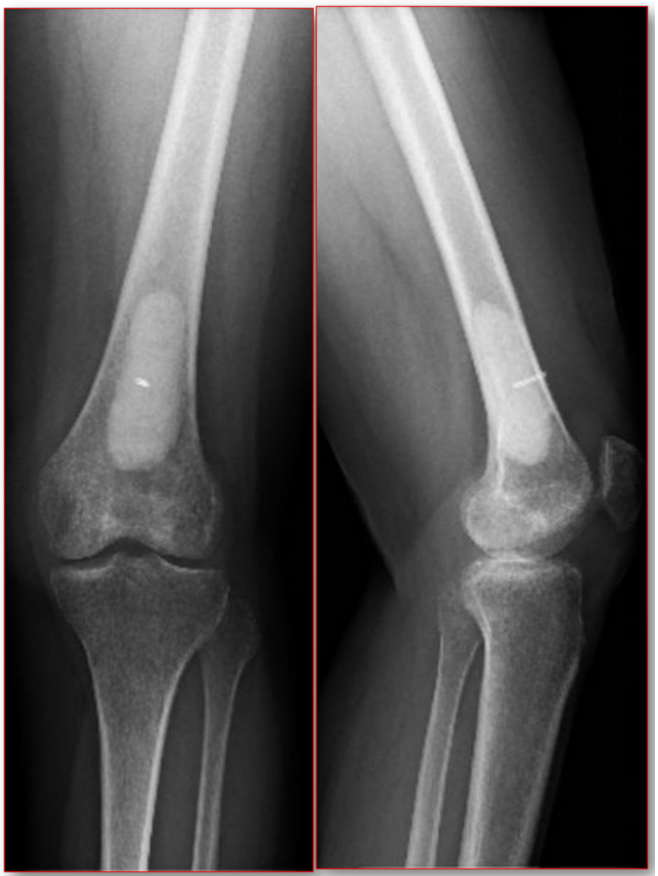

Figure 4. *Postoperative 3rd month AP and lateral x-rays*

DISCUSSION

Chondrosarcomas are malignant tumours of cartilaginous origin with a potential of both local aggressiveness and distant metastasis (3, 4). Treatment strategies for high-grade chondrosarcomas are well-established in the literature; while there is still a debate about the management of LGC. Since they rarely metastasize, the primary objective should be to preserve function with a less invasive surgical method when considering LGC. There are different surgical procedures described in the literature for the treatment of LGC (5-9). Shemesh et al. (2) found that recurrence rates were similar between the LGC patients treated with either intralesional curettage or wide excision in their meta-analysis. Bauer et al. (19) used this technique and achieved excellent results with a very low recurrence rate in their study consisting of 23 patients. In the study of Hanna et al. (9), 39 patients diagnosed with LGC were treated with intralesional curettage and cementation. They also reported good results without any metastasis or major complications.

Most authors agree that local adjuvants should be used for the prevention of tumoural spread after intralesional curettage of LGC. Streitbürger et al. (20) found that the 3 patients who were treated only with intralesional curettage (without the use of a local adjuvant) developed local recurrence after a mean follow-up of 26 months. However, there is no gold standard type of local adjuvant described in the literature. Cryotherapy, phenol application, cauterization, bone grafts or PMMA may be used as local adjuvants (1, 6, 8, 9). In our study, we used PMMA as the local adjuvant; therefore, we not only benefited from the cytotoxic and necrotizing effects of the cement, but also used it as an aid to our screw fixation.

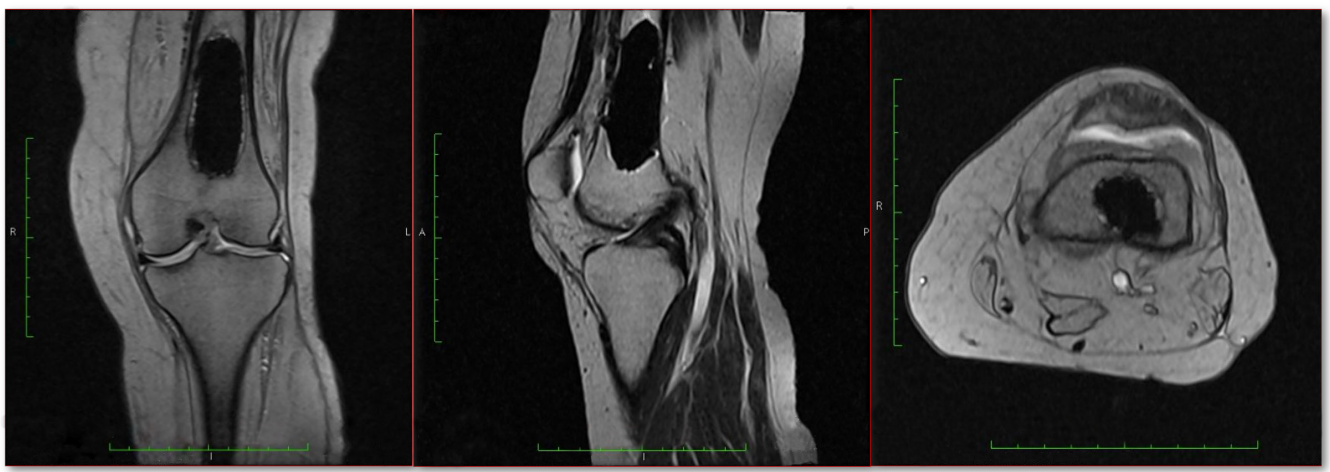

Figure 5. *Postoperative 6th month coronal, sagittal and axial MRI views of the lesion*

Different cement types are used in the literature for augmentation of screws and suture anchors to improve the fixation stability of both normal and osteoporotic bones (21-23). PMMA has been the most commonly used bone cement for augmentation of screw fixation, especially in spinal and trauma surgeries (12, 24, 25). Jee Soo Jand et al. (25) used this technique in metastatic spinal tumours in the past and found good results in terms of stability in poor-quality bone caused by malignancy. Toy et al. (26) examined reconstruction strength of cements with the augmentation of crossed screws and found that screw augmentation resulted in a stronger reconstruction than that obtained with cement alone in the reconstruction of distal femoral tumor defects. With our study, we also would like to encourage the usage of cement-augmented screw fixation for tumour surgery in long bones.

The literature also lacks data about about the effect of timing of screw placement after cement injection. Linhardt et al. (14) found no significant difference between screws inserted into soft or cured PMMA. However, they detected increased bone failure when softer cement was used, and increased screw-cement junction failure when cured cement was used; leading to a potential conclusion of softer cement easing and improving fixation of both screw-cement and bone-cement interfaces. Similarly, Flahiff et al. (13) stated that augmentation of "doughy" cement to the screw had resulted in significantly stronger initial fixation compared to the hard cement. We chose to apply the screws into the doughy cement in our study.

Additional osteosynthesis after intralesional curettage was also questioned by various studies. Campanacci et al. (4) found that the risk of pathological fracture after these interventions is 1,9%. Even though the risk of pathological fracture is low, it is considered as an important advantage for these patients in terms of early postoperative mobilization by increasing the stability. In the study of Ahlman et al.'s (8), 10 patients were treated with intralesional curettage and cementation in addition to cryoablation. They recommended routine internal fixation after the procedure in order to prevent any pathological fracture and increase stabilisation. Omlor et al. (10) found that complications were almost twice as high in patients with LGC in the distal femur who were treated with additional plates and screw fixation for osteosynthesis after intralesional curettage and cementation. In another study by Omlor et al. (11), the amount of blood loss was higher and surgery time and hospitalization periods were longer in patients diagnosed with LGC and enchondromas in proximal humerus and treated with intralesional curettage and cementation with an additional osteosynthesis. They also pointed to a possible artifact issue during the postoperative MRI controls of their patients, since plates and screws were again used as fixation materials.

Orthopaedic implants may prevent accurate interpretation on postoperative MRIs due to metallic artifacts and cause significant problems in the follow-up process (16). It is known that implants made of titanium alloy create fewer artifacts than those produced by stainless steel (16). Larger implants may produce obstructive artifacts which could complicate the MRI evaluation; while smaller ones produce less severe artifacts (15). Various methods have been described for reducing metal-related artifacts and optimizing imaging techniques in postoperative patients (15, 16). Based on the information provided by these studies, we applied smaller orthopaedic implants made of titanium alloy to our patients for the fixation of the cortical windows. We did not encounter any problem regarding obstructive artifacts in our postoperative control MRIs. However, more studies are needed to determine the relationship between the distortion rate on the MRI evaluation and dimensions of the implants used in the surgery.

There are some limitations to this study. First of all, this is a retrospective study in which a surgical technique is described with a relatively small number of patients. The method of cement augmented screw fixation has been used in spinal surgeries, especially for osteoporotic bones. However, the use of this technique in long bones and tumoral defects have not been clearly described in the literature. Undoubtedly, more studies with larger control groups are needed to determine the efficacy of this method and to determine on which patients to use this technique for surgery. Another limitation in our study was that the number of screws which were used for fixation was decided upon surgeon's preference. It would have been ideal if more standardized protocols were followed for the relationship between the dimensions of the cortical windows and the number of screws that were used for fixation. Further biomechanical investigations are also necessary for detecting the characteristics of cement augmented screw usage, the reconstruction properties in the fixation of cortices of long bones and determining how these implants work in the prevention of pathological fractures, in order to achieve more standardized guidelines.

CONCLUSION

Reconstruction of the cortical window with one or two thin titanium screws embedded in the bone cement may be a simple and reliable method of fixation in long bones without any complications regarding stability or risk of pathological fracture, in addition to the potential chance of obtaining better MRI results without any disturbances during the postoperative period. The convenient use of this method may be a good tool in the treatment of intramedullary tumours of long bones. Additional biomechanical and clinical studies need to be performed in order to evaluate the feasibility of this technique.

DECLARATIONS

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Psychiatry / Psikiyatri

Emotion Dysregulation Affects Functionality in Major Depressive Disorder

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ABSTRACT

Purpose: Mood disorders are recurrent chronic mental illnesses known to affect functionality. This study aimed to compare the coping strategies and emotion regulation difficulties in depression and bipolar disorder and observe the effects of coping strategies and emotion regulation on functionality.

Methods: Thirty-one patients with bipolar disorder (BD), 29 with major depressive disorder (MDD), and 27 healthy controls (HC) were included in the study. Participants completed the Coping Strategies Inventory (COPE) (adaptive coping strategies: COPE-A, maladaptive coping strategies COPE-M), the Bipolar Disorder Functioning Questionnaire (BDFQ), the Difficulties in Emotion Regulation Scale (DERS), the Hamilton Depression Scale (HAM-D), and the Young Mania Rating Scale (YMRS).

Results: In the BD group, a significant positive correlation was found between COPE-M and DERS scores ($p<0.005$, $r=0.361$), and a significant negative correlation was found between COPE-M and BDFQ ($p<0.005$, $r=-0.370$) scores. In the MDD group, a significant positive correlation was found between COPE-A and BDFQ scores ($p<0.001$, $r=0.711$), and a significant negative correlation was found between DERS and BDFQ ($p<0.001$, $r=-0.530$). The scores of BDFQ were statistically and significantly positively predicted by the COPE-A (B:0.415, $p=0.002$) and negatively by the DERS (B: -0.322, $p=0.016$) scores.

Conclusion: Emotion dysregulation may predispose to depressive symptomatology and negatively affect clinical course and functionality. Addressing emotion regulation difficulties and increasing the use of adaptive coping strategies in therapeutic interventions may contribute to the improvement of functionality as well as clinical improvement.

Keywords: emotion dysregulation, coping, bipolar disorder, depressive disorder, functionality

Duygu Düzenleme Güçlüğü Majör Depresif Bozuklukta İşlevselliği Etkiliyor

ÖZET

Amaç: Duygudurum bozuklukları, işlevselliği etkilediği bilinen tekrarlayan kronik ruhsal hastalıklardır. Bu çalışmada, depresyon ve bipolar bozuklukta başa çıkma stratejileri ile duygu düzenleme güçlüklerinin karşılaştırılması ve başa çıkma stratejileri ile duygu düzenlemenin işlevsellik üzerindeki etkisinin gözlemlenmesi amaçlanmıştır.

Yöntem: Çalışmaya 31 bipolar bozukluk (BB), 29 majör depresif bozukluk (MDB) tanılı katılımcı ve 27 sağlıklı kontrol (SK) dahil edildi. Başa Çıkma Stratejileri Envanteri (COPE) (adaptif başaçıkma stratejileri: COPE-A, maladaptif başetme stretejileri COPE-M), Bipolar Bozuklukta İşlevsellik Ölçeği (BDFQ), Duygu Düzenleme Güçlükleri Ölçeği (DERS), Hamilton Depresyon Ölçeği (HAM-D) ve Young Mani Derecelendirme Ölçeği (YMRS) katılımcılar tarafından doldurudu.

Bulgular: BB grubunda COPE-M ile DERS puanları arasında pozitif yönde ($p<0.005$, $r=0.361$), COPE-M ile BDFQ arasında negatif yönde anlamlı bir ilişki bulundu ($p<0.005$, $r=-0.370$). MDB grubunda COPE-A ile BDFQ ($p<0.001$, $r=0.711$) puanları arasında pozitif yönde, DERS ile BDFQ ($p<0.001$, $r=-0.530$) arasında negatif yönde anlamlı bir korelasyon bulundu. BDFQ, COPE-A tarafından pozitif (B:0.415, $p=0.002$) ve DERS tarafından negatif (B:-0.322, $p=0.016$) olarak yordandı.

Sonuç: Duygu düzenleme güçlüğünün depresif semptomatolojiye zemin hazırlayabileceği, klinik gidişi ve işlevselliği olumsuz etkileyebileceği düşünüldü. Terapötik müdahalelerde duygu düzenleme güçlüklerinin ele alınması ve adaptif başa çıkma stratejilerinin kullanımının arttırılması klinik iyileşmenin yanı sıra işlevselliğin iyileştirilmesine de katkıda bulunur.

Anahtar Sözcükler: duygu düzenleme güçlüğü, başa çıkma, bipolar bozukluk, depresif bozukluk, işlevsellik

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Mood disorders are recurrent chronic mental illnesses known to affect functionality. Despite adequate treatment, many individuals with mood disorders experience recurrent episodes and thus impairment in functionality that adversely affect the treatment response. In order to improve treatment response, it is necessary to better understand the psychological mechanisms that may contribute to the disease symptoms and to control the factors that predict relapse (1).

Negative life events and stress can cause recurrent episodes of mood disorders (2). Stressful events lead to significant emotional responses (3). Emotion regulation is the ability of a person to regulate emotional responses (4) Accordingly, it has been suggested that emotion regulation skills and coping strategies help in adapting to stress (5). It is known that coping strategies and emotion regulation skills are different concepts, but they are highly related to each other in terms of involving the efforts to regulate emotions in response to stressful events and situations (6). It has been reported that both coping strategies and emotion regulation skills contribute to the functionality in mood disorders (7, 8).

The style of coping with stress plays a substantial role in individual well-being and can be important in treatment. Coping is defined as "regulating actions under stress" (9). Coping strategies can be conceptualized as maladaptive or adaptive. Adaptive strategies, such as active behavioral strategies, lead to improved psychosocial functioning, while maladaptive coping strategies, such as denial of adverse situations, are associated with increase in severity of depression (10,11). It has been observed that individuals with bipolar disorder (BD) use maladaptive coping strategies in the face of negative affect more than healthy controls (7,12). Even between BD subtypes (Bipolar I and II), differences were found in coping strategies (11).

In this study, it was aimed to compare the coping attitudes and emotion regulation difficulties in depression and bipolar disorder. Also, it was intended to observe the effects of coping strategies and emotion regulation on functionality.

MATERIAL and METHODS

Participants: This is a cross-sectional descriptive study with data collected between September 2017 and March 2018. Patients with major depressive disorder (MDD) and BD in remission, who consecutively admitted to the psychiatry outpatient clinics in Trabzon Kanuni Training and Research Hospital were included in the study. Diagnoses were confirmed with the Structured Clinical Interview According to DSM-IV- TR- Axis I Disorders (SCID 1) (13,14). The control group was randomly selected among the individuals who applied to the other outpatient clinics in the same hospital. The inclusion criteria for the patient group were being between 18-65 years of age, being in remission for at least 6 months, being literate, and not having any psychiatric comorbidities. The inclusion criteria for the control group were not having received previous psychiatric treatment and not having a history of psychiatric illness in first-degree relatives. Exclusion criteria were illiteracy, hospitalization in the last 6 months, being outside the age range of 18-65 years, having another psychiatric comorbidity, presence of dementia, delirium, mental retardation, head trauma, or chronic neurological diseases. Written informed consent was obtained from those who agreed to participate in the study. The study was planned in accordance with the Declaration of Helsinki, and ethical approval dated 7.7.2017 and numbered 2017/27 was obtained from the ethics committee of Trabzon Kanuni Training and Research Hospital. Between the scheduled dates, 105 participants agreed to participate in the study. 9 participants with psychiatric comorbidities (3 participants with substance use disorder, 2 participants with generalized anxiety disorder, 1 participant with social anxiety disorder, 1 participant with obsessive-compulsive disorder, and 2 participants with mental retardation), 2 participants with neurological comorbidities (1 participant with epilepsy, and 1 participant with multiple sclerosis) and 7 participants who could not complete the tests were not included in the study. 31 patients with BD, 29 patients with MDD, and 27 healthy controls were included in the study.

Tools: Participants completed the Sociodemographic Data Form and the other scales.

Coping Strategies Inventory (COPE): It is a self-report scale consisting of 60 questions and was developed by Carver et al. (15). Turkish validity and reliability study was performed by Ağargün et al. (16). The Cronbach alpha values of the original form were between 0.45 and 0.92 and 0.79 for the Turkish form. Positive reinterpretation and development [1], mental disengagement [2], problem-focused

and emotionally focused coping [3], beneficial social support use [4], active coping [5], denial [6], religious coping [7], humor [8], behavioral disengagement [9], restraint coping [10], emotional social support use [11], substance use [12], acceptance [13], suppression of competing activities [14], planning [15], are the subscales of the inventory. [2],[3],[6],[9],[12] were determined as maladaptive coping strategies, the others were determined as adaptive coping strategies (15,16).

Bipolar Disorder Functioning Questionnaire (BDFQ): It consists of 52 items. It was developed by Aydemir et al. (17) and its validity and reliability study was conducted. The Cronbach alpha value of the scale was 0.91. It consists of 11 subscales. The sum of these subscales gives the total scale score. The scale does not have a cut-off score, and higher scores indicate increased functionality (17).

Difficulties in Emotion Regulation Scale (DERS): The DERS was developed by Gratz and Roemer (2004) and has 36-items (18). Awareness, clarity, nonacceptance, strategies, impulse, and goals are the subscales of the scale. The validity and reliability study of the Turkish version was performed by Rugancı and Gençöz (2010). The Cronbach alpha value of the scale was 0.94. The scale does not have a cut-off score, higher scores indicate more difficulty in emotion regulation (19).

Hamilton Depression Scale (HAM-D): The scale is used to measure the clinical severity of depression in the last week and consists of 17 questions. It was developed by Max Hamilton (20) and Turkish validity and reliability study of the scale was performed by Akdemir et al. (21). It is scored between '0' and '53' points. The Cronbach alpha value of the scale was 0.75.

Young Mania Rating Scale (YMRS): It was developed by Young et al. (22) and Turkish validity and reliability study was performed by Karadağ et al. (23). The Cronbach alpha value of the scale was 0.79. It is used to measure the clinical severity of mania. The scale consists of 11 items.

Statistics: Statistical analyses were performed with SPSS 29.0 (IBM, Armonk, New York, USA) program. Categorical variables were compared with the Chi-Square test. Sociodemographic and clinical variables were summarized with mean, standard deviation, and median, 25-75 percentile values. The data were compared to the normal distribution with the Shapiro-Wilk test and histogram graphics. Kruskal Wallis and Mann-Whitney U tests were used to compare continuous data that did not follow the normal distribution. Posthoc analyses for the variables that showed a significant difference in the Kruskal-Wallis analysis were performed with the Bonferroni corrected Mann-Whitney U test. Correlation and linear regression analyses were performed to examine the relationship between scale scores. Backward modeling was used in linear regression analysis. The statistical significance level was accepted as 0.05 in all analyses.

RESULTS

There was no statistical difference between the groups in terms of age, gender, marital status, educational status, income, number of suicide attempts, duration of education, and disease. Age at disease onset was significantly younger in the BD group than in the MDD group ($p=0.007$). Employed participants in the HC group were significantly higher than in the MDD and BD groups ($p<0.001$). The rate of living in the city was significantly lower in the MDD group than in the BD and HC groups ($p<0.001$). The number of depressive episodes is significantly higher in the MDD group ($p<0.001$). (Table 1).

The scores of BDFQ were significantly higher ($p<0.001$) and the scores of DERS were significantly lower in the HC group than BD and MDD ($p=0.007$) (Table 2).

In the BD group, a significant positive correlation was found between COPE-M and DERS scores ($p<0.005$, $r=0.361$), and a significant negative correlation was found between COPE-M and BDFQ ($p<0.005$, $r=-0.370$). In the MDD group, a significant positive correlation was found between COPE-A and BDFQ scores ($p<0.001$, $r=0.711$), and a significant negative correlation was found between DERS and BDFQ ($p<0,001$, $r=-0.530$) (Table 3).

The backward model was used in the linear regression analysis. In the MDD group, it was determined that the BDFQ was statistically significantly positively predicted by the COPE-A (B:0.415, $p=0.002$) and negatively by DERS (B: -0.322, $p=0.016$) (Table 4). The regression model was not significant for the predictors of functioning in the BD group.

Table 1: Sociodemographic and clinical characteristics of the groups

	HC n: 27	BD n: 31	MDD n: 29	P
Gender n(%)				
Female	17 (63.00)	21 (67.70)	23 (79.30)	0.384
Male	10 (37.00)	10 (32.30)	6 (20.70)	
Marital status n(%)				
Married	18 (66.70)	11 (35.50)	16 (55.20)	0.054
Single	9 (33.30)	20 (64.50)	13 (44.80)	
Occupation n(%)				
Not employed	2 (7.40)[a]	20 (64.50)[b]	22 (75.90)[b]	**<0.001**
Employed	25 (92.60)[a]	11 (35.50)[b]	7 (24.10)[b]	
Place of residence n(%)				
District	0 (0.0)[a]	4 (12.90)[a]	18 (62.10)[b]	**<0.001**
City	27 (100.00)[a]	27 (87.10)[a]	11 (37.90)[b]	
Income n(%)				
Minimum wage	8 (29.60)	8 (25.80)	11 (37.90)	0.587
Higher than min wage	19 (70.40)	23 (74.20)	18 (62.10)	
Age (year)				
mean±SD	36.41 ± 8.68	33.74 ± 11.17	33.79 ± 9.65	0.395*
Median (%25-%75)	31 (29-44)	34 (25-40)	32 (26.5-40.5)	
Education (year)				
mean±SD	10.07 ±4.61	11.29 ± 3.01	10.90 ± 3.16	0.616*
Median (%25-%75)	37 (29-44)	11 (11-13)	11 (8-13.5)	
Disease duration (month)				
mean±SD		92.81 ± 77.32	63.24 ± 67.25	0.056**
Median (%25-%75)		72 (36-120)	29 (18-108)	
Age of onset (year)				
mean±SD		22.74 ± 7.12	27.3 ± 9.02	**0.007****
Median (%25-%75)		21 (18-24)	25 (22-31)	
Number of depressive episodes				
mean±SD		0.42 ± 0.77	1.62 ± 0.20	**<0.001****
Median (%25-%75)		0 (0-1)	2 (1-2)	
Number of suicide attempts				
mean±SD		0.23±0.43	0.24 ± 0.44	0.888**
Median (%25-%75)		0 (0-0)	0 (0-0.5)	

** Kruskal- Wallis, ** Mann Whitney-U*
HC: healthy control, BD: bipolar disorder, MDD: major depressive disorder

Table 2. Comparison of the groups in terms of clinical measures

	HC (n: 27)	BD (n: 31)	MDD (n:29)	P
	mean±SD median (25%-75%)	mean±SD median (25%-75%)	mean±SD median (25%-75%)	
HAM-D	0.52±0.94[a]	3.90 ±2.52[b]	5.62 ±2.62[b]	**<0.001**
	0(0-1)	4(2-5)	6 (3.5-7)	
YMRS	0.26 ±0.59[a]	2.13 ± 2.75[b]	0.59 ± 1.68[a]	**0.001**
	0 (0-0)	1 (0-4)	0 (0-0)	
COPE-A	107.22±9.44	105.00 ± 14.74	103.48 ± 15.06	0.970
	107 (98-112)	93 (88-101)	108 (94-114)	
COPE-M	46.30 ±5.88	50.36 ± 8.87	47.24 ±9.18	0.081
	48 (42-49)	51 (46-57)	46 (42-54)	
BDFQ	129.19 ± 11.22[a]	93.58 ± 12.26[b]	86.76 ± 12.67[b]	**<0.001**
	133 (118-136)	93 (88-101)	88 (80.5-95.5)	
DERS	91.52 ± 10.92[a]	99.98 ± 16.88[b]	102.76 ± 14.83[b]	**0.007**
	89 (84-97)	101 (88-111)	103 (97.5-111)	

** similar subscript letters represent similar groups.*

HC: healthy control , BD: bipolar disorder , MDD: major depressive disorder
HAM-D: Hamilton Depression Scale, YMRS: Young Mania Rating Scale, COPE-A: Adaptive Coping Strategies, COPE-M: Maldaptive Coping Strategies, BDFQ:Bipolar Disorder Functioning Questionnaire: DERS: Difficulties in Emotion Regulation Scale

Table 3: Correlation analysis between scale scores

		HAM-D	YMRS	DERS	BDFQ	COPE-A
BD	HAM-D	1				
	YMRS	0.236	1			
	DERS	0.289	0.007	1		
	BDFQ	-0.018	0.052	-0.282	1	
	COPE-A	-0.198	-0.250	0.224	0.081	1
	COPE-M	-0.286	-0.325	0.361*	-0.370*	0.465**
MDD	HAM-D	1				
	YMRS	-0.214	1			
	DERS	0.305	0.137	1		
	BDFQ	-0.235	-0.092	-0.530**	1	
	COPE-A	-0.209	-0.140	-0.355	0.711**	1
	COPE-M	-0.089	-0.034	0.069	0.214	0.498**

**: p<0.05; **: p<0.01;*

** similar subscript letters represent similar groups.*

BD: bipolar disorder, MDD: major depressive disorder
HAM-D: Hamilton Depression Scale, YMRS: Young Mania Rating Scale, COPE-A: Adaptive Coping Strategies, COPE-M: Maldaptive Coping Strategies, BDFQ:Bipolar Disorder Functioning Questionnaire: DERS: Difficulties in Emotion Regulation Scale

Table 4: Predictors of functionality in the patients with MDD					
	Unstandardized Coefficients		**Standardized Coefficients**		
Variable predicted: BDFQ					
Predictive Variable	B	SE	Beta	t	p
Constant	76.967	20.601	-	3.730	<0.001
DERS	-0.322	0.125	-0.377	-2.587	0.016
COPE-A	0.415	0.123	0.493	3.381	0.002
adj.R^2=0.497; (F=12.869 p<0.001)					
DERS: Difficulties in Emotion Regulation Scale, COPE-A: Adaptive Coping Strategies					

DISCUSSION

In this study, it was aimed to observe the coping attitudes and emotion regulation difficulties and their relationship with functionality in depression and bipolar disorder. As the most important finding of this study, it was determined that using adaptive strategies in coping with stress and emotion regulation difficulties were significant predictors of functionality in the MDD group. Also, there was a positive correlation between emotion regulation and adaptive coping strategies in our study.

In our study, it was observed that individuals both in the BD and MDD groups had significantly more difficulties in emotion regulation than the healthy controls. These results are consistent with previous findings (24,25). Studies are reporting that depression is a differentiation in emotion processing due to dysregulation of negative affect (26). It is stated that difficulty in emotion regulation may also cause the persistence of depressive mood (10), and emotion regulation facilitates reducing the intensity or shortening the duration of dysphoric states that contribute to the recurrence of depressive episodes (26). Likewise, adaptive coping strategies predicted increased remission and decreased risk of relapse in depression (27). Recurrence of the mood episodes and progression of the episode are associated with poorer functioning (28). This may explain the outcome of our study that emotion regulation and adaptive coping strategies predict functionality in MDD.

In this study, the number of depressive episodes was significantly higher in the MDD group. It can be concluded that the MDD group was exposed to more negative affect and difficulties to regulate it. Emotional dysregulation has been reported to be associated with current depressive symptoms as well as previous depressive episodes (29). The reason for the absence of a similar prediction of functionality in the BD group may be due to the fact that they had fewer depressive episodes compared to the MDD group.

It was determined that there was no difference between the groups in terms of adaptive and maladaptive coping strategies. It has been reported in the literature that patients with bipolar disorder use maladaptive coping strategies at a higher level than healthy controls (7). Also, it was reported that patients with high severity of depression tend to use more maladaptive coping strategies (30). However, in both groups patients who were in remission for at least 6 months were included in our study, and it can be suggested that the indifference was due to the low clinical severity.

The first limitation of this study is the incapability to analyze the changes in coping strategies and emotion dysregulation in the clinical course due to the cross-sectional design. No follow-up data were available on how coping and emotion dysregulation changed when clinical severity changed. Another limitation is the absence of data on temperament and medications that may affect coping and emotion regulation. Finally, the small sample size and the use of self-report scales are important limitations. Compared to the clinician-applied scales, self-report scales can be more subjective.

CONCLUSION

In this study, the relationship between functionality and emotion regulation difficulties and coping attitudes was examined. Considering the findings of our study and the literature together, it can be stated that difficulty in emotion regulation may predispose to depressive symptomatology and negatively affect clinical course and functionality. Coping strategies and emotional regulation difficulties may differ as clinical severity changes. In the future, follow-up studies including acute episodes may provide important contributions to the literature. Addressing emotion regulation difficulties and increasing the use of adaptive coping strategies in therapeutic interventions contribute to the improvement of functionality as well as clinical improvement.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Physical Medicine and Rehabilitation /Fiziksel Tıp ve Rehabilitasyon

Timing of Cryotherapy Affects the Intensity of Pain Associated with Ultrasound-Guided Musculoskeletal Injection: A Retrospective Study

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ABSTRACT

Objectives: Cryotherapy is a well-known technique used to provide analgesia, especially in the early treatment of musculoskeletal injuries. This study aims to evaluate the effectiveness of pre-injection, post-injection, and combined cryotherapy on pain intensity associated with ultrasound-guided musculoskeletal injection.

Methods: In this retrospective study, a total of 120 participants who had received an ultrasound-guided musculoskeletal injection were subsequently categorized into four groups according to the timing of cryotherapy: PRE (cryotherapy only before injection), POST (cryotherapy only after injection), BOTH (cryotherapy both before and after injection), CON (no cryotherapy). Participants' visual analogue scale (VAS) scores before, during and after the injection were compared.

Results: Timing of cryotherapy had a significant effect on VAS Score ($p < 0.001$). Lowest VAS scores after injection were observed when cryotherapy was applied both before and after injection (0.63 ± 0.12).

Conclusion: Cryotherapy before and/or after injection decreases VAS scores either during injection and/or after injection. Also, the downward trend in VAS scores across all time intervals appears only when cryotherapy was applied both before and after injection.

Keywords: Cryotherapy, Musculoskeletal disorders, VAS Score

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Kriyoterapinin Zamanlaması Ultrason Eşliğinde Kas-İskelet Enjeksiyonu ile İlişkili Ağrının Yoğunluğunu Etkiler: Retrospektif Bir Araştırma

ÖZET

Amaç : Kriyoterapi, özellikle kas-iskelet sistemi yaralanmalarının erken tedavisinde analjezi sağlamak için kullanılan, iyi bilinen bir tekniktir. Bu çalışma, enjeksiyon öncesi, enjeksiyon sonrası ve kombine kriyoterapinin ultrason eşliğinde kas-iskelet sistemi enjeksiyonu ile ilişkili ağrı yoğunluğu üzerindeki etkinliğini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Ultrason eşliğinde kas-iskelet enjeksiyonu yapılmış olan toplam 120 katılımcı, kriyoterapi uygulamasının zamanlamasına göre sonradan dört gruba ayrıldı: PRE (sadece enjeksiyondan önce kriyoterapi), POST (sadece enjeksiyondan sonra kriyoterapi), BOTH (hem enjeksiyondan önce hem de sonra kriyoterapi), CON (kriyoterapi yok). Katılımcıların enjeksiyon öncesi, sırası ve sonrasında görsel analog skala (VAS) skorları karşılaştırıldı.

Bulgular: Kriyoterapi uygulamasının zamanlamasının VAS Skoru üzerinde anlamlı bir etkisi vardı ($p<0,001$). Enjeksiyon sonrası en düşük VAS skorları, enjeksiyon öncesi ve sonrası kriyoterapi uygulandığında gözlendi (0.63 ± 0.12).

Sonuç: Enjeksiyondan önce ve/veya sonra kriyoterapi uygulaması, enjeksiyon sırasında ve/veya enjeksiyondan sonraki VAS skorlarını düşürür. Ayrıca, tüm zaman aralıklarında VAS puanlarındaki düşüş eğilimi, yalnızca enjeksiyondan önce ve sonra kriyoterapi uygulandığında ortaya çıkar.

Anahtar Sözcükler : Kriyoterapi, Kas-iskelet sistemi problemleri, VAS skoru

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An ultrasound-guided injection is one of the effective treatment options in musculoskeletal diseases (1-3). Ultrasonography has become widely used during injection due to visualization of needle placement, distribution of the injected material, and surrounding anatomical structures in real-time, thus minimizing the risk of injury and maximizing the benefit from treatment (4,5). Along with other complications, the pain associated with the procedure can be reduced by minimizing the trauma in the local tissue and the number of attempts required to perform the procedure, however pain may still be present in patients who undergo these procedures (6,7).

Cryotherapy is a well-known technique used to provide analgesia, especially in the early treatment of musculoskeletal injuries (8). Cryotherapy increases the excitability threshold of sensory neurons at the site of application as a result of the decrease in neuronal metabolism and sodium-potassium pump activity, thereby providing the analgesic effect by decreasing the nerve conduction velocity (9). Additionally, cryotherapy provides the analgesic effect by decreasing cell metabolism, vasoconstriction, and reduction of metabolic waste, inflammation and muscle spasm (10). Although there are many methods for cryotherapy, such as ice towels, ice massage, gel packs, refrigerant gases, and inflatable splints, ice pack application is more preferred in daily practice because it is inexpensive and easily available (11).

The effects of cryotherapy or ice application on pain reduction have generally been studied for intra-oral injections (12), local anesthetic injection (13), and Botulinum toxin injections (14). Despite the well-known analgesic effect of cryotherapy and its place in the musculoskeletal standard of care, to the best of our current knowledge, there is no study in the literature evaluating the effect of cryotherapy on the intensity of pain associated with the ultrasound-guided musculoskeletal injection. Therefore, this study aimed to investigate the effectiveness of pre-injection, post-injection, and combined cryotherapy application on pain intensity associated with ultrasound-guided musculoskeletal injection, specifically during and after injection.

METHODS

This study received approval from Local Medical Ethics Committee and followed the guidelines of Declaration of Helsinki.

Participant Selection

Patients who had received a therapeutic injection treatment for a musculoskeletal disease or injury between March 2020 and March 2021 were selected. Patients who received local anesthetic injections, patients with comorbid diseases which may interfere with their sensation of pain were excluded from the study. Accordingly, a total of 120 participants were retrospectively included in the study. Participants were categorized into four groups according to the cryotherapy application before and/or after the injection: PRE (cryotherapy applied before injection), POST (cryotherapy applied after injection), BOTH (cryotherapy applied both before and after injection), CON (control group consisting of participants who had no cryotherapy at all). There were 30 participants in each group.

Participants' demographics (age, sex, level of education, smoking status), anthropometrics (body weight, height, body mass index), diagnosis, existence of comorbid diseases, type of the injected medication (hyaluronic acid, platelet-rich plasma (PRP), corticosteroids), injected anatomical region were noted, as well as VAS scores reported before, during and after the injection.

Cryotherapy and Injections Procedures

All injections were performed ultrasound-guided by the same sports medicine specialist (AE). Cryotherapy was applied by a cooling pad (28 X 29 -cm) wrapped in a waterproof cover. The cooling temperature was of 5 ^{o}C. Each ice pack application was done for 5 minutes. When cryotherapy was applied both before and after the injection, total time of application was 10 minutes.

Participants had received either hyaluronic acid, corticosteroid (1 ml of 40mg/ml methylprednisolone acetate) or a PRP injection. PRP had been prepared as described (15): Fifty milliliters (50 mL) of blood was collected from patients' veins in antecubital fossa into sodium citrate containing tubes. Tubes were centrifugated twice, first at 1500 rpm for 6 minutes, and second at 3500 rpm for 12 minutes. After the first spin, upper layer of plasma was transferred to empty sterile tubes. After the second spin, platelet pellets with few red blood cells at the bottom were collected and were homogenized by thoroughly mixing it with the upper 1/3rd of the plasma. Lower 2/3rd was discarded. PRP was activated by adding 1 mL 10% calcium chloride. Later the injection was performed.

Visual Analogue Scale

Patients were asked to rate the intensity of their pain on a 100-mm VAS. The scale was positioned horizontally and ends were labeled with the remarks "the least possible pain" and "the worst possible pain". VAS scores were collected from patients at arrival, during injection, and 10 minutes after the injection right before leaving the outpatient clinic. VAS is a valid and reliable tool for assessing the intensity of both chronic and acute pain (16,17).

Statistical Analysis

The variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov test) to determine normal or non-normal distributions. Descriptive analyses are presented using mean ± standard deviation (SD) and standard error of mean (SEM) for continuous variables and using frequency counts and percentages for categorical variables. Participants' characteristics were compared between groups by running either an analysis of variance test for continuous variables or a chi-square test for categorical variables. A two-way mixed analysis of variance test was performed for comparing the changes in VAS scores at three time-points between groups (between factor: group, within factor: time). For post-hoc analysis, a series of pairwise T tests were performed with Bonferroni correction. All analysis was performed using R Studio, Version 3.6.2. Statistical significance was accepted as $p < 0.05$.

RESULTS

Participants' characteristics are given in Table 1. The study groups had similar characteristics with each other. Participants were diagnosed with the following conditions: Supraspinatus tenosynovitis/partial rupture (n=29), chondromalacia patella (n=21), gonarthrosis (n=18), lateral epicondylitis (n=17), meniscopathy (n=11), Achilles tendinopathy (n=10), coxarthrosis (n=5), anterior talofibular ligament sprain (n=4), DeQuervain tenosynovitis (n=2), calcaneal spur (n=2), and Morton's neuroma (n=1).

Mean VAS scores with SEM are given in Table 2. Figure 1 shows the changes in VAS scores across time points. The cumulative probability plot presented in Figure 2 demonstrates the divergence of VAS improvement on the participant level with the most improvement in the BOTH group. A two-way mixed analysis of variance test was run in order to evaluate the effect of time, group, and time:group interaction on VAS scores. All three had significant effect on VAS score (effect of time: $F(2,232) = 245.332$, $p < 0.001$; effect of group: $F(3,116) = 14.764$, $p < 0.001$; effect of time:group interaction: $F(6,232) = 58.164$, $p < 0.001$).

The simple main effect of group was found significant at all three time points (Before injection: $F(3,116) = 8.40$, $p < 0.001$; During Injection: $F(3,116) = 29.6$, $p < 0.001$; After Injection: $F(3,116) = 58.0$, $p < 0.001$).

Pairwise comparisons showed similar baseline VAS scores among these groups: PRE vs. POST, PRE vs. CON, CON vs. POST, and BOTH vs. POST ($p > 0.99$, $p = 0.3$, $p = 0.08$, and $p = 0.08$, respectively.) However, baseline VAS measurements varied significantly among the groups BOTH vs. PRE and BOTH vs. CON ($p = 0.002$ and $p < 0.001$, respectively). During injection, the difference between VAS scores were insignificant among groups who received ice application prior to injection (PRE vs. BOTH, $p > 0.99$) and who did not receive any ice application prior to injection (POST vs. CON, $p > 0.99$). On the other hand, comparisons between the groups who received cryotherapy before injection and the groups that did not, showed significant results: PRE vs. POST, PRE vs. CON, POST vs. BOTH, POST vs. CON (all $p < 0.001$). All pairwise comparisons of VAS scores between groups after the injection were significant at $p < 0.01$.

The simple main effect of time was also found significant for all groups (CON: $F(2,58) = 4.96$, $p = 0.04$; PRE: $F(2,58) = 71.8$, $p < 0.01$; POST: $F(2,58) = 64.9$, $p < 0.01$; BOTH: $F(2,58) = 306.0$, $p < 0.01$).

Although the simple main effect of time was significant for the CON group as well, the pairwise comparisons showed that, in the CON group, VAS scores did not change significantly between timepoints (Before vs. During: $p = 0.2$, Before vs. After: $p > 0.99$, During vs. After: $p = 0.2$). In the PRE group, comparisons of VAS scores between Before vs. During, and Before vs. After were both significant at $p < 0.001$, whereas the difference between During vs. After was insignificant ($p > 0.99$). In the POST group, results of the comparisons between Before vs. During was insignificant ($p > 0.99$), whereas there was significant change between Before vs. After and During vs. After ($p < 0.001$, both). Finally, in the group BOTH, all pairwise comparisons were significant ($p < 0.001$, all).

Table 1: Participants characteristics						
		PRE (n=30)	**POST (n=30)**	**BOTH (n=30)**	**CONTROL (n=30)**	**p**
Age, years		50.63±8.63	50.53±10.97	52.5±9.04	47.63±9.48	F(3,116)= 1.27716 p= 0.285
Sex	Male	14 (46.7%)	10 (33.3%)	9 (30%)	11 (36.7%)	$X^2(3,120)=2.009$, p=0.57
	Female	16 (53.3%)	20 (66.7%)	21 (70%)	19 (63.3%)	
Body Weight, kg		74.76±9.68	76.6±9.90	76.2±13.97	78.63±11.35	F(3,116)= 0.57276, p= 0.634
Height, cm		173.16±7.95	172.4±7.79	172.1±8.75	173.8±6.68	F(3,116)= 0.27833, p= 0.840
Body Mass Index, kg/m²		24.97±3.26	25.85±3.64	25.6±3.92	26.03±3.46	F(3,116)= 0.57025, p= 0.635
Level of Education	University	27 (90%)	25 (83.3%)	27 (90%)	27 (90%)	$X^2(3,120)=0.9704$, p=0.808
	High School	3 (10%)	5 (16.7%)	3 (10%)	3 (10%)	
Smoking	Smoker	1 (3.3%)	1 (3.3%)	3 (10%)	1 (3.3%)	$X^2(6,120)=5.4608$, p=0.486
	Nonsmoker	12 (40%)	9 (30%)	9 (30%)	6 (20%)	
	Quit Smoking	17 (56.7%)	20 (66.7%)	18 (60%)	23 (76.7%)	
Comorbid Diseases†	Yes	6 (20%)	7 (23.3%)	7 (23.3%)	6 (20%)	$X^2(3,120)=0.1964$, p=0.978
	No	24 (80%)	23 (76.7%)	23 (76.7%)	24 (80%)	
Anatomical region of injection‡	Hand&Wrist	0 (0%)	1 (3.3%)	0 (0%)	1 (3.3%)	$X^2(9,120)=7.1432$, p=0.622
	Elbow	6 (20%)	3 (10%)	6 (20%)	2 (6.6%)	
	Shoulder	10 (33.3%)	6 (20%)	4 (13.3%)	9 (30%)	
	Hip	1 (3.3%)	0 (0%)	0 (0%)	4 (13.3%)	
	Knee	10 (33.3%)	14 (46.7%)	16 (53.3%)	10 (33.3%)	
	Foot&Ankle	3 (10%)	6 (20%)	4 (13.3%)	4 (13.3%)	
Site of Injection §	Right	23 (92%)	20 (76.9%)	18 (78.3%)	24 (85.7%)	$X^2(3,102)=2.6616$, p=0.446
	Left	2 (8%)	6 (23.1%)	5 (21.7%)	4 (14.3%)	
Dominance of the injected site §	Dominant	18 (81.8%)	15 (65.2%)	15 (75%)	17 (80.9%)	$X^2(3,86)=2.1342$, p=0.545
	Non-dominant	4 (18.1%)	8 (34.8%)	5 (25%)	4 (19.1%)	
Intraarticular injection	Yes	11 (36.7%)	15 (50%)	18 (60%)	18 (60%)	$X^2(3,120)=4.4049$, p=0.220
	No	19 (63.3%)	15 (50%)	12 (40%)	12 (40%)	
Injected medication	Sodium Hyaluronate	6 (20%)	9 (30%)	12 (40%)	7 (23.3%)	$X^2(9,120)=3.7087$, p=0.716
	PRP	16 (53.3%)	14 (46.7%)	12 (40%)	14 (46.6%)	
	Corticosteroid	8 (26.7)	7 (23.3%)	6 (20%)	9 (30%)	

Data is displayed as either "mean ± standard deviation" or "n (%)". †Comorbid diseases: PRE: Hypertension (n=5), Asthma (n=1); POST: Hypertension (n=4), Asthma (n=2), Coronary Artery Disease (n=1); BOTH: Hypertension (n=5), Asthma (n=1), Hypercholesterolemia (n=1); CONTROL: Hypertension (n=4), Asthma (n=1), Peripheral vascular disease (n=1). ‡Grouped as 4 categories (hand&wrist&elbow, shoulder, hip&knee, foot&ankle) for a more accurate analysis. §Site of injection and dominance were not available in all patient charts, hence missing data.

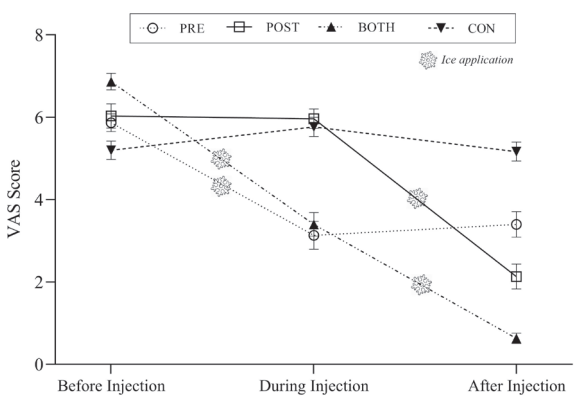

Figure 1: *VAS Scores of participants.*
Error bars show standard error of mean. Ice symbol denotes the timing of cryotherapy.

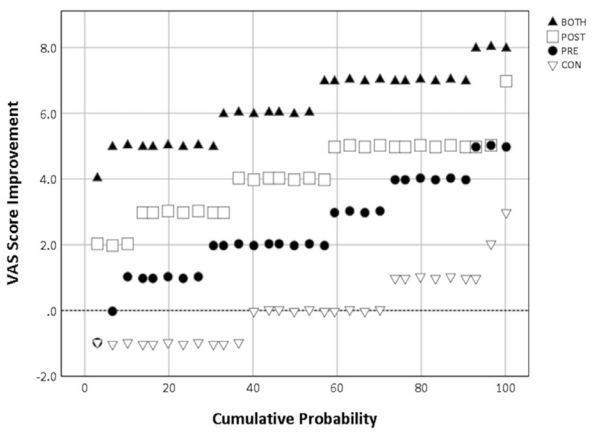

Figure 2: *Cumulative probability plot of VAS score improvements (pre-injection VAS –*
post-injection VAS) in the participants.

Table 2: Visual analogue scale (VAS) scores of participants at different time points.

Group	Time of Measurement	Mean VAS Score	Standard Error of Mean
PRE	Before Injection &	5.87	0.21
	During Injection #ϕ	3.13	0.33
	After Injection #&ϕ	3.40	0.30
POST	Before Injection	6.03	0.29
	During Injection *&	5.97	0.23
	After Injection *&ϕ	2.13	0.30
BOTH	Before Injection *ϕ	6.87	0.20
	During Injection #	3.40	0.28
	After Injection *#ϕ	0.63	0.12
CON	Before Injection &	5.2	0.22
	During Injection *#	5.7	0.23
	After Injection *#&	5.1	0.23

**Significantly different than PRE at the same timepoint (P<0.001), #Significantly different than POST at the same timepoint (P<0.001), &Significantly different than BOTH at the same timepoint (P<0.001), ϕSignificanlty different than CON at the same timepoint (P<0.001).*

DISCUSSION

The objective of this study was to investigate the effect of cryotherapy on pain intensity associated with ultrasound-guided musculoskeletal injection procedures. To the best of our current knowledge, this is the first study to demonstrate the effectiveness of cryotherapy on pain associated with musculoskeletal injection therapy. In this sense, the important aspect of our study would be the fact that it proves the knowledge that cryotherapy, which is widely used in daily clinical practice to reduce pain intensity without sufficient data in the literature, reduces pain during and after injection.

We noted statistically significant decreases in the intensity of pain felt during injection compared to pre-injection in the PRE and BOTH groups, but such a reduction was not present in either the POST or the CON groups. Accordingly, in cases where low pain intensity is desired during the musculoskeletal injection procedure, cryotherapy before injection might be recommended. Similarly, patients may experience pain during botulinum toxin type-A injection, which may cause discomfort for both the patient and the physician who apply the treatment. In a prospective, randomized, single-blind controlled study, the authors evaluated the effect of cryotherapy on the treatment zone before botulinum toxin type-A treatment on the pain felt during injections (16). Similar to our results, the authors found that pain is significantly reduced on the side where cryotherapy is applied.

We also observed statistically significant reductions in the pain intensity after injection compared to during injection in the POST and BOTH groups, while such a decline was not present in either the PRE or the CON groups. Additionally, we observed a significant decrease in post-injection VAS scores in the PRE, POST, and BOTH groups compared to pre-injection. However, there was no significant change in post-injection VAS scores in the CON group compared to pre-injection. Furthermore, a downward trend in VAS scores was observed only in the BOTH group across all time intervals. For this reason, both pre-injection and post-injection cryotherapy application might be recommended to reduce injection-related pain, both during and after injection.

Şahin et al. aimed to investigate the effect of the Buzzy application, which is a device that combines cold, vibration, and distraction, on pain and satisfaction during gluteal intramuscular injections of diclofenac sodium (18). The authors compared only the post-injection VAS scores of the application and control groups, and they found that the post-injection VAS scores were statistically significantly lower in the application group. The strengths of our study are grouping participants into four, as three of the study groups having cryotherapy application at different times and the control group having no cryotherapy application, and evaluating the differences in VAS scores between groups as well as the change in VAS scores within the group.

Apart from the abovementioned studies, the effects of cryotherapy or ice application on pain reduction have also been studied in the field of dentistry. In a randomized cross over study, which compared the effectiveness of ice and lidocaine 5% gel for topical anesthesia of oral mucosa, the authors found that using ice for topical anesthesia of oral mucosa before the dental injection caused lower VAS pain scores in comparison to using lidocaine gel (19) . The authors concluded that using ice, as the cheap and readily available method, for topical anesthesia of oral mucosa before the dental injection is effective.

Commonly used methods for cryotherapy are ice packs, ice towels, ice massage, gel packs, refrigerant gases, and inflatable splints. Lathwall et al. compared the efficacy of different precooling agents (ice cone and refrigerant) and topical anesthetics (benzocaine) on pain perception during intraoral injection in pediatric dentistry, and they observed lower mean VAS scores in the ice cone group as compared to refrigerant and benzocaine (12). The authors explained the increased effectiveness of ice compared to the refrigerant, possibly due to increased contact time with tissues. In another study, Bechara et al. investigated whether skin cooling decreases pain during the botulinum toxin type-A injection for patients with focal axillary hyperhidrosis (20). Participants were divided into two groups as follows: Group 1: Skin cooling with cold air system and no cooling on the other side; Group 2: Skin cooling with cold air system and ice cubes on the other side. Contrary to the results of Lathwall et al. (12), the authors found that ice and air cooling reduces pain during injection with the same effectiveness in patients with focal axillary hyperhidrosis (20). In this study, we used only ice packs for cryotherapy application without applying refrigerant or other cryotherapy methods in any study group. For this purpose, further studies might be planned to evaluate the pain reduction effectiveness of different cryotherapy agents during and after musculoskeletal injections.

Matthew et al. conducted a study on patients undergoing Mohs micrographic surgery with local anesthesia, and the authors aimed to determine whether nitrous oxide, ice, vibration, or topical anesthetic improves analgesia for local anesthetic injections (21). The authors found that nitrous oxide, ice, and vibration caused a decrease in the post-injection pain VAS score compared to pre-injection, in the order of the most to the least in the decrease. In addition to that, the authors reported an association of higher pain scores with age <50 years, male sex, and surgery on the nose, lip, ear, or eyelid. In this study, the evaluation of the relationship between pain scores and patient characteristics was not our primary purpose; in fact, we specifically aimed to assess the differences in the injection pain intensity according to the time of ice application. Furthermore, in all four groups, participants had similar characteristics, including age, sex, anthropometric measures, comorbid diseases, the anatomical region, and site of injection, whether the injection is intra-articular or not, and the type of the injected medication.

This study has also some limitations. The first of the limitations in our study was that not all of the joint injection groups were the same joint type. Joints closer to the skin surface, such as the lateral epicondyle or de quervein tenosynovitis, could be compared among themselves, and deeper joints such as the shoulder and knee could be compared within themselves. A secondary limitation was the use of the same ice application time to the superficial and deep joints. Although there is no clear time for applying ice to which joint, how often and for how long in the literature, one of the points to be considered in future studies may be the duration of the application.

CONCLUSION

In conclusion, cryotherapy before and/or after injection decreases VAS scores either during injection or after injection. The advantage of the cryotherapy technique is that it is inexpensive, easily available, and effective in reducing pain, which might be caused by musculoskeletal injection treatment.

DECLARATIONS

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Conflict of Interest: The author declares that there is no conflict of interest

Ethics Approval: This study received approval from Local Medical Ethics Committee (02.04.21/3174).

Availabality of Data and Material: The materials described in the manuscript will be freely available to any scientist wishing to use them for noncommercial purposes, without breaching participant confidentiality.

Author Contributions: MPY, SST writing the original draft, review and editing, MPY,SST,AE conceptualization, formal analysis, investigation, methodology. AE data collection.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Obstetrics and Gynecology / Kadın Hastalıkları ve Doğum

Bibliometric Analysis of Joint Publications on Human Papilloma Virus Vaccine and Cervical Cancer

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ABSTRACT

Purpose: In this study, it is aimed to reveal the output, trends and important developments of researches globally by bibliometric analysis of joint publications on Human Papilloma Virus (HPV) vaccine and cervical cancer.

Methods: It is a bibliometric visualized study using the Web of Science (WoS) database. A search query was made with keywords. As a result of the search, 158 out of 923 articles were excluded because they did not meet the specified criteria. 771 articles were analyzed. VOSviewer 1.6.12 was used to visualize bibliometric analyzes and network analysis was performed. Calculated values were presented as frequency (n) and percentage (%).

Results: It was found that the most common publications on HPV vaccine and cervical cancer were in 2021 (n=94). In the countries with the highest number of research articles, the USA is in the first place with 281 research articles, followed by the UK and Australia. Our country, Turkey, had 16 publications in this field. The first magazine "Vaccine" and "PLOS one" published about 11% of its articles. The three most frequently used keywords were "cervical cancer", "human papillomavirus" and "HPV".

Conclusion: In recent years, the number of studies focusing on HPV vaccine and cervical cancer has increased. It is seen that developed countries have done the most studies on the subject. To improve the global output of research in this area, it would be beneficial to establish strong research cooperation between developing and developed countries.

Keywords: cervical cancer, HPV vaccine, HPV, bibliometric analysis

Şule ÖZDEMİR
Kübra ŞAHİN

Human Papilloma Virüs Aşısı ve Serviks Kanseri Konularında Yapılan Ortak Yayınların Bibliyometrik Analizi

ÖZET

Amaç: Bu çalışmada Human Papilloma Virus (HPV) aşısı ve serviks kanseri konularında yapılan ortak yayınların bibliyometrik analizini yaparak küresel olarak araştırmaların çıktısını, eğilimlerini ve önemli gelişmeleri ortaya çıkarmak amaçlanmıştır.

Yöntemler: Web of Science (WoS) veritabanı kullanılarak bibliyometrik görselleştirilmiş bir çalışmadır. Anahtar kelimelerle arama sorgusu yapıldı. Arama sonucunda 923 makaleden 158'i belirlenen kritere uymadığından çıkarıldı. 771 makale analiz edildi. Bibliyometrik analizlerin görselleştirilmesi için VOSviewer 1.6.12 kullanıldı ve ağ analizi yapıldı. Hesaplanan değerler frekans (n) ve yüzde (%) olarak sunuldu.

Bulgular: HPV aşısı ve serviks kanseri konularında yapılan ortak yayınların en fazla 2021 yılında (n=94) olduğu bulundu. En fazla araştırma makalesine sahip ülkelerde, ilk sırada 281 araştırma makalesi ile ABD yer almakta olup İngiltere ve Avustralya'nın takip ettiği saptandı. Ülkemiz Türkiye'nin bu alanda 16 yayını bulunmaktaydı. Makalelerinin yaklaşık %11'ini ilk "*Vaccine*" and "*PLOS one*" dergisi yayınlamıştı. En sık kullanılan 3 anahtar kelime "*cervical cancer*", "*human papillomavirus*" ve "*HPV*" idi.

Sonuç: Son yıllarda HPV aşısı ve serviks kanseri üzerine odaklanan çalışmaların sayısı artmıştır. Konu üzerine en çok çalışmayı gelişmiş ülkelerin yaptığı görülmektedir. Bu alanda yapılacak araştırmaların küresel çıktısını iyileştirmek için gelişmekte olan ülkelerde ve gelişmiş ülkeler arasında güçlü araştırma işbirliği kurulması fayda sağlayacaktır.

Anahtar Kelimeler: sevikal kanser, HPV aşısı, HPV, bibliyometrik analiz

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Human papillomavirus (HPV) infection is the most common sexually transmitted disease in young and sexually active populations in developed countries. It is estimated that there are approximately 30 million new cases of genital HPV every year in the world (1). It is known that 70% of sexually active women and men will be infected with at least one HPV type throughout their lives, especially in the first 5 years of sexual activity. HPV is accepted as the most important factor for cervical cancer (2). Cervical cancer is the second most common type of cancer after breast cancer in women. It constitutes 3.6% of female cancers in developed countries and 15% in underdeveloped countries (3). According to the data of the World Health Organization (WHO), a total of 604,000 women worldwide were diagnosed with cervical cancer in 2020, and 342,000 women die from this disease annually (4). There are more than 200 subtypes of HPV and 15 subtypes are classified as oncogenic. An estimated 72% of cervical cancers globally are associated with these subtypes HPV 16 and HPV 18, and another 17% of cervical cancers are caused by HPV types 31, 33, 45, 52 and 58 (5, 6).

As a result of the increase in information about HPV and molecular and technological developments, studies on the agents of cervical cancer have progressed until the emergence of HPV vaccines. First in 2006 and 2007, these vaccines were included in the vaccination programs of most developed countries. There are three vaccines currently in use on the market. Quadrivalent vaccine (6, 11, 16, 18 types) in 2006, bivalent vaccine (16, 18 types) in 2007, and nonavalent (non-valent) vaccine (6, 11, 16, 18, 31, 33, 45, 52, 58 types) are licensed (7). It is recommended by WHO (8), that vaccination programs should target adolescent girls aged 9 to 14 years. It is also stated that these vaccines, if administered before sexual intercourse, provide protection against high-risk HPV type 16-18, which is responsible for approximately 70% of cervical cancer cases, and other cancers affecting the vulva, vagina, penis, anus and oral cavity (9). WHO launched the "Cervical Cancer Elimination Programme" in its global call on 17 November 2020. In order to eradicate cervical cancer from countries under this program, it is aimed to achieve and maintain an incidence rate of less than four per 100,000 women in all countries. To achieve this goal; 90% of girls should be fully vaccinated with HPV vaccine by age 15, 70% of women should be vaccinated by age 35 and screened again using high-performance testing by age 45, 90% of women with pre-cancer and 90% of women with invasive cancer should be treated (10).

The increasing medical literature on HPV vaccine and cervical cancer also allows for the publication of many current reports and a bibliometric study on the subject. Bibliometric analysis; it is defined as the quantitative analysis of scientific documents or publications by evaluating different bibliometric features (subject, year, contributing institution, keywords used, sources used, number of authors of works, citations, self-citations, etc.) (11,12). In addition, bibliometric analyzes; it provides a statistical and visible approach to examining trends, patterns, and biases in scientific studies, as well as providing a macroscopic view of research output in an individual academic discipline (13).

Therefore, in this study, it is aimed to reveal the output, trends and important developments of researches globally by bibliometric analysis of joint publications on HPV vaccine and cervical cancer.

MATERIAL and METHODS

Study Design and Search Strategy

Our research is a bibliometric visualized study using the Web of Science (WoS) database hosted by Clarivate Analytics, which offers a comprehensive search engine. WoS database is widely used in bibliometric studies. WoS was preferred because it covers many journals in the field of science and social sciences and provides basic information about other bibliometric indexes (14).

Search in WoS, publication year (1991–2021), document type (article), language (English), WoS index (Science Citation Index-Expanded (SCI-E)" "Social Sciences Citation Index (SSCI)", "Emerging Sources Citation Index (ESCI)). The online search was done on August 16, 2022.

The keywords used in the research were created from the literature and searched by subject area. The subject area (topic) searches for title, abstract, author, keywords and Key Words Plus. The search query is "Papillomavirus Vaccination" OR "Human "Papillomavirus Vaccination" OR "Human Papilloma Virus Vaccination" OR "Papillomavirus Vaccine" OR "Human Papillomavirus Vaccine" OR "Human Cancer Papilloma Virus Vaccine" OR "HPV Vaccine" and the title tab "Cervical Cancer" (title) OR "Cervical Intraepithelial Neoplasia" (title) was done.

Data Download and Extraction

The full records of 923 articles that met the search criteria were downloaded and the contents of the articles saved in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA) were reviewed. As a result of the review, research articles with title, abstract, introduction, materials and methods, findings, discussion and conclusion

sections were included in the study. These research articles were defined as "original article, original paper, research article, research paper, article, major article". Article content includes comments, short reports, letters, editorials, reports, case presentations, case series, etc. Since 152 publications did not meet the specified criteria, 6 publications were published in 2022, they were excluded from the data records. In this context, analyzes were made on 771 research articles.

Data Analysis and Interpretation

Microsoft Excel 2019 for Windows, VOSviewer 1.6.12 was used in the analysis of the obtained data. Calculated values were presented as frequency (n) and percentage (%). The required charts were created using Microsoft Excel 2019. Exported to VOSviewer for visualization of bibliometric analyzes and network analysis was performed. VOSviewer is a freely available and widely used tool for visualization mapping (15). Also, data were plotted for co-authoring countries and co-occurrence keywords visualization mapping using VOSviewer software.

RESULTS

The descriptive features of the research articles whose bibliometric analysis was performed within the scope of the study are shown in Table 1, and the distribution in the number of publications by years was shown in Figure 1. It was found that the most publications on the research topic were in 2021 year (n=94), 2020 and 2019 years (n=74).

It was determined that the authors with the highest number of research articles in the field of our study were Mona Saraiya and Jane J. Kim, and the author with the highest H index was Suzanne M. Garland. Table 2 shows in detail the characteristics of the authors who have at least 10 research articles in the field determined within the scope of the research.

Table 1. Descriptive features of research articles

Time range	1992-2021
Number of articles	771
Number of journals	287
Number of institutions	1463
Number of countries	110
Number of sources	15990
Keyword	1094
Number of authors	3816
Number of single-author publications	15
Number of publications per author	0.202
Number of authors per publication	4.95

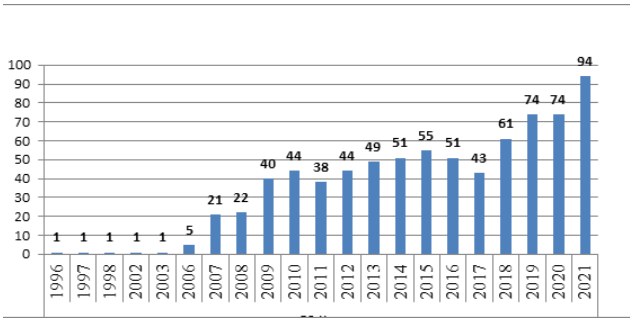

Figure 1. *Distribution of the number of research articles by years*

When the journals in which research articles were published were examined, it was seen that the journal "Vaccine" took the first place, followed by the journal "PLOS One". It was determined that the "International journal of cancerprevention", which had the highest impact factor with 7,316, was in the third place. The characteristics of the journals that published at least 15 articles were shown in Table 3 in detail.

When the countries with the highest number of research articles in the determined field are examined, the USA is in the first place with 281 research articles, followed by England and Australia. Our country, Turkey, had 16 publications in this field. The publication and citation numbers of the first 10 countries were shown in Table 4.

The number of publications of the countries and their cooperation with each other were visualized in Figure 2. In this way, there were 46 countries with at least 5 publications from 110 countries. As a result of the network analysis, three clusters were formed. The red cluster consisted of 18 countries such as France, Belgium, Spain, Sweden, Netherlands, Germany, Denmark and Italy. The country with the most publications in this cluster is France with 54 articles. It was found that it cooperated with the USA at most (20 times), for a total of 154 times. It was found that it cooperated with the USA at most (20 times), for a total of 154 times. Spain was second in this cluster with 38 articles. He collaborated with the USA at most (19 times), for a total of 132 times. The green cluster consisted of 15 countries such as the USA, England, Canada, People's Republic of China, Australia, India, Turkey, Norway. The country with the most publications in this cluster was the USA with 281 articles. It has collaborated with the UK at most (21 times), 251 times in total. England was in the second place in this cluster with 68 articles. It has collaborated with the USA the most (21 times), for a total of 163 times. The blue cluster consisted of 12 countries such as Malaysia, Brazil, Taiwan, South Korea, Thailand, and Portugal. The most collaborating country in this cluster was Brazil with 16 publications, 48 times.

Table 2. Characteristics of authors who have at least 10 research articles in the field determined within the scope of the research

Author	H index	Number of articles n(%)	Number of citations*	Institution	Country
Mona Saraiya	46	20 (2.59)	1510	CDC	USA
Jane J. Kim	41	20 (2.59)	950	Harvard University	USA
Karen Canfell	37	19 (2.46)	1040	University of Sydney	Australia
Megan A. Smith	25	11 (1.42)	902	University of Sydney	Australia
Kate T. Simms	17	10 (1.29)	838	University of Sydney	Australia
Emily A. Burger	20	10 (1.29)	634	Harvard University	USA
Suzanne M. Garland	65	10 (1.29)	194	University of Melbourne	Australia
Yutaka Ueda	34	10 (1.29)	97	Osaka University	Japan
Asami Yagi	12	10 (1.29)	97	Osaka University	Japan

**The number of citations belongs to the number of publications of the author in this field.*

Table 3. Characteristics of journals that have published at least 15 research articles in the specified field

Name of the journal	Number of articles n(%)	Impact factor	Q rank	Publisher's address
Vaccine	54 (0,07)	3.641	Q3	Elsevier Sci Ltd., the Boulevard, Langford Lane, Kidlington, Oxford OX 51 GB, Oxon, England
PLOS one	32 (0,04)	3.24	Q2	Public Library Science, 1160 Battery Street, STE 100, San Francisco, CA 94111
International journal of cancer	23 (0,03)	7,316	Q1	3.24 (3.788) Q2 Public Library Science, 1160 Battery Street, STE 100, San Francisco, CA 94111
Asianpacific journal of cancer prevention	23 (0,03)	ESCI index		Korean Soc Cancer Prevention , 502, Bldg C, Advanced Inst Convergence Technology-Aict, 145 Gwanggyo-Ro, Yeongtong-Gu, Suwon, South Korea, 16229
BMC public health	17 (0,02)	4,135	Q2	BMC, Campus, 4 CrinanSt, London, England, N1 9xw
Journal of cancer education	15 (0,02)	1,771	Q3	Springer, One New York Plaza, Suite 4600, New York, United States, Ny, 10004

Table 4. Characteristics of the 10 countries with the highest number of research articles in the specified field

Number	Country	Number of articles n(%)	Total Number of Citations
1	USA	281 (36.4)	8152
2	England	68 (8.8)	2771
3	Australia	63 (8.2)	2479
4	Chinese	56 (7.3)	973
5	France	54 (7.0)	4003
6	Canada	54 (7.0)	1729
7	Spain	38 (4.9)	3028
8	Belgium	38 (4.9)	2391
9	India	36 (4.7)	458
10	Japan	32 (4.2)	485

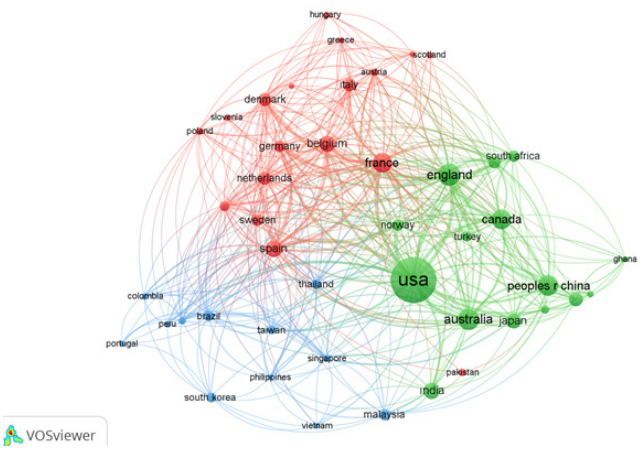

Figure 2. *Co-authorship network analysis of countries (n=46)*

The temporal variation of the publications of the countries by years is shown in Figure 3. It was seen that articles by countries such as China, Japan, India, Denmark, and Greece were published in recent years.

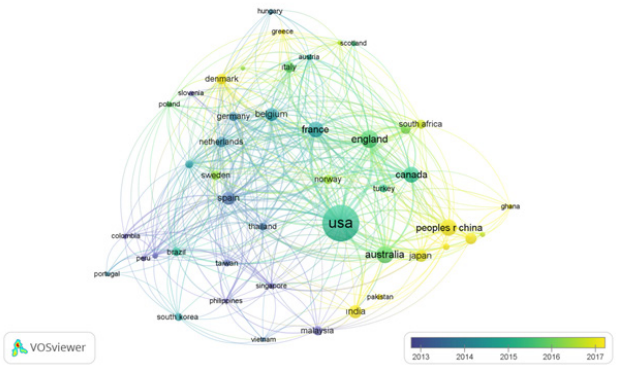

Figure 3. *The temporal variation of the publication dates of research articles by countries (n=46)*

As a result of the analysis, it was found that a total of 1094 keywords were used. The co-occurrence network analysis of keywords used 5 or more times was shown in Figure 4. The most frequently used keywords were "cervical cancer (361 times)", "human papillomavirus (167 times)" and "HPV (107 times)". When the network analysis of the co-occurrence of the keywords was examined, it was seen that four clusters were formed. It was found that there are 24 keywords in the first cluster (red). These keywords were like "cervical cancer", "human papillomavirus", "HPV", "vaccination", "screening", "prevention", "vaccine", "pap smear", "cost-effectiveness". The theme that emerged as a result of the keywords used in this cluster was named "cervical cancer, HPV and HPV vaccine relationship". The second cluster (green) consisted of 21 keywords such as "HPV vaccine", "HPV vaccination", "cervical cancer screening", "knowledge", "awereness", "attitude". The theme that emerged as a result of the keywords used in this cluster was called "knowledge, attitude and awareness towards cervical cancer screening and HPV vaccine". The third cluster (blue) consisted of 14 keywords such as "cancer screening", "papilloma virus vaccines", "mortality", "health education", "primary prevention". The theme that emerged as a result of the keywords used in this cluster was called "cervical cancer primary prevention and death". The fourth cluster consisted of 11 keywords such as "human papillomavirus (HPV)", "cervical intraepithelial neoplasia", "epidemiology", "prevalence", "genotype". The theme that emerged as a result of the keywords used in this cluster was called "cervical cancer and epidemiology of HPV".

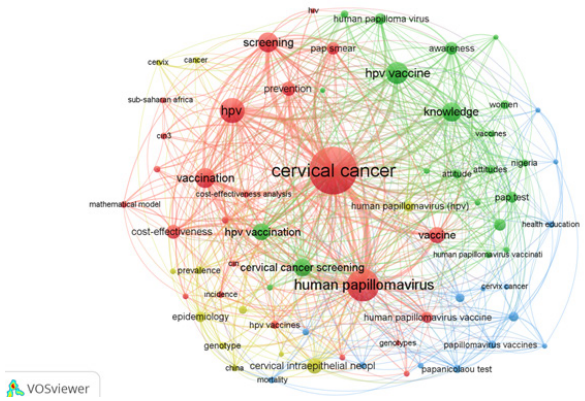

Figure 4. *Network analysis of the co-occurrence of keywords used in the determined area*

DISCUSSION

Our article is important as it is the first study in which bibliometric analysis of joint publications on HPV vaccine and cervical cancer was performed according to the WoS database, as far as we researched. Bibliometric analyzes provide comprehensive historical information about scientific publications by analyzing the structure of publications in a particular research area and show the productivity of countries, authors and organizations (16).

With the discovery of the HPV vaccine, animal experiments investigating protection against cervical cancer were started and the first publications focused on this subject were found in 1991 (17). In the bibliometric analysis, in which only the HPV vaccine was investigated in the literature, it was found that there was an average of 28% increase in the number of publications per year between 2001 and 2018. It has been shown that the rate of increase in publications reached 150%, especially between 2006 and 2007(18). It is thought that this increase is due to the inclusion of HPV vaccine in the vaccination program in developed countries in those years. As a result of our study, it is seen that the joint publications on HPV vaccine and cervical cancer have increased especially since 2018 and the most publications were in 2021. We thought the possible reason for this was the WHO (10) global call for a cervical cancer elimination program in 2020. The increase in HPV vaccine administration and cervical cancer screening may have contributed to the increase in joint publications in 2021.

The journals "Vaccine" and "PLOS one" published approximately 11% of their joint articles on HPV vaccine and cervical cancer. It shows that the "Vaccine" journal is the area of expertise and scope of the journal, which attracts the authors to publish in the journal, especially in the fields related to the HPV vaccine.

In the joint publications on HPV vaccine and cervical cancer, it is seen that the USA has the highest number of publications and there is a significant difference with other countries. In a study examining medical scientific publications, the country with the highest number of publications between 1995 and 2015 was found to be USA with 4.19 million publications, while China was the second country with 0.91 million publications (19). Similar to this result in our study, it is seen that the country with the most publications in the field we researched is the USA. The presence of a large number of clinical and research centers in the USA may have allowed further research on this subject. Similar to our study, in the bibliometric research on the anthrax vaccine, the highest number of publications was published by the USA, followed by the UK (20). The fact that there is more publication in the USA on vaccines suggests that it may be due to the fact that the USA allocates a significant budget to research and development in almost every research area. It is reported that the National Institutes of Health in the USA received an award of 30 billion dollars for medical research in 2014 (21). Some researchers in African countries and developing countries work on their own or independently instead of collaborating with developed countries (22). This may be one of the reasons why these countries produce fewer articles compared to other parts of the world. Another possible explanation for the fewer publications on the subject from other countries is the difficulties faced by authors from less wealthy countries in promoting and publishing their work. When the citation and related author were examined in our study, the dominant country was the USA again. In the results of the network visualization of the co-authorship relationship between the countries or organizations we found in our study, it was found that the countries that cooperated most with the USA on the subject were England, France and Spain. Therefore, researchers in countries with a burden of disease should seek to collaborate with researchers from leading countries such as the USA and the UK.

Keywords in an article indicate relevant and important points in the article (23). These points help represent potential trends in future research (24). It is important to easily scan the frequency and distribution of keywords in the article using bibliometric analysis to highlight the relevant points in research. According to our results, the 3 most frequently used keywords in joint articles on HPV vaccine and cervical cancer were "cervical cancer", "human papillomavirus" and "HPV". In the themes that emerged in line with the keywords, the subjects of cervical cancer and HPV and HPV vaccine relationship, knowledge, attitude and awareness towards cervical cancer screening and HPV vaccine, cervical cancer primary prevention and death, cervical cancer and HPV epidemiology were studied. As a result, it is seen that different areas related to the subject are mentioned. In addition to these, we believe that it would be beneficial to the literature to conduct more studies on hesitancy in HPV vaccine application.

Limitations

Our analyzes are based on articles in the WoS database. The remaining databases other than WoS, such as Pubmed, Scopus, and Google Scholar, were not included as they are technically non-mergeable. The database is still open and some data (number of citations) in the research may be updated continuously.

CONCLUSION

These findings are of interest to researchers and policy makers by conducting bibliometric analysis of co-published articles on HPV vaccine and cervical cancer. In recent years, the number of studies focusing on HPV vaccine and cervical cancer has increased. It was seen that most of the studies were done in developed countries. It is noteworthy that the country that is the leader in the most cited country, responsible author country, international cooperation and leading institutions is the USA. In order to improve the global output of research in this field, it will be beneficial to establish strong research cooperation between researchers and institutes in underdeveloped and developing countries and developed countries.

DECLARATIONS

Funding

The authors declared that this study received no financial support.

Conflicts of Interest

No conflict of interest was declared by the authors.

Ethics Approval

This study does not require ethics committee approval, as no data was obtained from any living thing during the

research process. A public, searchable Web of Science (WoS) database was used for research data.

Availability of Data and Material

Not applicable.

Authors' Contributions

All authors contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

Acknowledgement

Not applicable.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Public Environmental and Occupational Health / Halk ve Çevre Sağlığı

Being a Child in the Digital World: Balancing Anxiety Levels

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ABSTRACT

Purpose: The aim of this study is to examine the anxiety levels of children who are alone with the digital environment.

Materials and Methods: The research was carried out with 15 children aged between 14-18 in Ankara. Data were collected through in-depth interviews and analyzed by content analysis.

Results: When children's views on the concept of digital game are examined, it can be said that digital game has positive and negative aspects for children. While positive emotions are felt at the moment of success in the game, unhappiness, anger, anxiety and anxiety occur at the time of failure.

Conclusion: It can be said that children playing digital games are exposed to the anxiety and anxiety created by the virtual world while playing digital games, as a result of the answers given by the children to the questions regarding this concept.

Keywords: Anxiety, Digital Game, Addiction

Bekir Barış CİHAN
Ebru ARAÇ ILGAR
Nursel ÜSTÜNDAĞ ÖCAL

Dijital Dünyada Çocuk Olmak: Kaygı Düzeylerini Dengelemek

ÖZET

Amaç: Bu çalışmanın amacı, dijital ortamla baş başa kalan çocukların kaygı düzeylerinin incelenmesidir.

Gereç ve Yöntem: Araştırma, Ankara'da yaşları 14-18 arasında değişen 15 çocuk ile gerçekleştirilmiştir. Veriler derinlemesine görüşmeler yoluyla toplanmış ve içerik analizi ile analiz edilmiştir.

Bulgular: Çocukların dijital oyun kavramına ilişkin görüşleri incelendiğinde, dijital oyunun çocuklar için olumlu ve olumsuz yönlerinin olduğu söylenebilir. Oyunda başarı anında olumlu duygular hissedilirken, başarısızlık anında mutsuzluk, öfke ve endişe ortaya çıkıyor.

Sonuç: Dijital oyun oynayan çocukların bu kavramla ilgili sorulara verdikleri cevaplar sonucunda sanal dünyanın yarattığı kaygı ve kaygıya dijital oyun oynarken maruz kaldıkları söylenebilir.

Anahtar Sözcükler: Kaygı, Dijital Oyun, Bağımlılık.

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Childhood is a process that evolves day by day, creating a culture as it does so while also reproducing itself throughout this period. Play is the most significant instrument of childhood culture and the most efficient way for a kid to express himself (1). The game is characterized as "talent and intellect development, entertainment with specific rules, for fun" or "any form of agility-based competition organized to enhance physical and mental ability." (2).

Children learn abilities such as problem solving, exploring, thinking, reasoning, sharing, communication, power, balance, coordination, and self-organization via play (3).

With the advancement of technology, the notions of games and toys have expanded to encompass computer games (atari, commodore64, etc.), video games (Playstation, Xbox, Wii, etc.), and mobile games played on portable devices such as mobile phones, portable PlayStation, Gameboy, and so on. The words "video games," "mobile games," and "computer games" are all interchangeable. Because data entry is supplied with instruments such as a joystick, keypad, or keyboard in all three of them, while the game is observed through the screen (4). Based on these collaborations, video, mobile, and computer games are referred to as "digital games" in this study (5).

It is argued that with the rapid development of technology, rapid and unplanned urbanization, and the removal of open playgrounds, the attention and orientation levels of mainly young persons towards digital games are growing (6).

An anxious individual appears to be terrified of something, feels uneasy, and is in a delusory state (7). Anxiety, on the other hand, differs from fear in that it is objectless; although the object of fear is apparent, whether it is a person or an event, the object of anxiety is ambiguous (8). As a result, whereas fear refers to events with a known origin, anxiety refers to situations with an unknown cause (9).

Anxiety is defined as negative since it is irrational and disrupts mental activity, namely thinking. The elements that characterize anxiety as good are that it warns the person when confronted with the dreaded things and takes measures, directs the person to be happier and more successful, and, most significantly, it plays an active part in the formation of character and personality (10).

Given that diverse emotional changes occur when playing a digital game and that the ability to make decisions is active, it is clear that emotional states influence decision-making throughout the game. The purpose of this study is to investigate how emotional changes that occur when playing digital games affect the anxiety stimuli on youngsters.

METHOD

Research Model

The qualitative research approach was used to support this study, which explores the impact of digital games on children's anxiety levels. The qualitative research design was chosen because it allows for a detailed evaluation of the effects of digital games on children's anxiety levels (11) as well as the exploration of suggestions on this subject (11,12) based on the digital game experiences of the children from whom the data was obtained. In this study, a fixed qualitative research design (13), which was constructed differently from the quantitative research kinds, was utilized since it was intended to gather replies from the youngsters determined for the research.

Working Group

The research group included 15 children aged 14 to 18 from the region of Ankara. The research's study group was determined using the criteria sampling approach, which is one of the intentional sampling methods. Criterion sampling is made up of individuals, events, objects, or circumstances whose features are established by the research's objective (14).

Collection of Data

The semi-structured interview was realized to collect data for the study. In a semi-structured interview, the interviewer normally asks his questions without deviating from those he has prepared ahead of time. Students have the opportunity to ask further questions in order to gain a more in-depth understanding of the interviewees' viewpoints in accordance with the questions developed in accordance with the responses supplied by the students (15, 16). Interviews with the selected children were performed using a semi-structured interview form. The interviews we carried out lasted an average of 45 minutes, and the data was written down. By examining the responses, it was hoped to discover the link between the digital game and anxiety. Answers to the following study questions will be requested in accordance with the research's goal.

What feelings do you experience while playing video games? What are the distinctions between the times you play digital games and the times you do not play digital

games for you? What would you say if you were to express your emotions while winning and losing in a digital game? In what scenarios do you experience dread and anxiety while playing video games? Do you feel pressed when you play video games? What exactly is digital gaming to you, and what does it imply to you? What feelings do you experience when you lose and win at digital games? Do you worry about making quick judgments when playing video games?

Analysis of Data

In this study, the semi-structured form responses were examined using inductive analysis. Inductive analysis allows for in-depth examination of the dimensions that emerge from patterns within the context of the examined scenario (17). Essentially, the process involves gathering similar data within the context of specific concepts and themes and interpreting it in a way that the reader can understand. Data from qualitative research is analyzed in four stages. The first stage is data coding, the second stage is theme discovery, the third stage is code and theme arrangement, and the fourth stage is identification and interpretation of the findings (18). For internal validity in this study, the opinions of experts in qualitative research were consulted throughout the study and corrections were made accordingly. For external validity, purposive sampling and detailed description were used, and for internal reliability (consistency), the research data were analyzed by different experts in qualitative research. Encoder reliability Miles and Huberman (12) calculated as .88 using the formula (Consensus / Consensus + Disagreement X 100). After analyzing the interview transcripts, the researcher decided to the data into six major categories by coding it.

**Ethics Committee Approval:* Necessary permissions for data collection were obtained from the Ethics Committee. Yozgat Bozok University (dated 20/04/2022 and Decision No: 32/36)

RESULTS

In this section of the study, the students' perspectives on digital games, the immediate feelings and thoughts they have while playing games, the situations in which they feel fear and anxiety while playing digital games, what emotions they feel when they lose or win while playing digital games, and what emotions they feel when they do not play digital games are compared. The findings about the discrepancies across time periods were scrutinized.

What emotions do you feel most when playing digital games?

The digital game experiences of children playing digital games and the reflections of these experiences are presented in Figure 1 under the category of "Experiences and Reflections".

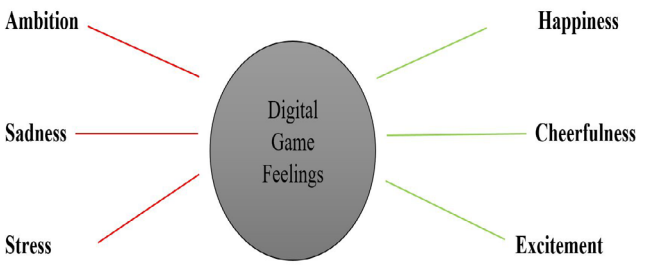

Figure 1. *Digital Game Feelings*

Which emotions do you feel most when participants play digital games? *When their answers to the question are examined, (V1) mentioned that; "I play the digital game mostly with my friends and it increases my happiness. At the same time, I get excited when playing digital games." (V2) said; "During the digital game, my emotions change according to the course of the game, if I played badly, my sadness prevails, but if I played well, I am very happy." Differently (V2) he mentioned; "I don't feel a dominant emotion in general, but I have fun, which makes me happy." (V3) emphasized as follows; "I feel the feelings of determination, ambition and winning very intensely," he said. On the contrary (V4) emphasized that; "I don't get much emotion, I just feel happy if I beat it." (V5) included the following sentences; "I feel excitement and tension at the same time." (V6) said; "Playing a game is a legendary feeling, I get extremely happy while playing games." (V7) emphasized that; "I feel more excitement and stress while playing games". Similarly (V8) stated as follows; "When I play digital games, I feel excitement, nervousness and anxiety." (V9) emphasized that; "I feel very hyperactive. At the same time, I am experiencing a lot of ambition, excitement and stress." (V10) said: "It is enjoyable, I am happy, it excites me to move to new levels."(V11) mentioned; "I feel excitement and tension at the same time." (V12) said; "More ambition, excitement and feelings of winning come to the fore". However, (V13) emphasized that; "I feel the feeling of excitement the most while playing digital games." Differently (V14), he stated; "I generally feel comfortable, but sometimes I get excited".(V15)*

As it is seen in the statements of the students, it was concluded that playing games reveals the feeling of happiness and excitement, but also triggers emotions such as tension and ambition.

If you compare the time you play digital games and the time you do not play digital games, what are the differences between these two times for you?

As a result of the answers given by the students, the differences between playing and not playing digital games are given in Figure 2.

Figure 2. *Feelings During and After the Game*

If you compare the time when the participants are playing games and the times when they are not playing digital games, what are the differences between these two times for you? When their answers to the question are examined;" *When I play games, I realize that my time passes very quickly and I can't spare time for other activities, but when I don't play, I can easily handle everything." (V1) In addition to this; (V2) stated, "When I play, I have fun and my time passes very quickly, but when I do not play, I get bored and time does not pass." Differently, when we look at the discourses of (V3), "There is no difference between when I play and when I do not play. It is because I only play to spend my free time." He gave place to the sentences "When I am not playing games, I am bored, I want to play games with my friends because we cannot leave the house because of the Covid-19 pandemic." (V4) stated, "If we compare the time I play with the times I don't play, I can say that the only difference is a little simplification of my life." (V5). (V6) stated that; "Time passes faster when playing digital games, but when I am not playing, I use my time better". On the other hand, (V7) said, "I always want to play games if my family quits, but they don't allow it. When I don't play, I sit idly by." (V8) emphasized that "When I compare the time I play and the time I don't play, I can say that I feel more productive during the process of playing games." (V9) stated, "I feel mentally unhealthy and aggressive when I don't play." Besides; (V10) stated, "I already play games in my spare time, if I don't play games, I watch TV." "When I don't play, I get bored and I feel the need to play. When I enter the game, I am happy and excited; I do not understand how the time passes, so I prefer to play" (V11). He stated, "When I am not playing, I am calmer and my adrenaline level is low" (V12). Differently; looking at the statements of (V13), he emphasized that "I don't feel a difference between when I play and when I don't." (V14) stated as follows; when I play, I feel distracted, but when I do not play, I feel more stressed." (V15) said: "When I play games, I feel braver because I do not experience any real loss, so when I am not playing, I perform behaviors that I do not dare in the game."*

As it is monitored in the statements of the students, they stated that when they play games, they feel more courageous by isolating themselves from real life, and they feel boring and stressed when they do not play games.

If you were to interpret your mood while winning and losing during the digital game, what would you say?

As a result of the answers given by the students, the differences between their moods when they win or lose digital games are showed in Figure 3.

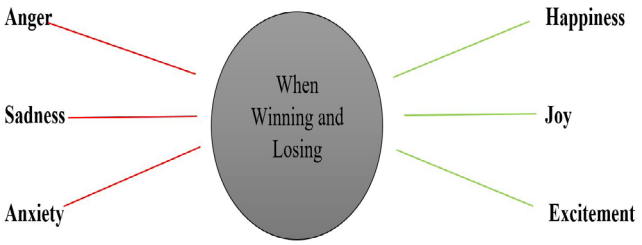

Figure 3. *Feelings in the moment of Winning and Losing*

If you were to interpret your mood while winning and losing during the digital game, what would you say? When their answers to the question are examined; *(V1) emphasized that; "I feel very sad when I lose, but I am very happy to win. I am very happy and excited when I win. (V2) said: "When I lose, I get angry depending on the reaction of the people I play, or I don't care, I look at the next games." Unlike these, when looking at the statements of (V3), he said, "When I lose, I feel anxiety and I do not accept responsibility, I blame others. If I win, I will be happy." (V4) stated as follows; "I am happy and joyful when winning, I feel sad and unhappy when I lose." (V5) emphasized that; "I am not sad when I lose, but I am happy if I win." (V6) emphasized that "I get angry when I lose. And when I win, I am happy." (V7) included the following sentences; "When I win, I feel great, I brag about*

my surroundings, but when I lose, I cannot accept it, I always attribute the reason for my loss to others." (V8) stated, "I feel very good and happy when I win, but when I lose. I get extremely nervous and irritable." Similarly (V9) stated, "When I win, I get extremely happy. When I lose, I also get extremely angry." (V10) stated the following: "When I win, I feel happy and success gives me pleasure. When I lose, I get ambitious and aim to win even more in the next game." From a different point of view, the words of (V11) were as follows; and I play the next chapter or level in a better mode. When I lose, I feel sad, I think where I went wrong, I find my mistake and start again." (V12) stated that; and I reflect this anger on them. I am happy and excited at the same time when I win." (V13) said; "I can continue the game comfortably while winning during the game. I can see that I can be ambitious and ambitious." Similarly (V14) conveyed; "I am very happy when I win and my mood is high. e is positively affected. Even if I lose, I get angry with myself because I know that I can do better." (V15) stated as follows; "Although it is sad to lose because of my ambition, it also makes me happy to win."

As it is viewed in the statements of the students, they stated that when the digital game is won, they are in the happiness and greed of winning, and they play the next part with more pleasure, and when they lose the game, they are under the influence of anger and tension caused by sadness.

In which situations do you feel fear and anxiety while playing digital games?

As a result of the answers given by the students, it is given in Figure 4 in which situations they experience feelings of fear and anxiety while playing digital games.

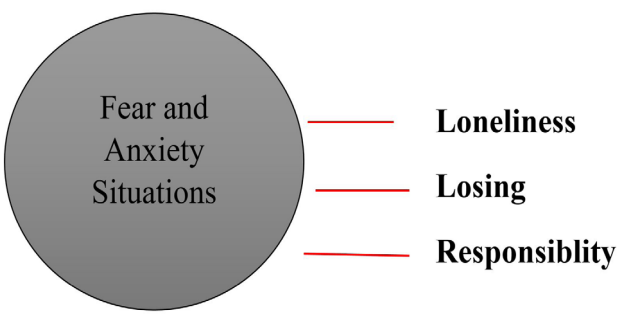

Figure 4. *Fear and Anxiety Conditions*

In which situations do you feel fear and anxiety while playing digital games? When their answers to the question are examined; *(V1) stated that; "I usually prefer team games, all my teammates are dead and if I am alone, I get scared and anxious." Differently (V2) said; "I don't feel fear and anxiety while playing, I think there is no need to stress myself for the game." (V3) stated that; "When I lose, I feel anxiety and fear, I cannot digest losing in any way." (V4) emphasized that; "When I lose or win, I worry about making the last move properly. (V5) said differently: "I never experience feelings of fear or anxiety in the games I play." (V6) stated that; "When I stay at the end of the game, I get nervous and I get scared at the moment of being killed in the game." (V7) emphasized that; "I get scared when creatures come across during the game, or I get excited when I get into conflict during the war." (V8) stated as follows; "I worry when I think my abilities are inadequate." (V9) said: "I get worried if I decrease in the game." (V10) said: "I worry and fear more when I am alone with the opponent player." Similarly (V11) said; "If it is a timed game, then I get scared. When the game decreases, when I face the opponent team and play with my teammates, I have anxiety and fear about fulfilling the responsibility given to me." (V12) continued as follows; "If the game is lost because of me, I feel fear and anxiety at the same time depending on the game I play. I feel the same feeling when the team comes to my field." (V13) said, "The feelings of fear and anxiety are usually related to the game. I usually feel it during combat when playing war games." (V14) said, "Fear and anxiety are I feel anxiety only when there is an enemy that I am not sure I can defeat." Differently (V15), he stated that; "I do not feel anxiety and fear because I am already in at this platform where I feel comfortable.".*

As it is seen in the statements of the students, they stated that they experienced the feeling of fear while playing the digital game when they were killed in the game and thus lost the game, and they experienced the anxiety if they did not apply the techniques told in the game correctly.

Do you feel pressure while playing digital games? What is digital gaming for you, what does it mean to you?

As a result of the answers given by the students, their opinions about pressure while playing digital games and their personal views about digital games are given in Figure 5.

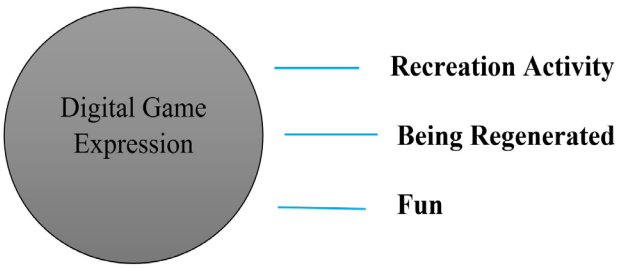

Figure 5. *Digital Game Expressions*

Do you feel pressure while playing digital games? What is digital gaming for you, what does it mean to you? When their answers to the question examined; *(V1) said; "I don't feel pressure. It has become a necessity for me, I feel unhappy and bored when I am not playing." Differently (V2) said; "Other people in the game show some pressure when I don't play the game well, but this pressure does not affect me because I enter the game to have fun." Similarly (V3) emphasized that; "I don't feel pressure, I just play to spend my free time, to discharge, so I don't feel any responsibility on me." Differently (V4) he said: 'When I'm playing with my friends or in a ranked game, there is pressure not to lose points. Digital gaming is indispensable for me because I can't find a playmate outside, but I have friends in games." (V5) said; "I never feel pressure when playing digital games. Digital gaming is a great distraction for me." (V6) said: "Because I play as a team, I try to win for the team and there is pressure. Digital gaming is stress relief and spending time for me." Similarly (V7) stated as follows; "It creates incredible pressure, I always experience that pressure until the end of the game. Digital gaming means success, it's my job to succeed." Differently (V8) said, "I don't feel a lot of pressure, but I do feel some pressure. Digital gaming means fun and spending time with my friends." Similarly (V9) emphasized that; "No, I don't feel it. It is a good option for me to spend time with myself and my friends." (V10) included the following sentences; "Yes, I feel, I try to fulfill the responsibilities necessary to win. Digital gaming is an exciting activity for me that I spend in my daily life, in my spare time and with my friends." (V11) stated as follows; "Yes, I feel pressure. Because the game has a purpose and I am trying to reach that goal. For me, I play digital games to make use of my free time, to evaluate the times when I am bored, and to have a pleasant time with my friends." Similarly (V12) said: "Yes, I feel pressure, although I experience stress and anger while playing digital games, I also experience happiness and the feeling of pleasure when I win. After a while, my mind is always on the game. I usually try to fill my free time with games." (V13) He stated as follows; "When I play alone, I don't feel pressure, but if it's a team game, I usually feel pressure to raise the team higher. I can usually say that games are a form of relaxation for me.". (V14) emphasized differently as follows; "I don't feel pressure when I play, because I play to distract myself. For me, gaming is a way of avoiding stress." Similarly (V15) said: "I don't feel stress and pressure in something that is a hobby for me, even though I spend a lot of time, I am aware that it is not real life. Digital gaming is just a tool for me to make free time fun."*

Do instant decisions worry you while playing digital games?

As a result of the answers given by the students, their views on instant decisions while playing digital games are given in Figure 6.

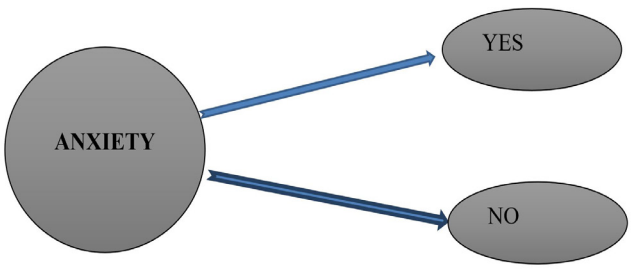

Figure 6. *Instant decisions and anxiety while playing digital games*

Do instant decisions worry you while playing digital games? When their answers to the question examined; *(V1) said; "It doesn't worry me because I'm always aware that it's a game". Similarly, (V2) mentioned; "It doesn't worry me, on the contrary, it prevents me from being indecisive and eating myself up, I don't make instant decisions." (V3) stated that; "Since the digital games I play are generally strategic, I have to make instant decisions all the time, so I'm used to instant decisions and I don't worry." Differently (V4) included the following sentences; "Yes, instant decisions change the course of the game, sometimes they lose while they win, that's why I'm worried." Differently (V5) expressed as follows; "Immediate decisions taken while playing digital games do not affect me, I do not worry." (V6) said; "I can't say I'm worried too much, but I can say I'm a little bit worried." (V7) said; "While playing a game, I never make a decision without being sure, I always make my decision after being sure, and this does not cause me anxiety." Similarly, (V8) emphasized that; "It doesn't make you feel any anxiety." (V9) said: "No, because I am used to making sudden decisions." (V10) expressed as follows; He said, "It's not worrying, I'm familiar with digital gaming and instant decisions." Differently (V11) he said; "Yes,*

it worries me, I wonder if I made a wrong decision. If I am in a team game, I consult my teammates to avoid making mistakes." Similarly (V12) stated that; "Depending on the digital game I play, I can say yes because unplanned snap decisions cause me anxiety." (V13) emphasized that; "Yes, instant decisions may worry me depending on the current state of the game." Differently (V14) he said; "No, snap decisions don't worry me because I'm careful to make decisions that can do as little harm as possible." (V15) stated as follows; since I am not worried about winning or losing, I try to follow the decisions made and focus on my game instead of worrying."

RESULT AND DISCUSSION

In this research, which intends to disclose the perspectives of children who play digital games on the notion of digital games, a total of six semi-structured questions were asked to the children, and their responses were examined using inductive analysis. What feelings do you experience the most when you play digital games? When the responses to the question were studied, it was determined that the digital game elicited powerful feelings in youngsters such as ambition, melancholy, tension and happiness, joy and excitement. Spending more time than necessary on digital games has resulted in aggressive behaviors, lack of emotion, issues maturing, and damage to relationships with others (19). Mustafaoğlu and Yasacı (20) discovered that digital games played in moderation had a soothing impact on teenage emotional release and are useful in forecasting, decision-making, and analysis. Researchers investigating the negative impacts of digital gaming and focusing on addiction have concentrated on the uncontrolled and extended play of digital games and the influence on the individual's mood (21).

Do you feel oppressed when you play video games? What exactly is digital gaming to you, and what does it mean to you? When the children's responses to the question were reviewed, they revealed a variety of perspectives on the subject of pressure. Some kids reported feeling pressure, while others reported feeling no pressure and, on the opposite, experiencing inner ease. When asked what the digital game meant to them, they frequently responded with recreation activities, regeneration, and amusement. Esen and Gündodu (22) discovered a link between peer support and digital addiction. It is thought that this is due to intense peer pressure during this time period.

In what scenarios do you experience dread and anxiety while playing video games? When the responses to the question are evaluated, it is clear that the children's fears and anxieties are unified in the notions of being alone during the game, losing the game, and accepting responsibility. According to Barut (23), adventure-thrill games are entertainment-type games that delight the user while also instilling anxiety and excitement in him. This category includes games like adventure, virtual or real vehicle racing, and bungee leaping. As a result, certain types of games might induce dread and anxiety in people.

Do you worry about making quick judgments when playing video games? When the responses to the question are evaluated, it is clear that there is no agreement. Some students reported that they felt anxious when making quick judgments, however other participants stated that they did not feel anxious during their conversation. Many researches have found that digital games are harmful to one's health. Romer, Bagdasarov, and More (24) found that heavy use of digital games causes depression in young and young adults regardless of the content, and this result is similar to the results of Lemmens, Valkenburg, and Peter (25) with German youth and Gentile et al (26) with American youth.

What would you say if you were to express your emotions while winning and losing in a digital game? When the answers to the question are examined, children stated that they felt anger, sadness, and anxiety during the loss of the digital game, but they felt happiness, joy, and excitement during the winning. Children who play digital games have bad sentiments and attitudes about themselves, have difficulty in their social relationships with others, and lose self-control. These issues are a serious problem that should not be overlooked in terms of cognitive, emotional and physiological development of children (27).

What are the distinctions between the times you play digital games and the times you do not play digital games for you? When the participants' responses to the question were reviewed, they stressed the dominance of the sensation of delight when playing the digital game and the feeling of restlessness when not playing the digital game. It has been suggested that many of the adolescents who play digital games play to get rid of stress and negative emotions (28). Irmak and Erdoğan (6) emphasized that digital gamers do not play these games despite their negative effects and feel psychologically deprived when they cannot play the game. Kowert et al. (29) found that people who play online games rather than offline games have a lower quality social environment.

Lemmens et al. (30) evaluated digital game addiction under seven criteria. The 4th and 6th criteria of these categories are as follows; Conflict: This refers to interpersonal conflicts that result from excessive gaming. These confrontations may be verbal, but they may also entail dishonesty and lying. Withdrawal: Unwanted emotional and physical repercussions that occur when the game is paused, even when the difficulty level is rapidly dropped. It is characterized by psychological symptoms such as introversion, anger, and trembling.

As a conclusion, when children's perspectives on the notion of digital games are analyzed, it is possible to conclude that digital games have both good and bad features for children. While happiness, anger, anxiety, and anxiety are felt when a player wins a game, sadness, anger, anxiety, and anxiety are felt when a player loses. As a result of the answers given by the children to the questions about this idea, it can be claimed that children playing digital games are exposed to the fear and anxiety caused by the virtual world when playing digital games.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Health Policy and Services / Sağlık Politikaları ve Hizmetleri

The Mediating Role of Patient Satisfaction in the Effect of Perceived Corporate Image on Patient Loyalty

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ABSTRACT

Objective: Corporate image, patient satisfaction, and patient loyalty have become crucial for the survival of private hospitals in the fiercely competitive environment. This study aimed to determine the mediating role of patient satisfaction in the effect of perceived corporate image on patient loyalty.

Methods: The study was conducted in the Marmara Region, Türkiye, between June 15, 2021 and October 15, 2021. The study data were collected from individuals aged 18 and over who resided in the Marmara Region, Türkiye, and received services from private hospitals in 2021. The study data were collected by online survey.

Results: The study results showed that perceived corporate image has a positive effect on patient satisfaction. Furthermore, both perceived corporate image and patient satisfaction have a positive effect on patient loyalty. Lastly, patient satisfaction has a mediating role in the effect of perceived corporate image on patient loyalty.

Conclusion: Both the perceived corporate image and patient satisfaction are determinants of patient loyalty. In the light of the study results, efforts are recommended to increase the positive perceived corporate image and patient satisfaction.

Keywords: Corporate Image, Patient Satisfaction, Patient Loyalty, Hospital

Serkan DENİZ
Mesut ÇİMEN

Algılanan Kurumsal İmajın Hasta Sadakatine Etkisinde Hasta Memnuniyetinin Aracılık Rolü

ÖZET

Amaç: Yoğun rekabet ortamında özel hastanelerin varlığını sürdürebilmesi için kurumsal imaj, hasta memnuniyeti ve hasta sadakati konuları çok önemli hale gelmiştir. Bu çalışma ile algılanan kurumsal imajın hasta sadakatine etkisinde hasta memnuniyetinin aracılık rolünün belirlenmesi amaçlanmıştır.

Yöntem: Araştırma 15 Haziran 2021 – 15 Ekim 2021 tarihleri arasında Marmara Bölgesi, Türkiye'de gerçekleştirilmiştir. Araştırma verileri Türkiye'de Marmara Bölgesi'nde ikamet eden ve 2021 yılı içerisinde özel hastanelerden hizmet almış 18 yaş veya üzeri bireylerden toplanmıştır. Araştırma verileri online anket yöntemi ile toplanmıştır.

Bulgular: Araştırma sonuçlarına göre kurumsal imaj algısının hasta memnuniyetini pozitif etkilediği belirlenmiştir. Ayrıca hem kurumsal imaj algısının hem de hasta memnuniyetinin hasta sadakatini pozitif etkilediği belirlenmiştir. Son olarak algılanan kurumsal imajın hasta sadakatine etkisinde hasta memnuniyetinin aracılık rolünün olduğu belirlenmiştir.

Sonuç: Araştırmanın sonuçları hem algılanan kurumsal imajın hem de hasta memnuniyetinin hasta sadakatinin bir belirleyicisi olduğunu göstermektedir. Araştırma sonuçları çerçevesinde olumlu kurumsal imaj algısının ve hasta memnuniyetinin arttırılmasına yönelik çalışmaların yapılması önerilmiştir.

Anahtar Kelimeler: Kurumsal İmaj, Hasta Memnuniyeti, Hasta Sadakati, Hastane

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Due to many reasons, including increased competition in the business world, technological advancements, changes in the market structure, diversification of demands and expectations of consumers, etc., consumer- and community-oriented work has become a must for today's organisations to be able to survive. Significant changes and developments are taking place in the healthcare industry. Hospitals have become forced to carry out consumer- and community-oriented operations to survive because of the changes in the provision of the healthcare services, the community's raised awareness of health, changing requirements and expectations, etc. (1). This situation has made matters such as corporate image, patient satisfaction, and patient loyalty important for hospitals.

Corporate image is defined as "stakeholders' beliefs, perceptions, feelings and attitudes towards an organisation" (2). Representing the picture of an organisation in the minds of audiences or stakeholders, the corporate image is what comes to the minds of the audience or stakeholders when they see or hear the name or logo of the organisation (3). The corporate image is the result of the interaction of the organisation with the audiences or stakeholders (4). The audiences or stakeholders of an organisation make assessments based on a variety of information about the organisation. Therefore, the image of a corporation may vary across audiences or stakeholders. In other words, one segment of society has a positive opinion about an organisation, while another segment may have a negative opinion about it (5). There are several factors affecting the formation of a corporate image. For hospitals they include the name, logo, architecture, and general hygiene of the hospital as well as the level of difficulty to get information from the hospital, how it handles complaints, the news in the press, the appearance and attire of its staff, the quality of the staff's communication with the patients, whether novel methods of diagnosis and treatment are used, waiting times, the adequacy of the medical equipment and devices, the quality of the services rendered, the attention paid to patient privacy and patients' rights, the information of the community about health-related issues, environmental awareness, etc. (6). The corporate image provides benefits to organisations in many aspects, including achieving a competitive advantage and profitability, increasing sales, interrelating positive relationships with the community and stakeholders, attracting investors and financial institutions, and ensuring employee satisfaction, consumer satisfaction, and loyalty. Therefore, it is very important for organisations to make efforts to create a positive image and maintain and manage it (7).

Patient satisfaction is another crucial issue for hospitals. Patient satisfaction is defined as "patient perception that the expectations have been met or exceeded" (8). Patient satisfaction involves subjective evaluations by the patients about the services provided to them (9). Patients make evaluations on whether the services provided to them by a healthcare organisation meet their demands and expectations after they receive services from them. As a result of these evaluations, patient satisfaction is achieved if the services received have met the demands and expectations of patients. However, if the services received have not met their demands and expectations, patient dissatisfaction occurs (8). There are several factors affecting patient satisfaction. These include the age, sex, educational background, social security, income status, demands, and expectations of the patient as well as the type of their disease, the care taken and the information given in the diagnosis and treatment process, attention paid to their privacy, the length of time taken for their diagnosis and treatment, attitudes and behaviours of the staff, etc. Likewise, factors such as quality of the healthcare service offered, equipment and technology of the organisation, cleanliness, physical appearance, and comfort of the organisation, and waiting times also affect patient satisfaction (10,11). Patient satisfaction provides substantial benefits for both patients and healthcare organisations. Satisfied patients pay regard to the advice given by the physician, comply with the treatment, have increased trust in the organisation, choose the same organisation again in case of need, and express positive opinions about the organisation to the people around them. Patient satisfaction helps healthcare organisations gain a competitive advantage, reduce costs, and increase profitability (12,13,14).

Patient loyalty is another important issue for hospitals. Patient loyalty is the deep commitment of patients to choose the same healthcare organisation again when they need, even if they have better alternatives (15,16). Loyal patients prefer the same hospital when needed, give positive opinions and advice about the hospital to the people around them, and resist going to other hospitals. Therefore, loyal patients are crucial for hospitals (8,17). Loyal patients reduces the marketing costs of hospitals and loss of patients and helps to establish long-term relationships with patients (18, 19). Patient loyalty is affected by factors such as corporate image, service quality, patient satisfaction, etc. (16, 20).

This study aimed to determine the mediating role of patient satisfaction in the effect of perceived corporate image on patient loyalty. Below are the study hypotheses developed on the basis of the objective and conceptual framework of the study.

H_1: Perceived corporate image has a positive effect on patient satisfaction.

H_2: Perceived corporate image has a positive effect on patient loyalty.

H_3: Patient satisfaction has a positive effect on patient loyalty.

H_4: Patient satisfaction has a mediating role in the effect of perceived corporate image on patient loyalty.

MATERIAL AND METHODS

The study was conducted in the Marmara Region, Türkiye, between June 15, 2021 and October 15, 2021. The study data were collected by online survey.

Samples

The study sample consisted of individuals aged 18 and over who resided in the Marmara Region and received services from private hospitals in 2021. Within the scope of the study 395 survey forms were collected.

Characteristics of the participants of the study, 58.5% (n=231) were female and 41.5% (n=164) were male and 22% (n=87) had a high school or lower degree, 29.6% (n=117) an associate degree, 38.5% (n=152) an undergraduate degree, and 9.9% (n=39) a graduate degree. While 52.7% of the participants (n=208) were single, 47.3% of them (n=187) were married. The average age of the participants was 31.65±10.47.

Measures

The data was collected by using a survey form that consisted of four sections. The first section contained questions to identify the demographic characteristics of the participants. Information on other measurement tools that used in the study is given below:

- Corporate Image Scale: The scale was developed by Derin and Demirel (21). The scale consists of one dimension and seven statements. Analyses showed that the level of reliability of the scale is high (α=0.894).
- Patient Satisfaction Scale: The scale was developed by Chang et al. (22). The validity and reliability of the Turkish version of the scale was confirmed by Durmuş and Akbolat (23). The scale consists of one dimension and four statements. Analyses showed that the level of reliability of the scale is high (α=0.905).
- Patient Loyalty Scale: The scale was developed by Tosyalı et al. (24). The scale consists of one dimension and seven statements. Analyses showed that the level of reliability of the scale is high (α=0.884).

The statements in the scales were measured by 5-point Likert-type scale options (1= strongly disagree, 5 = strongly agree).

Data Analysis

The statistical software SPSS 22.0 and Process Macro v4.0 were used to analyze the data. Descriptive statistics were calculated, and correlation and effect analyses were performed. The results of the data analyses were considered to be within a confidence interval of 95% with a significance level of 5%.

RESULTS

Based on the results of the analysis presented in Table 1, there was a positive correlation between perceived corporate image and patient satisfaction (r= 0.788). In addition, there were positive correlations between both perceived corporate image and patient loyalty (r= 0.712) and patient satisfaction and patient loyalty (r= 0.782).

Table 1: Descriptive Statistics and Correlation Analysis

Variables	Mean	SD	1	2
1. Perceived Corporate Image	4.074	0.481		
2. Patient Satisfaction	4.075	0.542	0.788*	
3. Patient Loyalty	3.989	0.528	0.712*	0.782*
*p<0.01				

As shown by the results of the analysis given in Table 2, perceived corporate image has a positive effect on patient satisfaction (β=0.889, p=0.000). Moreover, both perceived corporate image (β= 0.280, p=0.000) and patient satisfaction (β= 0.566, p=0.000) have a positive effect on patient loyalty. Based on these results, hypotheses H1, H2, and H3 were confirmed.

Table 2. Effect Analyses						
Effect	**β**	**S.E.**	**t**	**p**	**LLCI**	**ULCI**
Constant	0.453	0.144	3.156	0.002	0.171	0.736
PCI→PS	0.889	0.035	25.393	0.000	0.820	0.958
Effect	**β**	**S.E.**	**t**	**p**	**LLCI**	**ULCI**
Constant	0.544	0.139	3.905	0.000	0.270	0.817
PCI→PL	0.280	0.054	5.138	0.000	0.173	0.387
PS→PL	0.566	0.048	11.719	0.000	0.471	0.661

PCI: Perceived Corporate Image, PS: Patient Satisfaction, PL: Patient Loyalty

As shown by the results of the analysis given in Table 3, patient satisfaction has a mediating role in the effect of perceived corporate image on patient loyalty (β= 0.503) and further increases the positive effect of perceived corporate image on patient loyalty (β= 0.783, p=0.000). Based on this result, hypothesis H4 was confirmed.

Table 3. Analyses of Mediating Effect							
Effect		**β**	**S.E.**	**t**	**p**	**LLCI**	**ULCI**
Direct Effect	**PCI→PL**	0.280	0.054	5.138	0.000	0.173	0.387
Indirect Effect	**PCI→PS→PL**	0.503	0.053			0.389	0.599
Total Effect	**PCI→PL**	0.783	0.039	20.129	0.000	0.706	0.859

PCI: Perceived Corporate Image, PS: Patient Satisfaction, PL: Patient Loyalty

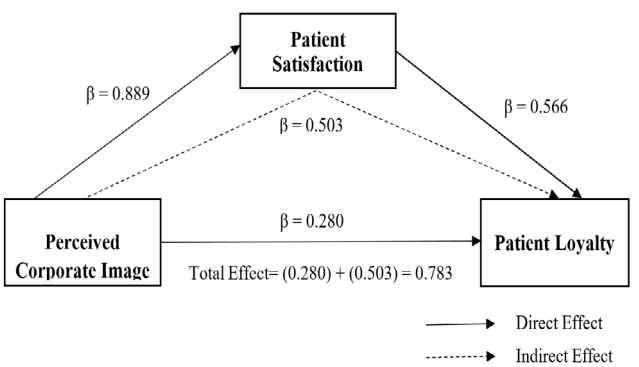

Figure 1. *Model Output*

DISCUSSION AND CONCLUSION

The present study results show that perceived corporate image has a positive effect on patient satisfaction. This result is supported by the results of similar studies in the literature (13,19,25). It can be claimed, based on the results of both the present study and those in the literature, that patients' positive perception of corporate image of a hospital where they received services increases their satisfaction. Another result obtained in the present study is that perceived corporate image has a positive effect on patient loyalty. This result is supported by the results of similar studies in the literature (13,16,18). Considering these results, it can be reported that a positively perceived corporate image increases patient loyalty.

It was also concluded from the present study that patient satisfaction has a positive effect on patient loyalty. This is supported by the results of similar studies in the literature (14,17,26,27). Within the framework of both the results of the present study and those of studies in the literature, it can be said that if patients are satisfied with the services provided by a hospital, they might choose that hospital again in future when they need healthcare services, and loyalty to that hospital might be created depending on the level of satisfaction. Lastly, it was established from the results of the present study that patient satisfaction has a mediating role in the effect of the perceived corporate image on patient loyalty. According to these results, the patients' positive perception of the corporate image of a hospital where they received services might affect their satisfaction positively and their satisfaction might indirectly increase the positive effect of the perceived corporate image on patient loyalty.

The results of the present study show that both perceived corporate image and patient satisfaction are determinants of patient loyalty. Achieving patient loyalty is vital for hospitals in the sense that it is difficult and highly costly to gain new patients in the severe competitive environment and with a view to not losing the existing patients (19). In the light of the study results, certain recommendations were made to increase the positively perceived corporate image and patient satisfaction. Hospital management should pay attention to physical conditions, appearances, architecture, decoration, and cleanliness to be able to project a positive corporate image to the community, stakeholders, and patients. In addition, employees should pay attention to their appearance and outfits, communicate positively with their patients and be kind to them. The quality of healthcare services offered, adequate equipment, not-too-long waiting times, and detailed information for patients during treatment must be ensured. The news and posts about the hospital must be followed and releases must be made to the public when needed. Social

responsibility projects and works for the benefit of society must be performed. Lastly, it is recommended that hospital leaders professionally manage corporate image efforts and involve employees.

In order to ensure patient satisfaction, the needs, demands and expectations of the patients should be constantly monitored and taken into consideration. Arrangements must be made to meet the needs, demands, and expectations of patients. The patients' level of satisfaction must be measured and improved as required. The patients must be treated with honesty and transparently. Detailed information must be given to the patients about the healthcare services offered to them, solutions must be created for their complaints, and quality service must be offered. Lastly, all employees of the hospital must assist patients and be kind to them.

This study is important for determining the mediating role of patient satisfaction in the effect of perceived corporate image on patient loyalty with regard to private hospitals. It is considered to be beneficial to conduct similar studies on the subject involving more participants and people who receive services from public hospitals.

Limitations

The study is limited to people who received service from private hospitals in the Marmara Region between June 15, 2021 and October 15, 2021. The low number of participants is another limitation.

DECLARATIONS

Funding

No financial support was received for the study.

Conflicts of Interest

There are no potential conflict of interest was reported by the authors.

Ethics Approval

Ethical approval that the study was ethically appropriate was obtained with decision number 2021-10/27 on 09.06.2021 from the Medical Research Evaluation Board of Acıbadem Mehmet Ali Aydınlar University.

Availability of Data and Material

The dataset of this study are available from the corresponding author on reasonable request.

Authors Contributions

All authors contributed equally to all parts of the study.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nursing / Hemşirelik

Psychosocial Problems Experienced by Infertile Women and Stigmatization: A Qualitative Study

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This study was presented as a poster with the title "Psychosocial Problems and Stigmatization of Infertile Women: A Qualitative Study" in the 5th International 16th National Nursing Congress held in Ankara, Turkey between 5-9 November, 2017.

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ABSTRACT

Purpose: This study aims to determine the psychosocial problems experienced by infertile women and their stigmatization statuses.

Methods: This qualitative study was conducted in the Assisted Reproductive Treatment Center of a university hospital in Turkey between November 2016 and May 2017. The sample of the study consisted of 42 infertile women who agreed to participate in the study. The data were collected using a semi-structured "Interview Form" consisting of eight open-ended questions to determine the psychosocial problems experienced by the women in relation to infertility. The collected data were analyzed with the method of content analysis.

Results: According to the results of the in-depth interviews conducted with the participants, four main themes emerged to include ten sub-themes revealing the psychosocial problems they experienced and their stigmatization issues as sorrow, feeling of guilt, childlessness stigma, loss of feeling of motherhood, stress (psychological), perceived social pressure, social isolation (social), lack of sexual drive, feeling of sexual failure (sex life) and financial loss (economic).

Conclusion: In the study, it was determined that the women who were receiving infertility treatment experienced many psychosocial problems and stigmatization due to their childlessness, and they limited their social lives to especially avoid questions directed to them about having a child and evade talking to pregnant women/families and women/families with children. Based on these results, it is recommended for nurses who work at assisted reproductive treatment centers and especially have the opportunity to communicate with infertile women for longer to determine the psychosocial problems experienced by these women throughout their treatment processes and provide the psychosocial support and counselling they need.

Keywords: Infertility, woman, social problems, nursing, qualitative study, stigmatization

İnfertil Kadınların Yaşadıkları Psikososyal Sorunlar ve Damgalanma: Nitel Bir Çalışma

ÖZET

Giriş: İnfertil olmaya bağlı damgalanma, toplumsal cinsiyet eşitsizliğine ve genel olarak toplum içindeki konumlarına bağlı olarak en fazla kadınlarda yaşanan bir sorun olarak karşımıza çıkmaktadır. Bu çalışma, infertil kadınların yaşadıkları psikososyal sorunları ve damgalanma durumlarını belirlemek amacıyla yapılmıştır.

Yöntem: Bu çalışma, Türkiye'de bir üniversite hastanesinin Yardımcı Üreme Tedavi Merkezi'nde Kasım 2016-Mayıs 2017 tarihleri arasında nitel olarak yapılmıştır. Araştırmanın örneklemini araştırmaya katılmayı kabul eden 42 infertil kadın oluşturmuştur. Veriler, kadınların infertilite ile ilgili yaşadıkları psikososyal sorunları belirlemeye yönelik sekiz açık uçlu sorudan oluşan yarı yapılandırılmış "Görüşme Formu" aracılığıyla toplanmıştır. Toplanan veriler içerik analizi yöntemiyle çözümlenmiştir.

Bulgular: İnfertil kadınlarla yapılan derinlemesine görüşmelerden kadınların yaşadıkları psikososyal sorunları ve damgalanma durumlarını ortaya koyan üzüntü, suçluluk duygusu, çocuksuzluk damgalanması, annelik duygusu kaybı, stres (psikolojik olarak etkilenme), algılanan sosyal baskı, sosyal izolasyon (sosyal olarak etkilenme), cinsel isteksizlik, cinsel başarısızlık duygusu (cinsel yaşam açısından etkilenme) ve maddi kayıp yaşama (ekonomik olarak etkilenme) şeklinde on alt temadan oluşan dört ana tema ortaya çıkmıştır.

Sonuç: Araştırmada infertilite tedavisi gören kadınların çocuksuzlukları nedeniyle birçok psikososyal sorun ve damgalanma yaşadıkları, özellikle çocuk sahibi olma konusunda kendilerine yöneltilen sorulardan ve hamilelerle konuşmaktan kaçınarak sosyal yaşamlarını kısıtladıkları belirlendi. Bu sonuçlara dayalı olarak üremeye yardımcı tedavi merkezlerinde çalışan ve özellikle infertil kadınlarla daha uzun süre iletişim kurma olanağına sahip olan hemşirelerin, kadınların tedavi sürecinde yaşadıkları psikososyal sorunları belirlemeleri, ihtiyaç duydukları psikososyal destek ve danışmanlığı sağlamaları önerilmektedir.

Anahtar Kelimeler: İnfertilite, kadın, sosyal sorunlar, hemşirelik, nitel çalışma, damgalanma

Infertility is considered a life crisis for the individual that is biologically hurtful, psychologically threatening, socially embarrassing, economically expensive, and complicated (1). Although not being able to have a child emotionally affects both sexes, it has been reported that women are affected much more than men are, they experience more intense stress and pressure, and their anxiety and depression rates are higher (2-8). In addition to all these influences, in married couples, it is usually the woman who shows help-seeking behaviors due to childlessness, receives treatment, and participates in the treatment process in person even if she is not the source of infertility (6). This is because, in some societies, the inability to have a child is almost always attributed to the 'woman' alone, and even if the cause of infertility is not related to them in general, women are blamed for it. As a result, this situation can harm women, especially biologically, psychologically, economically, socially, and emotionally, and negatively affect their quality of life (6,9,10).

In developing countries, children are seen to be highly valuable due to social, cultural, and economic reasons. In such countries, childlessness may lead to personal, social, and familial problems accompanied by many stressors, reduced security, and stability in marriage, and the inclusion of the right of the man to remarry in the agenda, and all these factors result in the ostracizing of especially infertile women (3-5,11). The possibility of remarrying is low for infertile women who are left or divorced by their husbands, living alone is not socially approved, and lack of social and economic support for most women make the psychological trauma experienced by infertile women even deeper (12,13). As a result of this, infertility may turn into an unpleasant, hurtful stigma which is not desired in society with its complicated and destructive outcomes (4).

Infertility-related stigmatization is a problem that is mostly seen among women due to gender inequality and the general status of women in society (4,6,10). Many studies have determined that infertile women are exposed to verbal violence by the families of their spouses and experience stigma (4,10,14,15).

In addition to infertility-related stigma, the tests that are applied, assisted reproductive treatments that are used, and the fact that these tests and treatments are mostly administered to women lead to additional emotional stress in women and cause them to feel responsible for the infertility situation (5).

In the literature in the country where this study was conducted, it is seen that the effects of infertility on couples or women have been investigated in quantitative studies (11,16). There are few studies that have examined infertility effects by using qualitative methods (1,6,7). In the province where the study was conducted, no studies were found to qualitatively investigate the effects of infertility on women receiving infertility treatment. As opposed to quantitative methods, qualitative methods allow a more detailed determination of the views and thoughts of individuals. For healthcare workers, especially nurses working at infertility units, to be able to holistically examine infertile couples/women and help them experience this process in a more compatible manner, they need to have an in-depth knowledge of problems and experiences in this process. This way more effective infertility care and treatment may be provided by healthcare workers, and the probability of the success of the treatment that is applied may increase. Additionally, knowing about the social and psychological outcomes of infertility will be guiding for health policies. This study was planned to determine the psychosocial problems and stigma of women who were received infertility treatment in a city center in the country located in the Northern Hemisphere.

MATERIALS AND METHODS

Design

This is a qualitative study.

Sample

The participants of this study were selected from among the participants in the quantitative step, which was the first stage of the two-stage study, by applying the criterion sampling method. The sample of the qualitative study included 42 women who received a score of 43 or higher from the 'Infertility Affectedness Scale' which was used as the quantitative data collection tool in the study among 202 infertile women who visited the Assisted Reproductive Treatment Center (ARTC) at the university hospital due to infertility between 15 November 2016 and 15 May 2017 (Figure 1).

Data Collection

The in-depth interviews were held with the participants who agreed to participate in interviews by using the 'Semi-Structured Interview Form' and an audio recording device. The data were collected by face-to-face interviews with the women after their written consent was obtained in an appropriate room in the treatment center.

Before starting the interviews, permission was asked from the women to use the audio recorder. The statements of those who permitted the use of the audio recorder (29 women) were both recorded by the audio recorder and noted down by the researcher using the interview form. In the interviews with the women who did not give permission (13 women), notes were taken on the statements of the interviewees only on the interview form. At the beginning of the interview, for the interviewees to sincerely respond to the questions and for eliminating their hesitations about the study, the researcher explained to each interviewee that they would be given a number based on their order of interview (e.g. Participant 1, Participant 2…), and it was ensured that only this number would be used during the interview, so that the identity (real name) of the interviewee would be kept confidential. While saving the documents obtained from the interviews, these participant numbers were used instead of the women's names. The in-depth interviews with the 42 participants lasted for about 45-60 minutes.

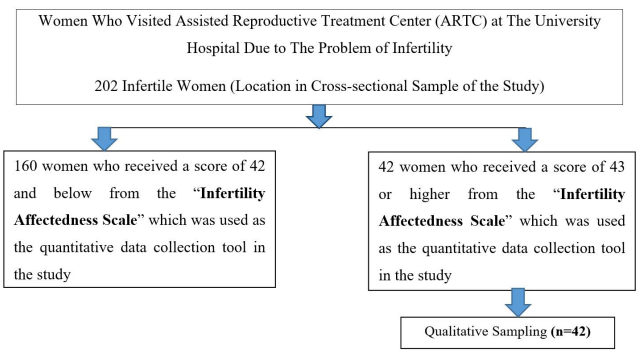

Figure 1 *Flowchart of study participants*

Data Collection Tools

The data were collected using a semi-structured interview form as a qualitative data collection instrument for the in-depth revelation of the views and thoughts of the participants on how they were affected by infertility in the psychosocial sense and their statuses of experiencing stigma due to infertility. This method was selected as it provides the researcher with interaction, flexibility, and opportunity of examination. In the interviews, eight open-ended questions were asked. The interview started with the question 'What did you feel when you first heard about the diagnosis of infertility?' During the interview, when needed, alternative questions towards one purpose without leading the interviewee for each question and additional questions to gain more in-depth information were asked.

Data Analysis

The data were analyzed in two steps: the transcription of the recorded data collected during the interviews and the content analysis. In the first stage, the transcripts were prepared by transferring the recorded conversation on the voice recorder to the computer, restoring, and transcribing it on the computer repeatedly, as well as converting the results into a written document. The nonrecorded interviews were transferred to the computer as a Microsoft Office Word (Microsoft Word 2010 Program) document. In the second step, all written documents were transferred to the NVivo 10 Program for content analysis, and the selected codes and themes were evaluated by taking into account the opinions and recommendations of experts and consultants who are experienced in the analysis of qualitative data. In the second phase, the codes generated for each interview question were examined first, the common connections between the codes were determined, and the related codes (sub-themes) were brought together. Finally, the themes of the data were determined. The collected data are presented in this article using the code names of the participants and direct quotations of their views. The determined codes, sub-themes and themes were presented to two separate expert academicians who had knowledge and experience in qualitative research and were not involved in the study. The data were checked for validity and reliability, and the necessary corrections were made. Care was taken to ensure that the citations made to provide internal validity were related to the determined codes and themes and were capable of explaining them.

RESULTS

Sociodemographic Characteristics

The mean age of the participants was 31.36±4.95 (min: 21, max: 40), 45.2% were high school graduates, 78.6% were homemakers, 73.8% had nuclear families, 64.3% had equivalent incomes and expenses and living in the city, 83.3% had been married for 3 years or longer, the spouses of 73.8% were 30-39 years old, the spouses of 40.5% were high school graduates, and the spouses of 90.5% were working (Table 1).

Table 1. Sociodemographic characteristics of the women (n=42)

Sociodemographic characteristics		n	%
Mean age31.36±4.95 (Min:21; Max:40) years			
Age	21-30 years	18	42.9
	31-40 years	**24**	**57.1**
Educational level	Primary-Secondary school	12	28.6
	High school	**19**	**45.2**
	Higher education	11	26.2
Employment status	Not employed (Homemaker)	**33**	**78.6**
	Working	9	21.4
Type of family	Nuclear family	**31**	**73.8**
	Extended family	11	26.2
Income status	Income less than expense	11	26.2
	Income and expense equivalent	**27**	**64.3**
	Income more than expense	4	9.5
Place of living	City	**27**	**64.3**
	District	5	11.9
	Village	10	23.8
Age of marriage	18 years or younger	9	21.4
	19-29 years	**29**	**69.0**
	30 years or older	4	9.5
Duration of marriage	1-3 year(s)	7	16.7
	3 years or longer	**35**	**83.3**
Age of spouse	20-29 years	4	9.5
	30-39 years	**31**	**73.8**
	40 years or older	7	16.7
Educational level of spouse	Primary-Secondary school	15	35.7
	High school	**17**	**40.5**
	Higher education	10	23.8
Spouse employment status	Not employed (retired-unemployed)	4	9.5
	Working	**38**	**90.5**

Table 2 Infertility-related characteristics of the women (n=42)

Infertility-related characteristics		n	%
Source of Infertility	Female-factor only	**13**	**31.0**
	Both male-factor and female-factor	14	33.3
	Unknown cause	15	35.7
Cause of female-factor infertility	Reproductive pathways closed or damaged	1	7.7
	Immunological causes	2	15.4
	Cervical causes	4	30.8
	Ovulation irregularities	**6**	**46.2**
Infertility diagnosis duration	Less than 1 year	**19**	**45.2**
	1-2 year(s)	**15**	**35.7**
	3 years or longer	8	19.1
Infertility treatment duration	Less than 1 year	**29**	**69.0**
	1-2 year(s)	**9**	**21.4**
	3 years or longer	4	9.6
Decision to receive infertility treatment	Woman herself	3	7.1
	Woman's spouse	1	2.4
	Woman and spouse together	**38**	**90.5**
Current infertility treatment	Medication	**24**	**57.1**
	Intrauterine insemination	17	40.5
	In vitro fertilization	1	2.4
Meeting infertility treatment costs	Couple themselves	12	28.6
	Social security plan	4	9.5
	Both themselves and social security plan	**24**	**57.1**
	Support of family and relatives	2	4.8

Infertility-Related Characteristics

Among the participants, 31.0% had female-factor infertility problems, irregular ovulation was the cause of infertility for 46.2%, the diagnosis duration of 80.9% and the treatment duration of 90.4% were 2 years or shorter, 90.5% made the treatment decision together with their spouses, and 57.1% received medication as infertility treatment and met their infertility treatment costs from both their own budgets and their social security plans (Table 2).

Psychosocial Problems Experienced by the Participants and Their Stigmatization Statuses

From the in-depth interviews conducted with the participants, four main themes emerged to include ten subthemes revealing the psychosocial problems they experienced and their stigmatization statuses as sorrow, feeling of guilt, childlessness stigmatization, loss of feeling of motherhood, stress (being affected psychologically), perceived social pressure, social isolation (being affected socially), lack of sexual drive, feeling of sexual failure (being affected in terms of sex life), and financial loss (being affected economically). How these psychosocial problems and stigma were expressed by the participants is shown below with direct quotes from their responses (Table 3).

Table 3. Quotes, codes, subthemes and main themes obtained from the views of infertile women

Quotes	Codes	Subthemes	Main themes	
"I am very sad. I think about how happy I would be if I had a baby. That is, I am very sad, I can't state it…" (Participant 1; 30 years old, infertile for 4 years) *"I feel my husband is sad. He is also very sad, naturally affected by this situation"* (Participant 7; 27 years old, infertile for 3 years) *"Everyone, my family, our family is sorrowful for this situation" (*Participant 8; 34 years old, infertile for 4 years)	-Expressing your sadness due to not having children -Feeling upset of your spouse because they don't have children	Sadness	Theme 1	Being affected psychologically
"I always blame myself. I feel really bad, because it is my mistake. I wouldn't be like this if my periods were regular, unfortunately, it comes from me." (Participant 14; 28 years old, infertile for 3 years) *"I still blame myself, thinking we are experiencing these problems because of me…"* (Participant 22; 29 years old, infertile for 4 years) *"People around me always blame me. They say we can't have children because of my defect. They say it is so because of me, especially my husband's family, some relatives..."* (Participant 15; 32 years old, infertile for 4 years)	-Feeling guilty thinking that they have no children because of their own fault -Expressing that the environment blames because they are not children	Feeling of guilt		
"I hear from around sometimes, they say "there are an incomplete family, childless, they don't even count as a family". These words affect me very much. They unavoidably make one feel incomplete". *"I heard they were calling me a half-woman, fruitless tree in the neighborhood and around. This is what I heard."* (Participant 11; 29 years old, infertile for 4 years)	-Being seen as half, incomplete by the environment -Feeling flawed and incomplete because they don't have children	Childlessness stigma		
"I would also like to give birth, have a child. I would very much want to experience that feeling, feeling of giving birth, motherhood." (Participant 13; 28 years old, infertile for 3 years) *"Being a mother is something else. I don't know, you value increases in the eyes of everyone."* (Participant 10; 36 years old, infertile for 6 years)	-Do not want to experience the feeling of motherhood -Don't be sad because you can't experience the feeling of motherhood	Loss of feeling of motherhood		
"The treatment stage is very difficult. Treatment is stressful, waiting is stressful." (Participant 40; 30 years old, infertile for 5 years) *"What will happen at the end of the treatment, will I get pregnant? Thinking of these, waiting for the outcome is very stressful."* (Participant 3; 29 years old, infertile for 3 years) *"Everyone keeps asking about the outcome of the treatment. My stress increases even more then."* (Participant 19; 27 years old, infertile for 3 years)	- Stress of waiting for the outcome of the treatment - The close circle keeps asking about the outcome of the treatment	Stress		
"My husband's family constantly pressures me. What happened? Still nothing? They keep saying these things." (Participant 42; 33 years old, infertile for 5 years) *"My mother and others constantly ask, is there a pregnancy? They ask me about my period schedule, what happened, did you get your period or not, this way, I constantly feel under pressure …"* (Participant 17; 32 years old, infertile for 4 years)	-The close circle always asks whether they are pregnant or not -The spouse's family constantly asking about the pregnancy status	Perceived social pressure	Theme 2	Being affected socially
"I limit my social life. I don't want to go to the homes of those with children or those expecting. I get very sad when I see..." (Participant 5; 31 years old, infertile for 3 years) *"I closed myself between four walls. I don't want to see anyone. I think it is best to stay home."* (Participant 7; 30 years old, infertile for 3 years)	-Limiting social life -Not wanting to meet people who have children	Social isolation		
"I always experience a lack of sexual drive. I don't want to have sex, I try to avoid my husband" (Participant 15; 32 years old, infertile for 4 years) *"When my husband asks for sex, I avoid it as much as possible, I don't have any desire in me, I really don't like sex."* (Participant 11; 29 years old, infertile for 4 years)	-Avoiding sexual intercourse -Dislike sexual intercourse	Loss of sexual desire	Theme 3	Impact on sexual life
"I have sex with my husband with the fear that I won't get pregnant this time either. …because we didn't have a child despite regular sex for years." (Participant 27; 27 years old, infertile for 3 years) *"I always have sex with the fear that I will fail to get pregnant again. Each occasion of sex is another source of stress for me."* (Participant 13; 28 years old, infertile for 3 years)	-Do not have sexual intercourse for fear of not conceiving again	Feeling of sexual failure		
"Travelling back and forth for treatment, medication costs, treatment costs, they affect me much in the financial sense." (Participant 33; 28 years old, infertile for 2 years) *"I can't work because I come from afar. Travelling back and forth for treatment also affected my work life. We are in more financial difficulty because I don't work."* (Participant 36; 34 years old, infertile for 4 years)	-Difficulty in meeting the treatment costs -Inability to work due to the treatment process	Financial loss	Theme 4	Being affected economically

DISCUSSION

This study revealed that the participants experienced several psychosocial problems despite the fact that the vast majority of them had diagnosis and treatment durations of two years or shorter. Studies have determined that due to infertility, women experience psychosocial problems such as sorrow, loneliness, stigma, social isolation, concerns, depression, attention deficit, anxiety, and sexual dissatisfaction (2,8,10,17). In agreement with the results of this study, results reported in the literature have shown that infertility leads to psychological and social problems in infertile couples, especially women (18-21). Other studies with infertile women in the same country as this study have also revealed that women experience high levels of stress and psychosocial problems (1,12). A previous study revealed that high levels of family participation in the treatment process and the unrealistic expectations of families from the treatment process are perceived as an additional stressing factor among infertile women (14). In similarity to the findings of this study, in their qualitative study, Naab et al. (13) revealed two main themes (psychological and social experiences) and eight sub-themes (anxiety, depression, stress, isolation, stigmatization, pressure, marriage problems, and support) based on their interviews with infertile women. It was reported that women experience more stress than men do as they are unable to get pregnant and due to social pressures (12). In contrast to the findings in this study, two separate studies found that infertile participants experienced concerns especially regarding their advancing age and the possibility of their spouses marrying other women (17,22). The finding in this study that none of the participants stated concerns about their spouses getting married to someone else may be explained by the participants' higher levels of hope that they could have babies as most of them were young, and the durations of diagnosis and treatment for most were two years or shorter.

The participants of this study stated that they kept away from social environments to avoid questions about having children and encountering families with children. Other studies have reported that infertile women experience social isolation due to infertility (1,5,23). In a qualitative study on infertile couples, some participants reported that they limited their social relationships with their families and others to avoid questions on whether they were having a baby (24). Another study conducted with infertile women revealed that the women did not want to talk to individuals that knew that they were having infertility problems, and they were disturbed by questions asked by people around them to satisfy their own curiosity (12). The qualitative study conducted by Naab et al. (13) showed that infertile women experienced two types of social isolation; they preferred to isolate themselves from social environments to avoid being negatively affected by the words of others, which was in line with the result in this study, and they reported that they were ostracized by people around them from social activities, which was different to the result in this study. It is thought that avoiding social environments and activities saves infertile women from the psychological pressure of being questioned about their status of having children.

In this study, the participants expressed that they were stigmatized by society as they were unable to get pregnant and had no children, society made them feel incomplete and defective, and they were blamed for not being able to have children. Several studies have reported that infertile women are stigmatized for being childless, their participation in family decisions is obstructed, they are belittled, kept out of rituals such as weddings or celebration ceremonies, they are not accepted as real women, and they are defined as 'men' and 'useless' (6,14,25). Other studies have found that infertile women became distressed when they were asked questions about their childlessness status, they felt guilty and inadequate, and they were stigmatized by society for their childlessness (10-12,19,23,25,26). Another study demonstrated that whether the problem of infertility is related to them, it is mostly women who apply for infertility treatment, look for solutions, have to bear treatment costs, and even if their spouse is the source of the infertility problem, they are stigmatized as infertile, and stigma hurts more than the infertility itself (6). In parallel with the findings of this study, in a qualitative study on infertile couples, a participant working as a teacher stated that parents did not want to register their children to her classroom with the thought that she would be impatient and inconsiderate against children as she cannot have a child (24). In a study conducted with women living in metropolitan cities of the same country as this study, contrary to our findings, infertile women were found to experience a low level of stigma (27). It is believed that this difference in the findings may have been caused by that living in a metropolitan city would allow women to experience less stigma in comparison to living in the Anatolia region where this study was conducted. In a qualitative study carried out with infertile women, in difference to the findings of this study, the participants stated that they were perceived by people around them as women using family planning methods or controlling their pregnancy by secretly doing something

to avoid pregnancy or as if they were deliberately, by their own choice, not having children (13). It is believed that the finding in this study that the participants were stigmatized due to infertility as incomplete and defective may have been caused by the fact that none of them had children (primary infertility), while the finding of Naab et al. (13) that the women in their study were stigmatized as deliberately choosing to not have children may have been caused by the fact that half of their participants had children (secondary infertility).

In this study, the participants stated that they felt under pressure as they were constantly exposed to questions on whether they could get pregnant yet by both their families and their spouses' families, especially their mothers-in-law. Other studies conducted in the same country have shown that infertile women are accused of being unable to have children, especially by their husbands' families, subjected to discrimination and violence, and even exposed to pressure from their mother-in-law and threats of divorce by their mother-in-law (1,12). In a study conducted with infertile women, it was determined that childless women were constantly worried about being abandoned by their husbands and were under pressure from their husbands' families to remarry or divorce (28). Naab et al. (13) found that the pressure perceived by infertile women from their mothers-in-law and relatives was mostly caused by being forced to divorce their spouses and their spouses getting married to other women. In another qualitative study, as opposed to many findings in the literature, it was ascertained that infertile women did not frequently experience threats of divorce or their spouses remarrying as they were relatives with their spouses (6). The finding in this study that the participants did not have a perception of pressure regarding being forced to divorce or their spouses being remarried may have been caused by the fact that their durations of diagnosis and treatment were mostly two years or shorter.

Some participants in this study stated that they suffered financial losses due to the costs of their infertility treatment. In the study conducted by Jafarzadeh-Kenarsari et al. (24) on the support needs of infertile couples, the participants emphasized the financial difficulties of infertility treatment, and they had expectations of support from the government for their treatment costs. Most couples deal with many financial problems, usually as a part of infertility treatment programs that are not covered by insurance agencies. Problems with the cost of infertility have been reported in the literature (14). Findings in the literature have supported the findings related to the problem of financial loss emphasized by the participants of this study.

Limitations

The results of this study are limited to women who presented to the ARTC of a university hospital for infertility treatment, met the inclusion criteria for qualitative research and were interviewed in depth.

CONCLUSION

In this study conducted with women who visited the infertility center of a university hospital in a country in the northern hemisphere, it was found that women experienced many psychosocial problems linked to infertility such as grief, stress, social pressure, and social isolation, as well as stigma. For infertile couples and especially women to experience this process in a healthier position, healthcare workers need to assess the process not only as a medical but also as a psychosocial health problem, and it is needed to develop intervention programs towards preventing the psychosocial problems and stigmatization experienced by infertile couples, especially women, who feel the burden of being infertile more intensely.

DECLARATIONS

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Ethics Approval: All protocols for this study were approved by the Sivas Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (Decision No: 2016/10-19). To conduct the present study, the ethical principles for medical research on human subjects established by the Declaration of Helsinki were followed.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nursing / Hemşirelik

A Qualitative Study on the Experiences of Fathers Involved in Vaginal Delivery: Real-Life Experiences

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ABSTRACT

Purpose: The birth of a baby is one of the most meaningful moments partners can experience throughout their lives. This study was conducted to determine the emotions, thoughts, and experiences of fathers involved in vaginal delivery.

Methods: This study was a qualitative research using phenomenological approach and theoretical thematic analysis approach was used in data analysis. The 22 couples participated in the study. The data were separately obtained from fathers involved in the delivery and their partners using the face to face in-depth interview method within four hours after delivery.

Results: The data were categorized into five themes: emotions, thoughts, and experiences of fathers involved in delivery; purpose of involvement; positive and negative feelings, roles, and responsibilities of fathers; expectations from health professionals; and meeting the baby for the first time. The fathers who were confused when they first entered the delivery room experienced ambivalent feelings, especially during the last phases of the active period and the expulsion phase.

Conclusion: Fathers should be involved in the childbirth process so that the parents can experience a favourable childbirth experience, the relationship between partners strengthens, the family life is affected positively, and the newborns are born into an environment in which they feel safe.

Keywords: Newborn; Childbirth; Experiences; Fathers; Emotional

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Doğuma Katılan Babaların Doğum Deneyimlerine İlişkin Niteliksel Bir Çalışma: Gerçek Yaşam Deneyimi

ÖZET

Amaç: Bir bebeğin doğumu eşlerin hayatları boyunca yaşayacağı en anlamlı yaşam deneyimlerinden biridir. Bu araştırma vajinal doğuma katılan babaların doğum sürecinde yaşadıkları duygu, düşünce ve deneyimleri ile bu deneyimlerinin anne üzerine olan etkisi belirlemek amacıyla gerçekleştirilmiştir.

Materyal ve metodlar: Bu araştırma fenomenolojik yaklaşımın kullanıldığı nitel bir araştırmadır ve verilerin analizinde kuramsal tematik analiz yaklaşımı kullanıldı. Araştırmaya 22 çift katıldı. Veriler doğuma katılan babalardan ve eşlerinden ayrı ayrı yüz yüze derinlemesine görüşme yöntemiyle doğumdan sonraki dört saat içinde elde edilmiştir.

Bulgular: Veriler beş temada kategorize edildi: doğuma dahil olan babaların duyguları, düşünceleri ve deneyimleri; katılım amacı; babaların olumlu ve olumsuz duyguları, rolleri ve sorumlulukları; sağlık profesyonellerinden beklentiler; ve bebekle ilk kez tanışmak. Doğumhaneye ilk girdiklerinde şaşkınlık yaşayan babaların özellikle aktif dönemin son evrelerinde ve ekspülsiyon evresinde ambivalan duygular yaşadıkları belirlenmiştir.

Conclusions: Ebeveynlerin olumlu doğum deneyimi yaşamaları, eşlerin ilişkisinin güçlenmesi, aile hayatlarının pozitif yönde etkilenmesi ve yeni doğanın güvenli hissettiği bir ortama doğması için babaların da doğum sürecine eşlik etmesi gerekmektedir.

Anahtar kelimeler: Yenidoğan; Doğum; Deneyim; Baba; Duygu

Childbirth is one of the most important experiences in the lives of parents. The most important support during childbirth for parents is the partners themselves (1). Although the involvement of fathers in the delivery was initially considered to increase the infection incidence and negatively affect the relationship and sexual life of couples, men have started to play an active role in delivery rooms since 1960 (2). The involvement of fathers in the delivery not only helps them to support their partners, but also increases parental adaptation and paternal bonding. The father who accompanies the mother during labor will help to reduce the fear, anxiety, and loneliness of the mother and help her to have a more favorable childbirth experience (3). Moreover, the involvement of fathers in the delivery not only enables fathers to meet their newborn and share the experience of childbirth, but also is beneficial to the psychological support of women. Healthcare professionals should inform couples about the involvement of fathers in childbirth and should help fathers perform their responsibilities by supporting them during the delivery. Furthermore, the fathers' involvement in childbirth is both a need of the mother and a parental role that the father should experience (4). In Turkey, there are great differences in the society in terms of language, religion, and culture. Generally, fathers take a passive role in the delivery process and wait for the delivery to be completed away from their partners outside the delivery room. Additionally, there is the general idea that the birth of a child is a process only affecting the woman, and that the involvement of the father would obstruct the delivery and even have a negative impact. Therefore, Turkish fathers are not involved in the delivery and this is a social norm indoctrinated in men. There are many idioms and proverbs indicating that mothers and fathers should be away from each other during the delivery such as: "The mother gives birth to one child and the father to a thousand". In Turkey, fathers have a passive role in the childbirth process, which is a learned social imposition (5). However, special needs of fathers, who are both parents and the most important supporters of mothers, during pregnancy, childbirth, and parenthood should be determined and included in prenatal trainings by healthcare professionals, which can help fathers to be ready and eager to play an active role in childbirth (6). Knowing the feelings and thoughts of fathers in detail will provide detailed information to the health care professional in the provision of antenatal health services. It will also be guiding and encouraging for other men.

Research Questions

1. What are emotions and thoughts of fathers involved in the delivery?
2. What are the experiences of fathers involved in the delivery?
3. What are the roles and responsibilities of fathers during this process?

METHODS

Research design: This is a qualitative study. The study was conducted in a delivery room of a university hospital with fathers who volunteered to participate in the study between August 2018 and January 2019.

The study was designed as follows: Partners were allowed to enter the delivery room in addition to the routine medical personnel of the delivery room. The fathers were encouraged to support their wives and actively participate in the delivery. The fathers were encouraged to stay in the delivery room as long as their wives were there. In the hospital where this study was conducted, pregnant women are accepted to the delivery room in the latent phase of the delivery and stay there for 4 hours after the delivery (bleeding control phase). No male companions are allowed in the delivery room and postpartum service of the hospital. Table 1 shows the study design and the forms used in the study.

Table 1. Study Flow Chart

	1. Interview	2. Interview	3. Interview
Time of Application	Latent/Active Phase of Delivery	From active phase to postpartum	4 hours after the delivery (bleeding control phase)
Setting	Training Room	Delivery Room	Training Room
Interventions	-Participants were informed about the study, their written/verbal consent was obtained; -Participants were taken into the delivery room;	-Routine care was applied in the delivery room; -Fathers were encouraged to stay with their wives during the delivery and postpartum process; -Fathers were supported during this process;	Interviews were carried out about the delivery experience
Forms used	Introductory Information Form		The semi-structured interview guide

Sample: The study included fathers who were 18 and older, who agreed to be with their wives during the delivery, who agreed to participate to the study, and whose wife had a normal live vaginal delivery. Exclusion criteria were a c-section delivery, risky pregnancy, or premature delivery. The simple random method was used for the sample selection. The study included 26 couples. However, the study continued with 22 couples because one of the pregnant women had to undergo cesarean section and three of the partners could not accompany their partners through the end of the delivery. Table 2 shows the participants' sociodemographic characteristics.

Table 2. Participants' sociodemographic characteristics (N=22)

	Mother		Father	
Variables	X̄±Sd.	Min-max	X̄±Sd.	Min-max
Age	28.72±6.34	19-40	33.81±6.97	20-45
Gravida	2.68±1.55	1-6		
Parite	2.04±1.09	1-4		
Education Level	% (n)		% (n)	
Primary school or lower	68.1 (15)		54.4 (12)	
High School	27.3 (6)		36.4 (8)	
Undergraduate	4.5 (1)		9.1 (2)	
Employment Status				
Employed	13.6 (3)		100 (22)	
Unemployed	86.3 (19)		0 (0)	
Marital status				
Married	100 (22)		100 (22)	

X̄: Mean, Sd.: Standard Deviation

Qualitative interviews: The data were collected using the semi-structured interview guide, which was developed by the researchers to analyze the sociodemographic characteristics and delivery-related emotions and thoughts of fathers. The data were obtained from fathers involved in the delivery using the face to face in-depth interview method by researchers within the delivery room. The interview carried out with parents took approximately 30-45 minutes. The interviews held with the participants were recorded. All data obtained from the interviews were transformed into written format (Microsoft Office Word) within 24 hours and stored in the computer. No changes were made to the statements of the couples whilst changing the format. Data collection was terminated when the data from the sample reached saturation and began to repeat itself.

The semi-structured interview guide was composed of five open-ended and closed-ended questions to examine the father's childbirth experiences and support during the delivery. "Why did you want to be involved in the delivery process?", "What did you feel about accompanying your partner in the delivery process?", "What did you do to support your wife?", "Do you think that you were able to support your wife during this process?", and "What did you feel when you first saw your baby?". At the end of the interview, the participants were asked if there was something they wanted to add (1,4,5).

Ethical Consideration: Ethical approval was obtained from the Muğla Sıtkı Kocaman University Ethical Review Board (No:180119/113) on 17 July 2018. Participation was voluntary and confidential and written informed consent was obtained prior to participation in the study.

Data Analysis: Statistical Package for Social Sciences 21.0 package program was used to analyze the quantitative data of the research. Colaizzi's (1978) method of data analysis was applied to the transcripts, which had been proofread and cross-checked with the audio recordings, 3 times for exactitude, and to acquire familiarity with the content. The records of the interview were analyzed by 2 researchers independent of each other in terms of the experiences, feelings, and thoughts of the fathers. The researchers categorized the statements and concepts by repeatedly reading the results obtained from the interview guide and carrying out an analysis for the interview text (7). The codes were listed in categories. Then, all researchers came together and discussed to create a thematic framework.

RESULTS

Nine of the fathers (40.90%) reported that it was the first delivery for their wives. All fathers reported that they participated in the delivery for the first time. Table 3 show the themes, subthemes, and summaries of participants' statements formed after the in-depth interviews carried out with fathers. The data were categorized into five themes;

1. Fathers' Purpose of Participation in the Delivery

In-depth interviews showed that for the father, the purpose for participating in the delivery included supporting their partner and creating an environment of trust. Fathers' expressed their feelings about the involvement in the delivery as follows.

Table 3. Themes and Subthemes Formed After the Involvement of Fathers in the Delivery

Themes and subthemes	Fathers' statements
1. Fathers' purpose of participation in the delivery	
Supporting their partner	I did not want to leave my wife and our baby alone Being with my wife was very important to me
Creating an environment of trust	I wanted to be with my wife because I did not want to leave her alone in an environment she is not familiar with I wanted my wife to know I am right beside her and she is safe with me
Witnessing the process	To see the birth of our baby To be a part of this process To see our baby for the first time with my wife
2. Fathers' Feelings	
Happiness, Joy, Excitement	Being with my wife made me very happy This happiness is very different; we are a mother and father now I am so happy because this experience positively contributed to our lives I am so joyful and happy
Being proud of oneself	I felt very happy and proud Knowing that I was supportive made me proud I am proud of myself for not leaving my wife and my baby alone
Self-confidence	It increased my self-confidence I felt valuable
Fatherhood	I realized that fatherhood is not easy and means not waiting behind the door of the delivery room I realized that I did not learn to be a father during the previous deliveries of my wife Moreover, being a father is beautiful
Respect to the mother	I could not handle this process; I could not do it. Women are really strong I realized that my wife was very strong
Satisfaction	We had a beautiful delivery experience Being with my wife and doing something for her and our baby was amazing I am so thankful that I was by her side
Confusion	I realized that delivery is an extraordinary event At first, I was very confused in the delivery room I did not know what I should do
Fear, anxiety, panic	To be honest, this period scared me very much I was so scared that something would happen to my wife when her pain increased This pain... Oh my god how was she able to bear it! I was so scared
3. The Role and Responsibilities of the Father	
Active participation	We started this path together. We were always together during her examinations and everything we will continue to do so I tried to be with my wife and support her. I wet her mouth with water and wiped her forehead when she sweat
Coach	I helped her to do breathing exercises I held her hand, hugged her, massaged her back, put a pillow behind her back
Team member	We started this path together and will continue together I realized that I was one of the important factors in the delivery
4. The Support of Healthcare Professionals	
Effective communication	We were in a great communication with the healthcare team Their communication and behaviors were great
Supportive care	Everyone in the delivery room was very successful. They were there for us every time we needed them Everyone knew what they were doing The midwifes were constantly in communication with me
Empathy	They truly understood us and solved every need of us
5. Meeting the baby	
Happiness, joy, sentimentality, proud, miracle, satisfaction	It was not just happiness, it was beyond that It is an incredible feeling I was so happy When I first saw the baby, I was so happy

Supporting their partner: All participating fathers reported that they wanted to be involved in the delivery to support their wives. Fathers' statements were as follows: Father 1 said "I did not want to leave my wife and our baby alone. Being with my wife was very important to me."

Creating an environment of trust: It was observed that not only did mothers feel lonely in the delivery room, fathers also thought that their partners felt lonely in the delivery room. Therefore, all the fathers wanted to be with their partners in the delivery room in order not to leave them alone. Fathers' opinions on this subject are as follows: Father 14 stated "I love my wife so much. It is our first baby and first childbirth experience. I wanted my wife to know I am right beside her, she is not alone, and she is safe with me."

Witnessing the process: It was determined that one of the objectives of the fathers participating in the delivery was that they wanted to witness the process. Fathers' statements were as follows: Father 6 said "I wanted to be with my wife in case I could help in any way, also I wanted to see the process of my wife because I wanted to be with her and be a part of this process."

2. Fathers' Feelings

Fathers reported that as the labor continued, they experienced different emotions. All fathers reported that they were confused when they first entered the delivery room. They indicated that they experienced ambivalent feelings, especially during the last phases of the active period and during the expulsion phase. The feelings of fathers were given with their own expressions in the subthemes.

Happiness, Joy, Excitement: It was identified that all the fathers in the study experienced the feelings of happiness, joy and, excitement. All participants mentioned this feeling, and some of them made the following statements: Father 9 mentioned "Being a part of the delivery was miraculous, I witnessed how sacred childbirth and being a mother is. I am so joyful." Father 16 exclaimed "I am so joyful and happy... It is hard to describe."

Being proud of oneself: Half of the fathers participating in the study reported that they were proud of themselves. Father 17 stated "I was proud of myself for being able to support my wife... I learned that fathers can be a part of the delivery, too."

Self-confidence: Father 2 stated "It is so great that I was with my wife and my child. I felt valuable."

Fatherhood: Many of the fathers witnessing the delivery used the statement "I acknowledged my fatherhood". Father 19 stated "I realized that I did not learn to be a father during the previous deliveries of my wife. I am very happy that we experienced this process together."

Respect to the mother: All fathers witnessing the delivery reported that they started to respect their wives and all mothers. Fathers' statements about this matter were as follows: Father 18 declared "I realized how strong women are." Father 14 exclaimed "I could not handle this process; I could not do it. Women are really strong." Father 13 said "I realized that my wife was very strong. I love her."

Satisfaction: One of the most common emotions reported by the fathers was gratitude. Fathers' statements were as follows: Father 22 commented "It was delightful to be with my wife and do something for her and our baby."

Confusion: Father 10 articulated "At first, I was very confused in the delivery room, I did not know what I should do... My wife was very happy after the delivery that I was by her side. I was also very happy to see her like that."

Fear, Anxiety, Panic: Father 10 said "I was so scared that something would happen to my wife." Father 20 exclaimed "This pain... Oh my god how was she able to bear it! I was so scared."

3. The Role and Responsibilities of the Father

The study determined that fathers had multiple roles and responsibilities in the delivery room. It was observed that verbal expressions that represent active participation such as us, collaboration, and togetherness were frequently used by fathers. The statements of fathers about their roles and responsibilities during the delivery are as follows:

Active participation: All of the fathers reported that they played an active role in the delivery in some way. Father 21 stated "I did not wait behind the door desperately... I was with my wife and baby since the first moment. Now, I am going to do so as well.

Coach: Father 15 articulated "She had so much pain... She was suffering... I helped her to do breathing exercises... Held her hand, hugged her, massaged her back, and put a pillow behind her back. I tried to do my best to relieve her pain and encourage her."

Team member: Father 5 said "Instead of waiting for information behind the door of the delivery room with curiosity and anxiety, I wanted to be with them, comfort and touch them." Father 7 stated "... I only wanted to be with my wife to support her. But as the process continued, I realized that I was one of the important factors in the delivery."

4. The Support of Healthcare Professionals

The positive support of a well-organized and professional healthcare team for the women in labor and her husband during the delivery was obvious. This support was expressed as follows by the fathers.

Effective communication: Father 12 said "The healthcare team was always with us...they supported us... Their communication and behaviors were great... We felt safe."

Supportive care: Father 3 stated "There were moments I lost control and was confused... The midwives were constantly in communication with me."

Empathy: Father 10 said "At first I was very confused in the delivery room... Midwives and nurses were aware of that... They comforted, informed, and understood me." Father 4 commented "... The midwives were very helpful. I applied the exercises and massages they showed me. They truly understood us and solved every need of us."

5. Meeting the Baby

Feelings: Happiness, joy, sentimentality, proud, miracle, satisfaction: All fathers who met their babies reported that they felt an intense happiness, which was an indescribable feeling. Fathers' statements are as follows: Father 11 said "I cried with joy when I first saw my baby. I did not expect this meeting to be like this." Mothers reported that they were very happy and felt valuable because their partners were with them during the delivery. Additionally, mothers reported that their delivery experience was more beautiful and that they could cope with the pain more easily thanks to the support of their partners. As a result of, fathers' participation in childbirth had a positive effect on mothers' birth experiences.

DISCUSSION

The cultural environment of parents affects their delivery expectations and parental roles. In Turkey, fathers are not allowed in the delivery room and cannot witness this miraculous moment because they are left in the background. In the Turkish society, the idea that the delivery is a process specific to women remains a societal belief. Although it is less common than in the past, the involvement of the father in the delivery is still seen as tabu (5). Most of the studies on childbirth experiences are about women. Therefore, this study includes important information about the perspective of the father.

The cultural environment of women affects their delivery expectations and parental roles. In this study, the presence of the father in the delivery room positively affected the delivery experience of the mother, which was very special and important for the women. All but one of the mothers reported that they felt happy, valued, and safe. Similarly, another study stated that the involvement of the father in the delivery process helps women feel safer. The fact that fathers fulfill the needs of their partners during this process positively affected both mothers and fathers (4). Moreover, in the meta-analysis of Johansson et al., it was found that with the support of the fathers to the mothers, the duration of labor was reduced, women experienced less anxiety and depression, anesthesia needs were reduced, and the recovery process was faster (8).

Fathers reported that they experienced strong emotions at the end of the delivery process. Additionally, they stated that involvement in the process with supportive and coaching roles positively changed their perspective on life. Fathers further reported that their relationship with their partners got stronger, they realized how strong their partners were, and their respect for women increased. In another study found that the childbirth experience increased the respect of men for their partners and strengthened the family bond and the relationship between partners (9). The study results are in compliance with the literature.

Throughout the study, fathers suppressed their own fear, anxiety, panic, and confusion and supported their partners. Similarly, in studies carried out with fathers involved in the delivery, fathers hid their negative feelings such as fear and anxiety to display a strong attitude and not negatively affect the delivery process (1).

The support of midwives and nurses are accepted as a facilitating factor in the involvement of fathers in the delivery, and weak communication and unfulfilled expectations are among the obstructive factors. Every father participating in the study reported that they had a positive

childbirth experience. The support of the midwife was observed to be one of the important factors in establishing this positive experience. The support and presence of the midwives who informed the fathers about the process of labor and delivery was a strong factor for the positive experience of father. Similarly, the literature shows that the support of midwives are very valuable for fathers (3, 10, 11). In this study, the majority of the fathers reported that the midwife provided the needed and expected support, which contributed to the positive childbirth experience.

Fathers who participated in the delivery reported they experienced strong and deep emotions when they first met their babies. Moreover, it was observed that fathers bonded with their babies right after the delivery. Fathers reported a positive childbirth experience and described their first encounter with their babies with positive words such as happiness, joy, proud, and miracle. Another study showed that the involvement of the father in the delivery strengthened the emotional bond between the newborn and the father (12).

LIMITATIONS OF THE STUDY

The results of this study are limited to those in the sample.

CONCLUSION

Fathers should also be involved in the delivery process so that the parents can experience a positive childbirth experience, the relationship between partners strengthens, the family life is affected positively, and the newborn arrives in an environment in which they feel safe. The involvement of fathers in the delivery helps women to be emotionally more motivated, more courageous, and deliver in a more peaceful environment. Supporting the presence of fathers in the delivery room is important for a favourable childbirth experience of families and building healthy family bonds.

DECLARATIONS

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Ethical Consideration: Ethical approval was obtained from the Muğla Sıtkı Kocaman University Ethical Review Board (No:180119/113) on 17 July 2018. Participation was voluntary and confidential and written informed consent was obtained prior to participation in the study.

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