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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

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Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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CONTENTS

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Measurement of the Reliability and Quality of Online Surgery Videos with Artificial Neural Networks

İdris Kurtuluş

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ABSTRACT

Introduction: The effect of the internet on education has started to increase more and more with the Coronavirus disease-2019 (COVID-19) pandemic. Although many researchers have used online resources during the pandemic, their quality and reliability and the way these two aspects could be evaluated online has remained a problem. This study aims to measure the reliability and quality of online videos about inguinal hernias by using the DISCERN questionnaire and to see if the quality and reliability of these online videos are determined accurately and fast with artificial neural networks (ANNs) by teaching them some easily accessed variables about the videos.

Methods: A total of 30 online videos searched on Google with the keywords of "TEP," and "totally ekstraperitoneal inguinal hernia repair" from February 15 to March 1, 2021 with the approval of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethical Committee were included in this research (approval number: 303, date: 29.12.2021). The videos were found using the "videos" tab of Google. The DISCERN questionnaire was applied to the videos and the results of the questionnaire were tried to be estimated with ANNs by teaching them some easily accessed variables about the videos. The results of the questionnaire and results of the predictions were compared.

Results: A total of 30 videos were evaluated. Benefitting from the scores of the DISCERN questionnaire, a total of three groups were formed with K-means clustering analysis. The scores of the low-quality videos were between 0 and 26.50, of the medium quality videos between 26.50 and 34.9, and of the high-quality ones between 34.9 and 48. In determining the video quality in the ANNs estimation model, "the number of likes" (a video received) was found to be the variable with the highest effect (on the model) with an importance coefficient of 0.245. Its normalized importance was found to be 100%. "Country" with an importance coefficient of 0.060 was found to be the variable with the lowest effect (on the model). Its normalized importance was found to be 24.4%. The median value of the scores obtained from the DISCERN questionnaire was 28, while the median value of the DISCERN scores estimated with the ANNs was 27.50. No statistically significant difference was observed between the distribution of the estimated scores and the scores obtained from the DISCERN questionnaire ($p=0.314$). Additionally, there was no statistically significant difference between the video groups formed according to the scores of the DISCERN questionnaire, and the video groups formed according to the DISCERN scores that were estimated with the ANNs ($p=0.771$). A total of 20 videos were found to be low quality with the DISCERN questionnaire, while 19 videos were estimated to have low quality with the ANNs. The number of medium-quality videos was six according to the DISCERN questionnaire and five according to the ANNs. There were a total of four high-quality videos in the DISCERN questionnaire and six in the ANNs. It was observed that the quality group of 86.6% of the videos (26 videos) was predicted accurately with the ANNs.

Conclusion: The quality and reliability of most TEP videos on the Internet were quite low. The instruments in the literature make searches retrospectively, and using them is quite time consuming. ANNs seem to be quite successful in estimating the reliability and quality of online videos. The reliability and the quality of the videos could be shown to users fast with online electronic labels developed thanks to the ANNs.

Keywords: DISCERN, totally ekstraperitoneal hernia repair, quality and the reliability of videos, TEP, artificial neural networks

Introduction

It has been more than a year since the start of the Coronavirus disease-2019 (COVID-19) pandemic. The beginning of the vaccination process offers hopes about the issue yet concerns about it continue to increase as the virus is mutating. This recent development has adversely affected many industries/sectors (1). Serious problems have started to emerge in the area of education. The negative effect of the COVID-19 pandemic on medical education has started to be experienced to varying degrees. Complications have also surfaced in the education of general surgery. Although academics have tried to narrow the gap the pandemic has created in education by setting up online courses and congresses, debates about the efficiency of online education are continuing since

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it is not known how to standardize it. However, it seems it is high time a reform is done in surgical education. Using teletechnologies could make a revolution in surgical education as much as using augmented reality, which enables students to observe surgeons while they perform operations and to have interactions from distant locations for more extensive experience, could do (2).

In their article, which focuses on medical education in Turkey during the COVID-19 pandemic, Tokuç and Varol (3) have stated that medical education is an area open to changes and developments as other fields are, and educators should analyze the effects of current changes (on education) with their students to determine new education principles and applications. Websites that offer various contents and information have already become a part of our lives with the prevailing of the internet quick worldwide. Accessing online materials has become particularly significant for surgeons due to such technological developments. YouTube, TVASURG and WebSurg are the best known websites (among health professionals), and some of them are open access websites that allow their users to share and watch videos at academic levels (4). However, no instruments measure the standardization of the parameters of the online websites, such as the reliability, quality and certification of their contents at an instant and fast. Researchers have only been able to conduct retrospective analyzes of the issue with different methods.

Our purpose in this study is to measure the reliability and quality of online videos about inguinal hernias with the DISCERN questionnaire and to see whether the quality and reliability of the online videos are determined accurately and fast with artificial neural networks (ANNs) by teaching them some easily accessed variables about the videos.

Methods

A total of 30 online videos searched on Google with the keywords of "TEP," and "totally ekstraperitoneal inguinal hernia repair" from February 15 to March 1, 2021 with the approval of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethical Committee were included in this research (approval number: 303, date: 29.12.2021). The videos were found using the "videos" tab of Google. The videos included in the study are videos publicly accessible by web browsers. A DISCERN questionnaire was applied to the videos and the results of the questionnaire were tried to be estimated with ANNs by teaching them some easily accessed variables about the videos. The results of the questionnaire and results of the predictions were compared. Online videos with the purpose of advertisement were excluded from the study.

The countries where the videos were uploaded, the people who uploaded the videos, the period during which the videos were available, their broadcast language, the duration of the videos, and the number of times they were watched and liked were noted down.

The DISCERN questionnaire was applied to all the videos by the same general surgeon. The HONcode certification of the videos was taken into consideration and their Video Power Index (VPI) was calculated.

The DISCERN scores were calculated for each video and a total of three groups were formed with the K-means cluster analysis by using them. It was determined which videos belonged to which group. Then, an estimation model of ANNs was established. In this model, the scores of the DISCERN questionnaire were tried to be estimated according to the countries where the videos were uploaded, the people who uploaded the videos, the period the videos was available online, their broadcast language, their duration and the number of times the videos were watched and liked, as well as their HONcode certification and VPI. Again, the DISCERN scores obtained with the estimation model of ANNs were grouped with K-means clustering analysis. The clusters obtained according to the results of the DISCERN questionnaire and the clusters predicted according to the estimated DISCERN questionnaire scores were compared. It was not observed whether there was a difference between them.

In the ANN model, 73.3% of the videos were planned to be used for training, 20% for testing and 6.7% as holdout (In our study, we used the Bernoulli distribution to separate our dataset. According to this distribution, 24 videos were selected for training and 6 videos for testing. To use hold-out in our study, we determined two of the 24 training videos as hold-out). Learning type was specified as online. The HONcode certification, the source of the videos / (the people who uploaded them), their language and countries were used as factors in the input layer, and the year of the videos, their VPI, and the number of times they were liked and disliked and watched and were used as scalar variables. The scores of the DISCERN questionnaire were used as dependent variables. (As the maximum DISCERN score is 80), the highest score of the random number generator was decided to be 80 to prevent it from forming an initial value from a random point in SPSS and to standardize the results before starting to form the estimation model of the ANNs. The automatic number appointment function of the random number generator was turned off.

The DISCERN Questionnaire

It was developed by researchers from the University of Oxford to determine the quality of health information and suggested options of treatment (5,6). The scores of the questionnaire ranged between 0 and 80. It is made up of three parts: the first part evaluates the reliability of a publication (questions; 1-8), the second part investigates the quality of the information about the treatment options (questions; 9-15), and the third part has a single question (question; 16) and evaluates the publication in its general aspects.

The first section uses a series of widely accepted evaluation criteria with respect to consistency, clarity, relevancy, objectivity, certainty and the references provided. The second section is quite specific to the DISCERN instrument and evaluates the quality of information about treatment options.

Web Certificate (HON=Health on NET)

Many websites offer certificates developed for the reliability of health information. Certifications are aimed at standardizing the reliability of information. The most widely used one is Health on the Net Foundation's HONcode certification. Health on the Net Foundation is an internationally accepted non-profit organization founded in 1995. Currently, more than 8000 websites in 102 countries use the HONcode certification. It provides its users with an electronic label called "HON label", and they load it on their browsers. The label easily shows if a website has the HON certification when it is clicked on (7).

Video Power Index

This is a scale that measures the popularity of a video. It has two basic parameters. They are about a video's being watched and liked. It was first used by Erdem and Karaca (8) It is calculated with the formula of "VPI=like ratio X view ratio/100."

Statistical Analysis

Statistical analysis was done with IBM SPSS V 25. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to verify the normalization of distribution. Mann-Whitney U test or Student's t-test was used for the comparisons between the groups. Chi-square test was used to compare the categorical information. Fisher's exact test and Pearson's chi-square test were used to evaluate categorical information. Questionnaire scores were grouped with K-means cluster analysis. An estimation model was established with the model of ANNs. The hold-out method was used for model selection and hyperparameter validation. The variables' normalized importance coefficients were calculated. The results were evaluated with 95% confidence interval and $p<0.05$ was accepted to be statistically significant.

Results

A total of 30 videos were evaluated. Table 1 shows the results of the descriptive statistics of the videos. A total of three groups were formed with the K-means clustering analysis according to the scores obtained from the DISCERN questionnaire. The videos with low quality were rated between 0 and 26.50, the videos with medium quality between 26.50 and 34.9, and the ones with high quality between 34.9 and 48. Of the videos, 66.6% were seen to be low quality, 20% medium quality and 13.4% low quality. Details of the data are shown in Table 2.

New DISCERN scores determined using ANNs were calculated using the scores obtained from the DISCERN questionnaire. In the ANN model, 73.3% of the videos were planned to be used for training, 20% for testing and 6.7% as holdout. A hidden layer was seen and eight subcategories were observed in it. The synaptic network of the ANNs is shown in Figure 1. Input and output data of the ANN model are shown in Table 3.

In determining the video quality in the ANNs estimation model, "the number of likes" was found to be the variable with the highest effect (on the model) with an importance coefficient of 0.245. Its normalized importance was observed to be 100%. "Country" was found to be the variable with the lowest effect (on the model) with an importance coefficient of 0.060 in the estimation model. Its normalized importance was observed to be 24.4%. Details of the data are shown in Table 4. The median value of the scores obtained from the DISCERN questionnaire was 28, and the median value of the DISCERN scores predicted by the ANNs was 27.50. There was no statistically significant difference between the distributions of the estimated scores and the scores obtained from the DISCERN questionnaire (p=0.314). Details of the data are shown in Table 5.

No statistically significant difference was observed between the groups formed according to the scores of the DISCERN questionnaire and the groups formed with K-means cluster analysis according to the DISCERN scores that were estimated with the ANNs (p=0.771). Of the DISCERN questionnaire, 20 videos were found to have low quality. According to the ANN results, 19 videos were observed to have low quality. The number of videos with medium quality was six according to the results of the DISCERN questionnaire, while it was five according to the results of the ANNs. Four videos had high quality according to the results of the DISCERN questionnaire and this number was six according to the ANNs. We observed that the quality groups of the videos were predicted to be 86.6% accurate (26 videos) with the ANNs. Details of the data are shown in Table 6.

Table 1. Descriptive statistics of the videos

		n=30
Country (frequency, %)	India	8 (26.7%)
	Turkey	3 (10.0%)
	Australia	7 (23.3%)
	America	5 (16.7%)
	Brazil	4 (13.3%)
	Unknown	3 (10.0%)
Language (frequency, %)	English	11 (36.7%)
	Turkish	3 (10.0%)
	Spanish	3 (10.0%)
	Without sound	13 (43.3%)
Video sources (frequency, %)	Academics	9 (30.0%)
	Medical specialists	7 (23.3%)
	Patients	4 (13.3%)
	Unknown	10 (33.3%)
HONcode certification (frequency, %)	Available/unavailable	2 (6.7%); 28 (93.3%)
Number of watches	Minimum/median/maximum	270/3975/44357
Number of likes	Minimum/median/maximum	9/52/451
Number of dislikes	Minimum/median/maximum	0/8/23
VPI	Minimum/median/maximum	20718/514602/7145699
DISCERN scores	WMinimum/median/maximum	21/28/48

VPI: Video Power Index

Table 2. Distribution of the videos made with K-means cluster analysis according to the DISCERN scores

	Low quality (0-26.50)	Medium quality (26.5-34.9)	High quality (34.9-48)
Video numbers (n=30)	20 (66.6%)	6 (20%)	4 (13.4%)

Discussion

In surgical education about hernia surgeries, a comparison between traditional methods of surgery and endoscopic methods reveals that there are theoretical and practical difficulties in learning and applying the latter. For this reason, learning and teaching of innovative methods of surgery tend to continue even after the training of the assistants. General surgeons who are interested in this field have been trying to learn about these techniques from various sources, including online

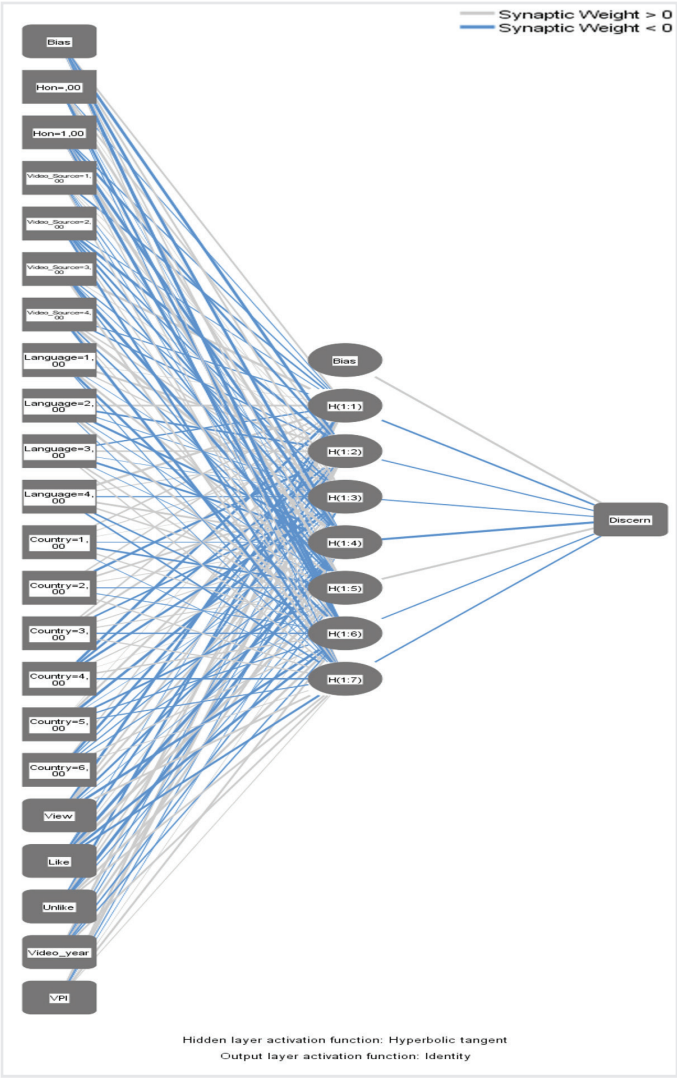

Figure 1. The synaptic network of the artificial neural networks

tools, courses and conferences. However, the COVID-19 pandemic still continues to affect the world although more than a year has passed since it starts. The beginning of the vaccination process offers hopes about the issue yet concerns about it continue to increase as the virus is mutating. This recent development has adversely affected many industries/sectors (1). Online education has become more widespread in many countries due to the pandemic. Such an orientation has frequently brought forth the questions of "What are the quality principles for the reliability of health websites?" and "How should they be measured?"

The DISCERN questionnaire is a website evaluation tool whose reliability, credibility and internal consistency have been regarded as positive in many studies (9,10). Users of the questionnaire are not limited to specialists and scientists, instead, any person with health literacy could use it to evaluate the quality of a website. The instrument is also popular among researchers and it is the most widely used tool in evaluating the quality of information on health (11). There were 16 questions on the questionnaire. Each question had a score from 1 to 5. However, applying the questionnaire is not easy. It was seen in our study that applying the questionnaire takes 30 min for each video, regardless of the duration of

Table 3. Data about artificial neural networks model

Sample (n=30)	Training		22 (73.3%)
	Test		6 (20.0%)
	Holdout		2 (6.70%)
	Learning type		Online
Input layer	Factors	1	HONcode certification
		2	Video source
		3	Language
		4	Country
	Covariates	1	Video year
		2	VPI
		3	Number of watches
		4	Number of likes
		5	Number of dislikes
	Number of units		21
	Rescaling method for covariates		Normalized
Hidden layer(s)	Number of hidden layers		1
	Number of units in hidden layer		8
	Activation function		Hyperbolic tangent
Output layer	Dependent variable	1	DISCERN
	Number of units		1
	Rescaling method for scale dependents		Standardized
	Activation function		Identity
	Error function		Sum of squares

VPI: Video Power Index

Table 4. Importance of variables in the estimation of video quality according to the ANNs

	Importance coefficient	Normalized importance
HON certification	0.124	50.5%
Video source	0.101	41.3%
Language	0.071	29.0%
Country	0.060	24.4%
Video year	0.141	57.4%
VPI	0.113	46.2%
Number of watches	0.068	27.8%
Number of likes	0.245	100.0%
Number of dislikes	0.077	31.6%

VPI: Video Power Index, ANNs: Artificial neural networks

the video. It is unreasonable for researchers to devote 30 min to each video they watch. It is undebatable that there is a need for an online system that could provide its users with ideas about the reliability and quality of the contents of a website.

Measuring parameters for such a system must be include of parameters that could be used and interpreted by machines fast as data on the Internet. How many times a video is watched, its language, the country it is loaded on the internet, the source it is loaded from, and its web certification are easily accessed parameters. There are also metrics such

Table 5. Distribution of DISCERN scores and the DISCERN scores estimated according to the ANNs (p=0.314)

	Minimum	Median	Maximum
DISCERN scores	21.00	28.00	48.00
DISCERN scores estimated according to the ANN	20.90	27.50	50.38

ANNs: Artificial neural networks

Table 6. Estimated distribution of the videos according to the DISCERN and ANNs (p=0.771)

	Low quality (0-26.50)	Medium quality (26.5-34.9)	High quality (>34.9)
Number of videos according to DISCERN	20 (66.6%)	6 (20%)	4 (13.4 %)
Number of videos according to ANNs	19 (73.2%)	5 (13.4%)	6 (13.4 %)

ANNs: Artificial neural networks

as VPI that could evaluate the popularity of online videos (8). The most common tool that could enable machines to learn with these metrics is ANNs.

ANNs are parallel and distributed knowledge processing structures which are developed with inspiration from the human brain, connected to each other with weight connections, and composed of processing units, each of which has its own memory. In other words, they are computer programs that imitate biological neural networks.

The first model for an ANN was developed in 1943 by neurophysiologist Warren Sturgis McCulloch and mathematician Walter Pitts (12). The ANNs are frequently used in preparing estimations, categorizations and early projections. Many researchers from the field of medicine use the ANNs as well (13-15). The basic structure of the neurons of the ANNs is made up of inputs, weights, summation functions, activation functions and outputs.

In evaluating the educational quality of a video, the Global Quality Scale developed by Mutter et al. (16) and the Journal of American Medical Association benchmark criteria proposed by Bernard et al. (5) are also used. In this study, the DISCERN questionnaire was preferred. We first investigated the videos that are about the surgeries performed with the total ekstraperitoneal (TEP) approach with the DISCERN questionnaire, and we later investigated whether the quality and reliability of these videos could also be estimated via ANNs.

In the first part of the study, the DISCERN questionnaire was applied to the videos and videos were divided into groups according to the results. The results of the DISCERN questionnaire showed that 66.6% of the videos had low quality, 20% had medium quality and 13.4% had good quality. As the second step, the DISCERN scores were appointed as dependent variables to the ANNs. The HON certification, the number of times videos were liked and disliked and watched, VPI, the sources of the videos, their languages, countries and years were used as inputs.

Prasanth et al. (17) used the HONcode certification to evaluate the quality of online information about testicular cancer yet they could not make a connection between the scores of the DISCERN questionnaire and the HON certification. Kartal and Kebudi (6) noticed that there is a positive correlation between VPI and (the scores of) the DISCERN questionnaire, and the number of times videos were watched and (the scores of) the DISCERN questionnaire, and there is a weak negative correlation between the years of the videos and the DISCERN (scores). They stated that there is no statistically significant difference between the DISCERN scores of the videos with respect to their sources and countries. In their studies on TEP videos on Youtube, Kanlioz and Ekici (18) found a positive correlation between the VPI scores and the number of times a video is watched, and the DISCERN scores and the number of times a video is liked. Additionally, they found that the DISCERN scores of the videos uploaded by academics are higher although there is no statistically significant difference between the two factors.

In our study, the variable with the highest importance coefficient was "the number of times a video was liked," which was a variable used in the ANNs. the year of the videos, if they had the HON certification, their VPI scores, the source of the videos, the number of times they were liked, their language, the number of times they are watched and their countries had, respectively, positive effect in predicting the DISCERN scores accurately.

In the basic structure of the ANNs' model, a mathematical function is formed using some learning algorithms with the multiple connections between inputs and outputs. Each unit is linked to each other with weights according to its importance in the dataset. These weights show the connection strength of the two units each.

In our study, there was no statistical difference between the DISCERN scores obtained through the ANNs and scores obtained via the DISCERN questionnaire itself (p=0.314). In the groupings of the video quality estimated with the ANNs and with the DISCERN questionnaire, four videos went to different groups.

However, there was no statistical difference between the video groups formed according to the scores of the DISCERN questionnaire and the video groups formed with K-means clustering analysis according to the DISCERN scores estimated with the ANN (p=0.771). In the DISCERN questionnaire 66.6% of the videos were seen to have low quality while this percentage was 73.3 in the ANNs. Twenty percent of the videos had medium quality according to the DISCERN questionnaire while this rate was 13.4 in the ANNs. In the DISCERN questionnaire 13.4% of the videos had high quality, and in the ANNs 13.4% of them had high quality. It was observed that with the ANNs, the quality category of 86.6% of the videos (26 videos) was estimated accurately.

The ANNs are made up of many neurons and they could conduct complex tasks simultaneously. They do deep learning. They could easily solve problems with linear relations or without them. They learn with machine learning and could make very logical decisions when they encounter similar situations. They could even make generalizations about the issues they have not seen before. In our study, it was observed that with the ANNs, the quality category of 86.6% of the videos (26 videos) was estimated accurately. It is sure that further studies need to be carried out in this field. Still, it is anticipated that fruitful results could be obtained by teaching ANNs other instruments of measurement

frequently used in the literature. It is hoped that users will be offered information about the quality and reliability of the videos they will watch with the creation of electronic labels such as the HON label by using the ANNs.

Study Limitations

The most important limitation of this study was that it was retrospective and the number of evaluated videos was low.

Conclusion

The quality and reliability of most online videos about inguinal hernia are quite low. The instruments used in the literature make research retrospectively and are time consuming. However, it seems that ANNs are quite successful in estimating the reliability and quality of the online videos. The reliability and quality of the videos could be easily shown to their audiences with online labels developed with the ANNs.

Ethics Committee Approval: Our study was approved by the Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: 303, date: 29.12.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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The Relationship of Kidney Injury Molecule-1 and Interleukin-1 Beta with Hepatic and Renal Functions in Pregnant Women with Thyroid Disease

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ABSTRACT

Introduction: Pregnancy is considered a low-grade inflammatory state presented with increased levels of pro-inflammatory markers. Despite the well-recognized association between inflammation and kidney injury, there is still a lack of available data concerning the role of thyroid hormone alterations in inflammation and acute kidney injury (AKI). We examined the relationship of kidney injury molecule-1 (KIM-1) and interleukin-1 beta (IL-1β) with renal and hepatic injury in hypothyroid, normothyroid (euthyroid), or hyperthyroid pregnant women.

Methods: A total of 77 pregnant women with no additional health problems were enrolled in the study. Serum KIM-1 and IL-1β levels were analyzed by ELISA.

Results: There were significant differences between normothyroid, hyperthyroid, and hypothyroid pregnants regarding creatinine, aspartate aminotransferase (AST), free T4, anti-thyroglobulin (anti-TG), anti-thyroperoxidase (anti-TPO), and plateletcrit (PCT) levels (p=0.018, p=0.032, p=0.011, p=0.001, p=0.003, and p=0.016, respectively). The mean creatinine levels of the hypothyroid group were significantly higher than those of the hyperthyroid group (p=0.015). The mean AST and PCT levels of the hypothyroid group were considerably higher than those of the normothyroid group (p=0.024 and p=0.014, respectively). In the correlation analysis, age was the single parameter that was significantly correlated with KIM-1 and IL-1β in all pregnant women (p=-0.024 and p=-0.018, respectively). In the hypothyroid pregnant women group, KIM-1 was correlated with creatinine levels and age (p=0.037 and p=0.022, respectively).

Conclusion: KIM-1 level in pregnant women with hypothyroidism can serve as a useful biomarker to show AKI.

Keywords: Interleukins, kidney injury molecule-1, pregnancy, thyroid dysfunction

Introduction

The American Thyroid Association recommends thyroid function test screening during pregnancy and the postpartum period to prevent mental-motor growth retardation due to altered thyroid hormone status (1). The impact of overt thyroid dysfunction, which is seen in 2-3% of all pregnancies, is well-known and presents with miscarriage, preterm delivery, mental retardation, pre-eclampsia, or hypertension (2). While 0.2% of pregnant women suffer from hyperthyroidism, the frequency of hypothyroidism may reach 3% but may vary according to age, gestational week, and weight of the pregnant (1,3).

In the guidelines of the American Throid Association, thyroid-stimulating hormone (TSH) <0.1 mIU/mL is used as the diagnostic criterion for hyperthyroidism, 0.1< TSH <2.5 mIU/mL euthyroid, TSH >2.5 mIU/mL hypothyroidism during pregnancy (1). Subclinical inflammation is defined as the presence of increased pro-inflammatory markers without evident clinical findings. Pregnant exhibit subclinical inflammation presented with minimal clinical results along with increased levels of inflammatory parameters. Some studies have determined the relationship of pro-inflammatory cytokines with hypo- or hyperfunction of the thyroid gland (4,5). As proven by human and experimental animal studies, maintaining the normal range of thyroid hormone levels is essential to suppress excessive inflammation (5).

An increasing amount of evidence indicated the association of inflammation with acute kidney injury (AKI) in the general population as well as in pregnant (6). The accumulation of pro-inflammatory cytokines in the glomerulus and altered fluid-electrolyte balance are the main pathogenic mechanisms involved in the inflammation-related kidney injury (7). KIM-1 was proposed to determine renal injury independent of the muscle mass and age of the patient. Besides, plasma levels of KIM-1

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are significantly related to kidney injury in hypertensive or obstructive nephropathy (8,9). Nowak et al. (10) determined the predictive role of KIM-1 in the progression of renal injury of patients with chronic kidney disease.

This study analyzed the relationship of KIM-1 and IL-1β with renal injury and hepatic damage in pregnant women with normo-, hypo-, or hyperthyroidism.

Methods

The study was conducted in the internal medicine outpatient clinics of our hospital. All 205 pregnant women referred between June and July 2019 with suspected thyroid diseases were included. Patients who were already using thyroid medication were excluded. These patients aged between 18 and 30 years without any known disease underwent a detailed physical examination. Demographic features were recorded, and they were divided into 3 subgroups according to the thyroid hormone status. Thirty pregnant (39.0%) had normal thyroid hormone levels, whereas 29 participants (37.6%) had hyperthyroidism, and 18 pregnant (23.4%) had hypothyroidism.

This study approval by the University of Health Sciences Turkey, Bağcılar Training and Research Hospital Ethics Committee (approval number: 2019.05.2.02.046, date: 24.05.2019). All participants provided written informed consent.

Blood samples were collected after 8-hour fasting. Biochemical analyses, including glucose, urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), calcium (Ca), sodium (Na), potassium (K), total protein, albumin, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were performed using spectrophotometric methods in a Siemens Advia 1800 device (Siemens Healthcare Sağlık Co., Turkey). Urinalysis was also performed by the spectrophotometric method in Siemens Advia 1800 device. TSH was analyzed by the chemiluminescence immunoassay method in a Siemens Advia Centaur device (XE-5000, Sysmex Corp. Kobe, Japan). Hemogram parameters were examined in the Cell Dyn Ruby (Abbott Park, Illinois, USA) device using the Multiangle Polarized Scatter Separation method. The glomerular filtration rate (GFR) was measured by the MDRD method. The participants' height and weight were measured using the Tanita Body Composition Analyzer (Tanita Corporation of America, Illinois, USA). Body mass index was calculated as weight/height^2 (kg/m^2). A urine albumin excretion rate exceeding 20 µg/min (30 mg/day), in the absence of uncontrolled hypertension or urinary tract infection, was defined as microalbuminuria. Microalbuminuria was assessed by measuring urine albumin to creatinine ratio.

Serum levels of IL-1 beta and KIM-1 were analyzed by the ELISA using commercially available kits according to the instructions of the manufacturer. Serum specimens and standards with biotin were put into a microtest cartridge coated with antihuman kit antibody. Subsequently, streptavidin-horse radish peroxidase enzyme conjugate was added to the cartridge to remove non-aligned antihuman kit antibody. After incubation, the intensity of the color was spectrophotometrically analyzed at 450 nm wavelength.

Statistical Analysis

In this study, statistical analysis was performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods [mean, standard deviation (SD)] in the evaluation of data, descriptive statistical methods (mean, SD) as well as the normality test were performed using the Shapiro-Wilk test. One-Way analysis of variance in intergroup comparisons of normally distributed variables, Tukey multiple comparison test in subgroup comparisons, Kruskal-Wallis test in intergroup comparisons, Dunn's multiple comparison test in subgroup comparisons, variables in each other. Pearson correlation test was used to determine their relationship, with the results were evaluated at a significance level of $p<0.05$.

Results

There was no significant difference between normothyroid, hyperthyroid, and hypothyroid pregnant concerning the mean glucose, urea, uric acid, ALT, LDH, Ca, Na, K, chlorine, total protein, albumin, total cholesterol, LDL, HDL, triglyceride levels, and hemogram parameters, except PCT (Table 1). Significant differences were determined in creatinine, AST, free T4, anti-thyroglobulin, anti-thyroperoxidase, and PCT levels between the groups (p=0.018, p=0.032, p=0.011, p=0.001, p=0.003, and p=0.016; respectively) (Table 1, 2). The mean creatinine, AST and PCT levels of the hypothyroid group were significantly higher than those of the hyperthyroid group (p=0.015, p=0.024 and p=0.014; respectively) (Table 3).

Serum KIM-1 and IL-1β levels were negatively correlated with the age of the participants (r=-0.258, p=0.024 and r=-0.268, p=0.018, respectively). KIM-1 was significantly related to the mean creatinine and age only in the hypothyroid group (r=0.277, p=0.037, and r=0.251, p=0.022, respectively) (Table 4).

Discussion

This study indicates that hypothyroid pregnant women are more prone to renal injury. In contrast to hyperthyroid and euthyroid pregnant, KIM-1 may show the loss of kidney functions in hypothyroid pregnant. The age of the pregnant women may effect renal injury in patients with hypothyroidism.

Besides the well-known association of thyroid dysfunction with preterm birth, low birth weight, and perinatal death, pregnant with hypo-hyperthyroidism is also more prone to renal injury (11). Although the exact pathogenetic relationship of AKI and hypothyroidism is not well-established, the most probable mechanisms are hypodynamic circulating blood flow and reduced GFR (12). Some case reports have showed that increased creatinine levels return to normal ranges and are maintained by initiating levothyroxine in hypothyroid individuals (13). Although decreased GFR and increased creatinine levels are usually reversible, depending on the chronicity and severity of the hypothyroid state, chronically increased creatinine levels may be seen. Kreisman and Hennessey (13) demonstrated a 35% increase in creatinine levels in 90% of hypothyroid individuals. Similar to the previously mentioned studies,

Table 1. Demographic and biochemical variables between euthyroid, hyperthyroid and hypothyroid pregnant

	TSH=0.10-2.5 euthyroid (n=30)	TSH <0.1 hyperthyroid (n=29)	TSH >2.5 hypothyroid (n=18)	p
Age (year)	28.5±5.75	29.93±6.47	29.5±3.88	0.616
Gestational parity (trimester)	2.67±1.56	2.46±1.45	2.28±1.02	0.769*
Gestational week (week)	18.7±9.32	13.69±6.71	15.83±8.44	0.070
Body mass index (kg/m^2)	26.28±4.88	24.1±4.63	25.73±4.29	0.189
Triglycerides (mg/dL)	151.3±65.71	122.97±83.28	134.83±60.42	0.320
LDL cholesterol (mg/dL)	117.6±51.31	97.28±39.21	118.22±33.55	0.137
Uric acid (mg/dL)	2.77±0.58	2.43±0.59	2.69±0.73	0.109
KIM-1 (ng/mL)	2.98±2.83	3.67±3.46	3.42±3.46	0.703*
IL-β (pg/mL)	1482±1889	1758.±1962	1787±2171	0.306*
Urea (mg/dL)	16.53±4.45	17.49±5.82	16.95±3.5	0.795
Creatinine (mg/dL)	0.54±0.09	0.5±0.07	0.58±0.12	**0.018**
AST (U/L)	14.84±4.58	16.5±4.39	19.63±7.57	**0.032**
ALT (U/L)	13.29±6.54	15.8±11.07	15.59±8.44	0.558
Vitamin D (ng/mL)	9.23±6.85	6.87±4.07	7.79±7.26	0.760*
Free T4 (ng/dL)	1.3±0.55	1.7±0.8	1.17±0.39	**0.011**
Anti-TG (IU/mL)	22.06±44.35	70.01±120.01	62.42±89.07	**0.001***
Anti-TPO (IU/mL)	16.38±22.77	24.95±36.95	114.23±188.11	**0.003***
Glucose (mg/dL)	96.84±23.05	92.49±23.69	89.72±15.9	0.530
Insulin (uIU/mL)	32.8±39.53	18.26±20.15	19.53±21.59	0.082*
HOMA-IR	9.68±16.02	4.92±6.85	5.02±6.78	0.073*

One-Way variant analysis* Kruskal-Wallis test. Significant p-values are shown in bold. TSH: Thyroid-stimulating hormone, LDL: Low-density lipoprotein, KIM-1: Kidney injury molecule-1, IL-β: Interleukin-1 beta, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, Anti-TG: Anti-thyroglobulin, Anti-TPO: Anti-thyroperoxidase, HOMA-IR: Homeostasis model assessment of insulin resistance

Table 2. Hematological parameters between euthyroid, hyperthyroid and hypothyroid pregnant

	TSH=0.10-2.5 euthyroid (n=30)	TSH <0.1 hyperthyroid (n=29)	TSH > 2.5 hypothyroid (n=18)	p
Leukocyte (10^3/uL)	9.33±2.66	9.23±2.36	9.56±2.65	0.926
Hemoglobin (g/dL)	11.74±1.18	11.64±1.05	12.07±1.31	0.471
Hematocrit (%)	36.34±3.1	37.28±3.02	37.23±3.13	0.508
Platelet (10^3/uL)	251,600±60,496	250,931±38,030	258,888±38,038	0.840
RDW (%)	13.58±1.47	13.94±1.66	13.58±2.1	0.729
MCV (fl)	87.27±5.52	85.16±5.83	85.76±7.34	0.473
MPV (fl)	7.7±1.61	7.87±1.24	7.96±1.41	0.812
PCT (%)	0.19±0.05	0.21±0.05	0.23±0.06	**0.016**
PDW (%)	20.19±6.16	18.21±3.13	22.01±7.5	0.134
Lymphocyte (%)	22.75±5.47	24.48±5.87	23.25±7.36	0.613
Lymphocyte (10^3/uL)	2.07±0.63	2.23±0.7	2.17±0.83	0.721
Monocyte (%)	5.96±1.92	6.8±1.69	6.27±1.35	0.250
Monocyte (10^3/uL)	0.54±0.19	0.61±0.18	0.61±0.22	0.348
Neutrophil (%)	69.47±6.18	66.85±7.03	68.18±8.37	0.446
Neutrophil (10^3/uL)	6.57±2.34	6.23±1.93	6.56±2.18	0.840

A significant p-value written in bold. TSH: Thyroid-stimulating hormone, RDW: Red cell distribution width, MCV: Mean corpuscular volume, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width

creatinine levels were significantly higher in hypothyroid individuals than in other groups in our research.

Reports regarding hyperthyroidism-induced AKI are scarce (11). Hyperthyroidism-induced renal injury is characterized by increased GFR and reduced serum creatinine, which respond well to antithyroid therapy (7). In contrast to hypothyroidism, tubular or tubulointerstitial damage is the most common pathogenetic mechanism in hyperthyroidism (7). Compared to normothyroid pregnant, the frequency of hyperemesis gravidarum and immune-mediated glomerular diseases are significantly higher in pregnant women with hyperthyroidism, which possesses a risk

Table 3. Pairwise comparisons of the significant variables between the different thyroid categories

Tukey multiple comparison test	Creatinine	AST	Free T4	PCT
Euthyroid/hyperthyroid	0.182	0546	**0.043**	0.169
Euthyroid/hypothyroid	0.388	**0.024**	0.783	**0.014**
Hyperthyroid/hypothyroid	**0.015**	0.194	**0.018**	0.460

One-Way variant analysis. A significant p-value written in bold. AST: Aspartate aminotransferase, PCT: Plateletcrit

Table 4. Correlations of KIM-1 and IL-β with thyroid renal and hepatic function tests in hypothyroid patients

		KIM-1	IL-β
TSH	r	-0.017	-0.037
	p	0.822	0.743
Free T4	r	0.069	0.043
	p	0.589	0.658
Age	r	**0.251**	0.121
	p	**0.022**	0.392
Gestational week	r	0.146	0.179
	p	0.264	0.154
BMI	r	-0.123	-0.083
	p	0.343	0.499
Triglycerides	r	-0.026	0.017
	p	0.845	0.912
LDL	r	0.068	0.099
	p	0.512	0.424
Creatinine	r	**0.277**	0.168
	p	**0.037**	0.301
ALT	r	0.122	0.123
	p	0.301	0.374
Vitamin D	r	-0.068	-0.069
	p	0.541	0.547
Glucose	r	-0.235	-0.241
	p	0.059	0.063

Pearson correlation test. A significant p-value written in bold. KIM-1: Kidney injury molecule-1, IL-β: Interleukin-1 beta, TSH: Thyroid-stimulating hormone, BMI: Body mass index, LDL: Low-density lipoprotein, ALT: Alanine aminotransferase

of acute renal damage (14,15). However, we failed to show an increase in the creatinine levels of hyperthyroid pregnant.

KIM-1 is a relatively recent marker proposed for use in the assessment of renal function in acute injury. It is considered superior to serum creatinine because of its independence from age, gender, and muscle mass (16). KIM-1 is regarded as a regulator of endocytosis in regenerating injured proximal tubule cells, as well as an indicator of the enhanced proliferation of the injured proximal tubules. KIM-1 release into urine precedes proteinuria and decrease in GFR (17). Egli et al. (18) showed no significant association between plasma KIM-1 levels and renal injury in the general population. In this study, although it did not reach statistical significance, KIM-1 levels of hypothyroid and hyperthyroid women were higher than those of normothyroid pregnant. Furthermore, in hypothyroid pregnant, KIM-1 was related to creatinine levels. Thus, KIM-1 level seems to more accurately reflect the increased creatinine level, which shows decreased renal functions.

In a prospective study aiming to evaluate the relationship of KIM-1 with renal functions of pre-eclamptic pregnant, the authors failed to indicate a significant correlation between these variables (19). However, a study conducted in premature infants pointed out that age is a substantial determinant of kidney injury and should be taken into account when evaluating the accuracy of KIM-1 (20). The relationship of IL-1β with the trimester of pregnancy and age of the pregnant are significant predictors of pre-eclampsia related renal injury (21). We found that the relationship of age with KIM-1 and IL-1β was prominent in all patients.

In Mazzaferri and Surks (22) study, the patient's age significantly impacted the manifestations of thyroid dysfunction, including renal injury. Also, in Zhang et al.'s (23) study, the relationship of age with renal injury induced by thyroid dysfunction was remarkable in a population with diabetes. Similar to the literature, we found an association between age and KIM-1 levels in hypothyroid pregnant.

Study Limitations

This study has some limitations like sample size was relatively small and the iodine status of the patients has not been studied. A remarkable number of patients with additional comorbidities or receiving therapy for chronic disorders were excluded. Finally, studying the role of thyroid hormone replacement or antithyroid therapy could provide complementary data on the inflammatory status and renal injury.

Conclusion

In conclusion, to the best of our knowledge, our study is the first report to examine the relationship between serum KIM-1 and IL-1β and thyroid hormone levels in pregnant women. Hypothyroidism is a risk factor for developing AKI during pregnancy, and KIM-1 is an indicator of functional renal loss, especially in pregnant with hypothyroidism. Although the presence of increased inflammation in pregnancies with altered thyroid function is well-established, further studies are warranted to reach a more precise conclusion.

Ethics Committee Approval: This study approval by the University of Health Sciences Turkey, Bağcılar Training and Research Hospital Ethics Committee (approval number: 2019.05.2.02.046, date: 24.05.2019).

Informed Consent: All participants provided written informed consent.

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Impact of Copper and Oxidative Stress Index Levels on Insulin Resistance, Lipid Profile and Hormonal Status of Patients with Polycystic Ovary Syndrome

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is one of the most common endocrine abnormalities of reproductive age and has a highly heterogeneous nature regarding its multisystemic symptoms. To elicit pathophysiological roots, metabolic mapping and between-correlations among key parameters are of vital importance. We generated a platform including cardinal hormones, lipids, homeostasis model assessment of insulin resistance (HOMA-IR) and oxidative markers [total-oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), copper (Cu)] related to pathophysiology.

Methods: This prospective case-control study included 46 patients with PCOS and 44 non-PCOS healthy women. Samples were obtained from the Obstetrics and Gynecology Clinic of University of Health Sciences Turkey, İstanbul Training and Research Hospital. TAS, TOS, and Cu levels were measured by automated methods.

Results: Anti-Mullerian hormone, total testosterone (TT), dehydroepiandrosterone sulfate, low-density lipoprotein, high-density lipoprotein (HDL), total cholesterol, TOS, OSI were increased in patients with PCOS with no significant differences in the mean values of other parameters. ROC analysis revealed that TOS and OSI had an acceptable predictive value for PCOS diagnosis. Plasma HOMA-IR, triglyceride, HDL, TT, and sex-hormone-binding globulin levels were correlated with OS markers.

Conclusion: Redox status was found to be sensitive to hormonal alterations. Metabolites were then were compared with the oxidative markers to reveal any relationship that may explain the causal link between metabolic and redox changes Ultimately, evaluating broad-based metabolic profiling of patients, the current study contributes to the literature, which has controversial data and correlation findings poses new questions requiring further research to elicit underlying mechanisms and so to set new targets for both prevention and treatment.

Keywords: Polycystic ovary syndrome, copper, oxidative stress, testosterone

Introduction

The most frequent endocrine disorder of reproductive age, polycystic ovary syndrome (PCOS), manifests with multisystemic symptoms associated with increasing incidence of obesity, metabolic syndrome, and diabetes in the young population. Much efforts have been made since then search for early indications of PCOS to avoid future complications before onset.

Like many complex pathologies in which both environmental and genetic factors interact in the etiology, PCOS has been associated with imbalanced redox status (1). Thus, oxidative stress (OS) holds great promise in understanding pathological processes and practical use as a therapeutic target. Earlier reports showed that insulin resistance (IR) is the central contributing factor that may originate from increased oxidative stress, leading to PCOS progression. Other factors have been described as obesity and abdominal adiposity (1). It has been shown that serum oxidative markers, such as homocysteine, malondialdehyde, and superoxide dismutase activity, were higher while glutathione was lower in patients with PCOS (1). The current study will test the total oxidant status (TOS)-total antioxidant status (TAS) and serum copper (Cu) levels and calculated the oxidative stress index (OSI) as indicators of the serum oxidative status of the participants. Enzymes that are involved in many biological mechanisms are an integral part of Cu, and Cu levels play a crucial role in the process of oxidative enzymes (cytochrome c oxidase, superoxide dismutase, ascorbate oxidase) (2). Only a few studies have investigated serum Cu levels in patients with PCOS (3-7). A recent meta-

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analysis reported that Cu in patients with PCOS was higher than healthy and PCOS women with IR (8). To our knowledge, the correlation of Cu levels with hormonal levels in patients with PCOS was studied only in one study (5), with no studies regarding its correlation with lipid parameters.

Correlation of hormonal levels in PCOS with OS markers was studied only in several studies (9-11) with inconclusive results. Our work will contribute to the literature showing new evidence on serum hormone levels and possible correlations with investigated oxidative markers), implying their etiological role in PCOS development.

Ultimately, this study showed new evidence on the serum levels of a specific hormone, lipid, and OS markers related to the pathophysiology of PCOS. Metabolic parameters will then be compared with oxidative markers to reveal any relationship that may explain the causal link between metabolic and redox changes. involving a set of parameters reflecting functions, our work will also contribute to the integrated understanding of PCOS.

Methods

A minimum number of 40 individuals were required for each group (given the effect size of 0.60 and p-value of 0.05), adjusting the 80% level in power analysis.

This prospective case-control study included 46 patients with PCOS and 44 non-PCOS healthy women aged between 18 and 43. Participants applying to the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Gynaecology and Obstetrics were selected from October 2020 to January 2021, and PCOS diagnosis was made in compliance with the Rotterdam criteria (12). The control group of 44 healthy, reproductive-aged women who voluntarily joined our study was recruited upon admission to our outpatient clinic for routine gynecologic examination. The control group body mass index (BMI) and age were matched to patients with PCOS in our study. All the control patients were selected from non-PCOS patients who were thoroughly examined before inclusion in the study. The serum levels of anti-Mullerian hormone (AMH), total testosterone (TT), follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone sulfate (DHEA-SO4), prolactin (PRL), thyroid-stimulating hormone (TSH), and lipid parameters [total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG)], were investigated with OS markers (TOS, TAS, Cu, OSI) and compared between the two groups.

The study was conducted under the Declaration of Helsinki and was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2515, date: 18.09.2020). Each participant gave written consent.

Inclusion Criteria

Patients who met the following two or three criteria were selected: oligo/anovulation, hyperandrogenism (HA) (clinical/biochemical), and polycystic ovaries on ultrasound. All individuals were 18-43-year-old women, and serum samples were collected during their first visit (after a confirmed PCOS diagnosis for patients and, if not, for controls).

Exclusion Criteria

Exclusion criteria for both the PCOS and control groups included pregnancy, congenital adrenal hyperplasia, adrenal/ovarian tumors, diabetes mellitus, hyperprolactinemia, hypothyroidism, Cushing disease, and oral contraceptive use hypogonadotropic hypogonadism. Individuals with chronic diseases (including cardiovascular-renal diseases), malignancies, active infection, and regular drug/alcohol/cigarette usage were also excluded from the study.

Forty-six patients with PCOS and 44 controls who matched for BMI and age were included in the study. Samples were obtained from the Obstetrics and Gynecology Clinic of University of Health Sciences Turkey, İstanbul Training and Research Hospital. Morning venous blood samples were obtained between 9 and 10 am between days 3 and 5 of the menstrual cycle; after centrifugation at 2000-3000 rpm at 4 °C for 20 min, serum samples were separated and frozen at -80 °C until assayed. The serum, TAS, TOS, and Cu levels were measured by automated methods.

Determination of Hormone and Lipid Levels

Hormone levels and lipid markers were analyzed in the biochemistry laboratory. LH, FSH, TT, DHEAS, PRL, and TSH serum levels were assessed using a UniCel DxI800 analyzer (Beckman Coulter, Brea, CA) immunoenzymatically. AMH levels were measured using the electrochemiluminescence immunoassay method (Roche-Cobas E411, Roche Diagnostics, Mannheim, Germany). Metabolic and lipid profiles (fasting glucose, HDL, LDL, TC and TG) were determined via spectrophotometric analysis [Beckman Coulter AU 5800 analyzer, Beckman Coulter, Brea, CA (Abbott Diagnostics, USA)]. Homeostasis model assessment of insulin resistance (HOMA-IR)=fasting blood glucose (mmol/L) x fasting blood plasma insulin (mU/mL)/22.5.

Determination of TAS

From Erel's (13) method, fully automatic colorimetry was used for serum TAS-level measurement (analysis done with Abbott ARCHITECT c8000 clinical chemistry analyzer). Measuring the number of OH-radicals is the principle of the Erel method. To produce the OH-radical, o-Diasidine ferrous ion with H_2O_2 had a Fenton-type chemical reaction, and a change in the color occurs. Changes in color could be prevented by neutralization of oxidants with serum antioxidants. Oxidative free radical reactions induced by OH-, determined the antioxidant capacity by this method. An alpha-tocopherol analog Trolox was used for this method.

Trolox equivalent, mmol/L given in the results. The method sensitivity is 3%.

Determination of TOS

Another method by Erel (14), used for measuring serum TOS levels by fully automatic photometry Erel (14) (analysis done with an Abbott ARCHITECT c8000 clinical chemistry analyzer. The oxidization of o-dianisidine ferrous ions to ferric ions was the principle of this method. The xylenol orange induced color changes are visualized as oxidation of ferric ions in an acidic environment. The number of oxidants in the serum is correlated with the color density. H_2O_2 is the standard method. H_2O_2 equivalent, µmol/L given in the results. The metsensitivityvity is 2%.

Calculation of OSI

The OSI (arbitrary unit)=TOS (μmol H_2O_2 Eq/L)/10×TAS (mmol Trolox Eq/L).

Determination of Serum Cu levels

The available Rel Assay Cu measurement kit (Gaziantep, Turkey) was used for serum Cu measurements by full photometry (c8000 Abbott ARCHITECT clinical chemistry analyzers). The color change of DiBr-PAESA from red-orange to violet in an alkaline environment is proportional to Cu levels in samples (μg/dL). The red-orange DiBr-PAESA conversion to violet by the alkaline environment is proportional to Cu levels in the sample (μg/dL). Cu sulfate absorbance changes were measured at around 572 mm.

Statistical Analysis

G Power software was used to calculate the study's sample size (2021, Heinrich-Heine-University, Düsseldorf). The Shapiro-Wilk test was applied to assess data distributions, and the data were normally distributed (p≥0.05). Group differences were defined using an independent sample t-test. The results are shown as the mean ± standard deviation, and p=0.05 was set as the level of statistical significance. Correlation analysis was carried out for each group. Receiver operating characteristic curve (ROC) analysis was performed to define the discrimination ability of the investigated serum parameters for PCOS. Discriminant analysis was performed to determine the prediction capacity of the parameters for PCOS. Analyses were performed with IBM SPSS version 27.0 software (IBM Corporation, Armonk, NY, USA).

Results

Demographic and clinical data are shown in Table 1. No differences in age or BMI were observed between the groups (p>0.05).

Significantly higher levels of AMH, TT, DHEAS, LDL, HDL, TC, TOS, and OSI and significantly lower levels of FSH were recorded in patients with PCOS (p<0.05). There was no significant difference in the mean values of LH, PRL, TSH, TG, Cu, and TAS (Table 1).

As an essential parameter for PCOS, the LH/FSH ratio appeared to have a strong positive association with TT, a moderate positive correlation with TGs and a moderate negative correlation with HDL levels (r=0.65, p=0.009, r=0.48, p=0.028, r=-0.46, p=0.024, Table 2). In patients with PCOS, TOS showed a strong positive correlation with OSI and Cu and a moderate correlation with HOMA-IR (r=0.94, p=0.001, r=0.59, p=0.023, r=0.40, p=0.011, Table 2). The mean HOMA-IR value was 2.79±2.06 in patients with PCOS.

Cu levels were strongly correlated with TOS, OSI and sex-hormone binding globulin (SHBG) (r=0.59, p=0.023, r=0.59, p=0.001, r=0.59, p=0.004, Table 2).

TAS was correlated with TT and HOMA-IR (r=0.47, p=0.023, r=0.53, p=0.001). Additionally, FSH was moderately correlated with AMH in the PCOS group (r=0.46, p=0.035, Table 2).

Investigating lipid profile associations with TGs showed a moderate positive correlation with the LH/FSH ratio and LH value in patients with PCOS (r=0.48, p=0.028, r=0.47, p=0.023), and HDL was negatively related to the LH/FSH ratio and TT (r=-0.54, p=0.012, r=-0.46, p=0.024 Table 2).

Table 1. Demographic and clinical data of the study population

	Control	PCOS	p value
Age (year)	24.7±5.4	22.8±5.4	ns
BMI (kg/m²)	24.3±3.4	25.6±6.5	ns
Fasting glucose (mg/dL)	89.4±8.3	89.8±9.5	ns
AMH (ng/mL)	3.9±3.3	8.5±2.3	0.001***
FSH (mIU/mL)	8.9±1.1	8.2±0.9	0.01**
LH (mIU/mL)	7.8±1.1	7.8±1.9	ns
TT (ng/dL)	46.7±1.2	52.7±5	0.001***
PRL (μg/L)	10.9±1.8	10.8±2.3	ns
DHEAS (μg/dL)	205.4±8.8	234.8±23.2	0.001***
TSH (ng/mL)	1.7±1.2	1.8±0.9	ns
TC (mIU/mL)	146.8±6.5	174.1±26.5	0.001***
TG (mg/dL)	89.1±23.1	80.5±32.4	ns
LDL (mg/dL)	84.8±10.2	112.5±28.2	0.001***
HDL (mIU/mL)	42.2±2.7	50.7±9.1	0.001***
TAS (mmol Trolox Eq/L)	1.5±0.1	1.5±0.2	ns
TOS (μmol H_2O_2 Eq/L)	3.4±0.7	4.5±1.6	0.001***
OSI (arbitrary unit)	0.2	0.3±0.1	0.001***
Cu^{2+} (μg/dL)	117.61±32.55	123.77±46.95	ns

***p<0.001 level of significance. Values are described as mean ± standard deviation (ns: non-significant; *0.01<p<0.05; **0.001<p<0.01; ***p<0.001 level of significance). BMI: Body mass index, AMH: Anti-Mullerian hormone, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TT: Total testosterone, PRL: Prolactin, DHEA-SO4: Dehydroepiandrosterone sulfate, TSH: Thyroid-stimulating hormone, TC: Total cholesterol, TG: Total triglyceride HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, Cu: Copper

The free androgen index (FAI) was calculated as TT/SHBG and obtained only for patients with PCOS (since only patients with PCOS had SHBG values). FAI displayed no significant correlation with any marker.

According to ROC analysis, significant results were obtained for TOS and OSI parameters (Figure 1). OSI had an AUC value of 0.68, and OSI had an AUC value of 0.69 (acceptable diagnostic ability) (Table 3).

None of our OS markers were different according to BMI in patients with PCOS. TOS, TAS, OSI and Cu levels were statistically insignificant in patients with BMI <25 kg/m² and BMI ≥25 kg/m² (p=0.104, p=0.094, p=0.174, p=0.952 respectively).

TOS and TAS levels were significantly higher in patients with PCOS with HOMA-IR ≥2 (p=0.045, p=0.021 respectively). TOS levels were 5,19 μmol H_2O_2 Eq/L. TAS levels were 1.54 mmol Trolox Eq/L in patients with PCOS with HOMA-IR ≥2. Cu and OSI levels were statistically insignificant between patients according to HOMA-IR values (p=0.449, p=0.152 respectively).

Discussion

In our study, multiple hormone and metabolic parameters were investigated with OS markers TOS and OSI, which were higher in the PCOS group as expected, whereas TAS and Cu levels were not different

Table 2. The correlation table displays the significant associations obtained in the PCOS

Pearson correlation	FSH (mIU/mL)	LH (mIU/mL)	TT (ng/dL)	LH/FSH	OSI (arbitrary unit)	Cu $^{2+}$ (µg/dL)	HOMA-IR	p value
AMH (ng/mL)	0.46*							0.035
LH/FSH			0.65**					0.009
TAS (mmol Trolox Eq/L)			0.47*				0.53**	0.023 0.001
BMI (kg/m^2)		0.52**		0.45*				0.011 0.041
TC (mIU/mL)								
TG (mg/dL)		0.47*		0.48*				0.025 0.028
LDL (mIU/mL)								
HDL (mIU/mL)			-0.46*	-0.54**				0.024 0.012
TOS (µmol H_2O_2 Eq/L)					0.94**	0.59**	0.40	0.000 0.023 0.011
OSI (arbitrary unit)						0.59**		0.000
SHBG (nmol/L)						0.59**		0.004

**Correlation was significant at the 0.01 level (2-tailed). *Correlation was significant at the 0.05 level (2-tailed). AMH: Anti-Mullerian hormone, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, BMI: Body mass index, TC: Total cholesterol, TG: Total triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, SHBG: Sex-hormone-binding globulin

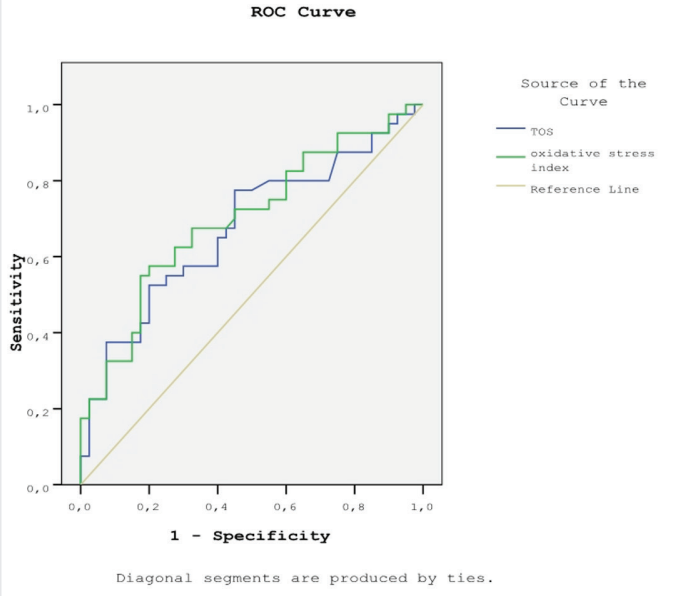

Figure 1. The ROC curve analysis for predicting PCOS. The blue line represents TOS; the green line represents OSI
ROC: Receiver operating characteristic, PCOS: Polycystic ovary syndrome, TOS: Total oxidant status, OSI: Oxidative stress index

between the groups. A discriminant analysis with TOS and OSI values detected PCOS with acceptable diagnostic ability. The direct correlation between OS markers and plasma HOMA-IR, TG, HDL, TT, or SHBG levels suggest that metabolic imbalance and hormonal disturbance contribute to increased oxidative status.

Despite not being adequate for predicting separately, the LH/FSH ratio may show accordance with specific metabolic characteristics of PCOS. One study showed that a high LH/FSH ratio was related to insulin, TT, and AMH levels in a subgroup of patients with PCOS (15). Our results showed that patients PCOS had a strong correlation between the LH/FSH ratio and TT. This may explain the causal relationship of TT secretion with LH levels and contribute to the common understanding of PCOS pathophysiology. Interestingly, the PCOS group LH/FSH ratio also positively correlated with TGs and BMI and a negative correlation with HDL. In a recent study, fasting vs random PCOS blood analysis showed low levels of TC and LH levels in fasting but no difference in LH/FSH levels (16). All these relationships may provide insight into PCOS physiology and help interpret PCOS metabolism with an integral approach. The impaired correlation between OS markers and the LH/FSH ratio in the PCOS group seems to indicate that serum hormone alterations occur independently of OS. Here, enhanced OS seems more of a result of metabolic imbalance rather than being an etiological factor. Previous research supported this hypothesis by claiming that PCOS-related OS does not directly on the hormone profile in PCOS and would likely result from metabolic perturbations such as IR, dyslipidemia and obesity (17).

HA is one of the main characteristics of the disease and indicates that PCOS after other causes of HA have been ruled out. Eliciting the pathophysiological role of the circulating androgenic hormones that lead to HA setting is of prime importance. The correlation analysis of DHEAS in one study of patients with PCOS showed no relationship with fasting glucose, lipids, or pathogenesis-related hormones, supporting the that DHEAS independently increases the metabolic alteration seen in PCOS (18).

TT levels were positively correlated with TAS levels in patients with PCOS. İncreased TAS activity and its association with TT and HOMA-IR suggest

Table 3. PCOS discrimination analysis with TOS and OSI parameters

	Diagnostic test					ROC curve		p
	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	95% CI	
OSI	**≥2.5**	63.0	73.0	68.6	64.4	**0.69**	0.584-0.814	**0.002****
TOS	**≥3.17**	78.0	55.0	62.5	68.8	**0.68**	0.557-0.795	**0.007****

*PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, **Receiver operating characteristic curve analysis test, AUC: Area under the curve, OSI: Oxidative stress index, TOS: Total oxidant status

that TAS activity contributes to HA and IR and vice versa, increasing the risk of atherogenesis.

To assess HA status more accurately in females, it is also suggested to include FAI (19). Few studies have investigated FAI levels and correlations with metabolic parameters in patients with PCOS (20-22). To the best of our knowledge, the correlation of FAI levels with markers of OS was not investigated in the population with PCOS. The FAI is a ratio of TT to SHBG (same units), and an indicator of physiologically active testosterone. One study found higher levels of FAI in overweight patients (BMI ≥27) with positive correlations of FAI with glycemia, HOMA-IR, TG, TC, and a negative relation with HDL cholesterol. This suggests that FAI-FT can be used for tract poor cardiometabolic outcomes in the population with PCOS (20). In another study, low FAI levels were associated with higher TC and HDL levels only in lean patients (21). FAI values did not correlate with BMI or any metabolic or OS parameters investigated in our study. Further studies are required to explore these associations.

Regarding other metabolic indicators, fasting glucose was not different between the groups, our findings regarding hormone and OS marker levels in the two groups were evaluated independently from the effect of IR. In this study, HOMA-IR <2 levels were associated with low TAS and TOS levels in PCOS, but no correlation of OS marker levels with BMI was found. The correlation of IR with OS markers has been reported in a few studies. Low levels of OS in patients with PCOS were found in patients with normal IR and low BMI PCOS (23,24). The lack of correlation of OS markers with BMI might produce distinctive and intrinsic defects in insulin secretion in patients with PCOS independent of obesity.

The correlation of testosterone levels with lipid parameters in PCOS shows that the lipid profile was less severely impaired in patients without HA than in those with HA (11,21). Also, HDL levels in our study were negatively correlated with TT. The TG levels were positively related to LH/FSH in patients, which may be value for indicate that LH secretion in PCOS might be related mainly to metabolic disturbances and atherogenesis and that high testosterone levels is secondary to the androgenic response to high LH levels in patients. Globally, the literature has many contrary results about the dyslipidemia patterns of PCOS. A study found that decreased HDL levels with increased TG and LDL in patients (25). Others reported similar HDL and LDL levels while showing a reduced capacity for cholesterol efflux and lipid particle atherogenic pattern and size in patients (VLDL and LDL) (26). Although each patient has a different lipid profile, previous and current findings may underline the enhanced risk of future cardiovascular complications in the population with PCOS. The fact that interfering factors highly influence lipid parameters makes it difficult to make the exact assumptions on the issue. Thus, further research adjusting these factors and including a larger sample size should be conducted to confirm the results.

In our study, trace element Cu levels correlated with TOS, OSI, and SHBG levels in PCOS, and levels were not significantly different from controls. Studies have focused mainly on Cu levels between PCOS and control groups, with sparse reports about its effects on metabolic and hormonal disturbances. In a recent meta-analysis, serum Cu-level prediction of PCOS was not statistically significant but in patients with PCOS with IR, Cu serum levels were higher than non-PCOS patients (8). Zheng et al. (5) reported that each 1-µg/L increase in Cu levels was associated with a change in reproductive hormone levels (LH, testosterone, fasting insulin, and TG), and they assumed that Cu might play a role in the pathogenesis of PCOS related to reproductive hormone levels. Although we found a correlation of Cu levels only with SHBG levels in PCOS, a strong correlation with OS markers showed that chronic Cu overload may have a negative effect on redox status in PCOS by prooxidant and oxidant mechanisms.

Our current study found that the oxidative markers TOS and OSI levels were significantly higher in PCOS than non-PCOS, while TAS values were not statistically different between PCOS and non-PCOS. TOS and TAS elevations were previously recorded for PCOS (19), and OSI was also reported to increase in previous works (23). The findings of a study essentially correspond to the current study and support our results with increased TOS and OSI with no difference in TAS levels (23). In a more recent study, serum OSI, TAS, and TOS levels were significantly different in the PCOS group than in the control group (27). OSI levels were investigated in patients with PCOS only recently (11,23,27-29), and our study is the first to provide a cut-off value for PCOS detection. With these and current findings, we conclude that OS markers are increased in PCOS, showing the imbalanced redox homeostasis of patients.

Study Limitations

Although each patient has a different lipid profile, previous and current findings may underline the enhanced risk of future cardiovascular complications in the population with PCOS. The fact that lipid parameters are highly influenced by interfering factors makes it difficult the exact assumptions on the issue. Thus, further research adjusting these factors and including a larger sample size should be conducted to verify the discussed results.

Conclusion

Essential hormone levels with lipid profiles and oxidative status of patients were evaluated, offering new evidence to this literature. Discussing the place of OS in PCOS, our premise is that rather than playing a primary role in the initial steps of pathophysiology, OS occurs more likely because of HA or IR. With the correlation findings among

hormone levels and oxidative markers, we pose new questions requiring further research to elicit underlying mechanisms and set new targets for prevention and treatment. The association of Cu and OS marker levels with clinical and laboratory findings suggest that these factors taken together are involved in aggravating the proinflammatory status in women with PCOS.

Ethics Committee Approval: The study was conducted under the Declaration of Helsinki and was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2515, date: 18.09.2020).

Informed Consent: Each participant gave written consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - N.A., Ş.S., F.Y.K., B.Ş.K., A.Z.G., Concept - N.A., Ş.S., Y.A.; Design - N.A., Ş.S., Y.A.; Data Collection or Processing - B.Ş.K., A.Z.G., Y.A.; Analysis or Interpretation - N.A., Ş.S., B.Ş.K.; Literature Search - N.A., A.Z.G., Y.A.; Writing - N.A., F.Y.K.

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The Diagnostic Efficiency of the Use of Non-Standard Surgical Instruments in Mediastinoscopy

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ABSTRACT

Introduction: Mediastinoscopy is an effective diagnostic method used in the diagnosing of benign granulomatous diseases and for lung cancer staging. However, the success of this method is directly proportional to the amount of pathological material taken. This study aimed to compare the diagnostic efficiency of the diagnostic superiority of the use of standard surgical instruments (SSI) and non-standard surgical instruments (NSSI) in mediastinoscopy in patients with mediastinal lymph nodes, which are thought to be pathological, according to different diseases.

Methods: One hundred and seven patients who underwent mediastinoscopy were divided into two groups according to the use of SSI (n=89) and NSSI (n=18). Analysis was made of age, gender, pre-diagnosis, fluorodeoxyglucose-positron emission tomography and substance uptake values of the groups, pathology if endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) had been performed, operation notes (use of video mediastinoscope, use of SSI or NSSI, sampled mediastinal lymph node stations), complications and pathology results analyzed.

Results: The use of NSSI was found to be statistically significantly higher in patients with previous EBUS-TBNA (p=0.013), in operations in which a single mediastinal station was sampled (p=0.004), and in cases where the pathological diagnosis was tuberculosis (TB) (p<0.001). A tissue with diagnostic value was sampled in all patients who needed NSSI were used in mediastinoscopy, no complications were observed, and TB was diagnosed at a rate of 60% (p=0.013).

Conclusion: The use of NSSI, such as long and thin mediastinoscopy aspirator and forceps, endoscopic scissors, injection needles, and endoclip in addition to SSI in mediastinoscopy increase the success of diagnosing TB.

Keywords: Mediastinoscopy, non-standard surgical instruments, invasive staging, tuberculosis

Introduction

Mediastinoscopy (Med) is a surgical method used to obtain sufficient samples from lymph nodes or masses located in the superior middle mediastinum (1). For many years, this surgical method has been widely used for the invasive staging of lung cancer (LC), and the diagnosis of lymphoma (Lym) or granulomatous diseases (GD) (2,3).

Low-dose computed tomography (CT) is of great importance in screening for LC in patients at risk (4). Fluorodeoxyglucose-positron emission tomography (FDG-PET) has 80% sensitivity and 88% specificity in the staging of LC, but has been repted to show increased false positivity in granulomatous, inflammatory, and infectious diseases (5). The specificity of PET increases and sensitivity decreases as the lymph node progresses (6). In sampling with endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA), the diagnosis of L or GD may still not be as successful as LC (3). Although lymph nodes can be seen with EBUS, a high density of cells can be sampled with needle aspiration in LC, while sufficient cells may not be aspirated with needles due to the low tissue density, especially in GDs (7,8). The thickness and hardness of the pathological tissue may even hinder the biopsy. Mediastinoscopy is an effective diagnostic method in the diagnosing of benign GDs and for LC staging. However, the success of this method is directly correlated with the amount of pathological material harvested. A factor negatively affecting the success of the method may be the presence of encapsulated mediastinal lymph nodes or mass at a depth that standard surgical instruments (SSI) cannot reach and are hard to sample. Therefore, the additional use of surgical instruments originally designed for other operation types [non-standard surgical instruments: (NSSI)] may be considered to improve the sampling success in mediastinoscopy. Blunt dissection with Med aspirator with or without a video mediastinoscope and punch biopsy with Med forceps is performed as standards in mediastinoscopy. Lazzaro and LoCicero (9) stated that endoscopic scissors, endodissectors and, when necessary, endoclips were additionally used

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during mediastinal lymph node sampling. In this definition, it is stated that the endodissector is used for tamponage during hemorrhage, while clips are used to stop subcarinal bronchial artery hemorrhage.

The study aimed to compare the efficacy of the use of NSSI in addition to SSI to increase the amount of tissue harvested from lymph nodes regarding diagnostic value for various diseases.

First Null Hypothesis to be Tested

Using NSSI in addition to SSI during Med does not improve the diagnostic efficiency in patients with mediastinal lymph nodes that are thought to be pathological.

Second Null Hypothesis to be Tested

Using NSSI in addition to SSI during Med does not improve the diagnostic efficiency for reactive hyperplasia, malignancy, sarcoidosis, or tuberculosis (TB) in patients with mediastinal lymph nodes that are thought to be pathological.

Methods

A retrospective scan was made of the files of patients who had undergone Med operations in the thoracic surgery clinic of our hospital between December 2019-2020, and those with complete surgical notes were included in the study. Files were excluded if the data were incomplete with respect to the use of videomediastinoscope, SSI, NSSI, specification of the sampled mediastinal lymph node stations, complication development and the amount of the material taken. The evaluation was made of 107 patients who underwent Med, with respect to age, gender, pre-diagnosis, FDG-PET and substance uptake values (SUV), EBUS-TBNA if present, pathology, surgery notes (use of videomediastinoscope, use of SSI or NSSI, sampled mediastinal lymph node stations), complications, and pathology results. The 107 patients included in the study were separated into those where SSI was used during Med [control group, (n=89), group A] and those where NSSI was also used [study group, (n=18), group B]. Approval for the study was granted by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval number: 2020-59, date: 17.12.2020).

Mediastinoscopy Procedure Using the SSI

Cervical Med was performed using either a standard mediastinoscope (Figure 1A) or a videomediastinoscope (Figure 2A) based on the surgeon's preference. Standard Med aspirator (Figure 1B) for lymph node dissection and standard Med forceps (Figure 1C) for lymph node sampling was sufficient to reach the tissue in the targeted area (station). The tissue was usually released with the aspirator and sampling was performed with forceps, based on the surgeon's experience. If necessary, the same process was repeated at other stations.

Mediastinoscopy Procedure Using NSSI

Cervical Med; videomediastinoscopes (Figure 2A) were used as an increased the view is necessary due to the variety of instruments required.

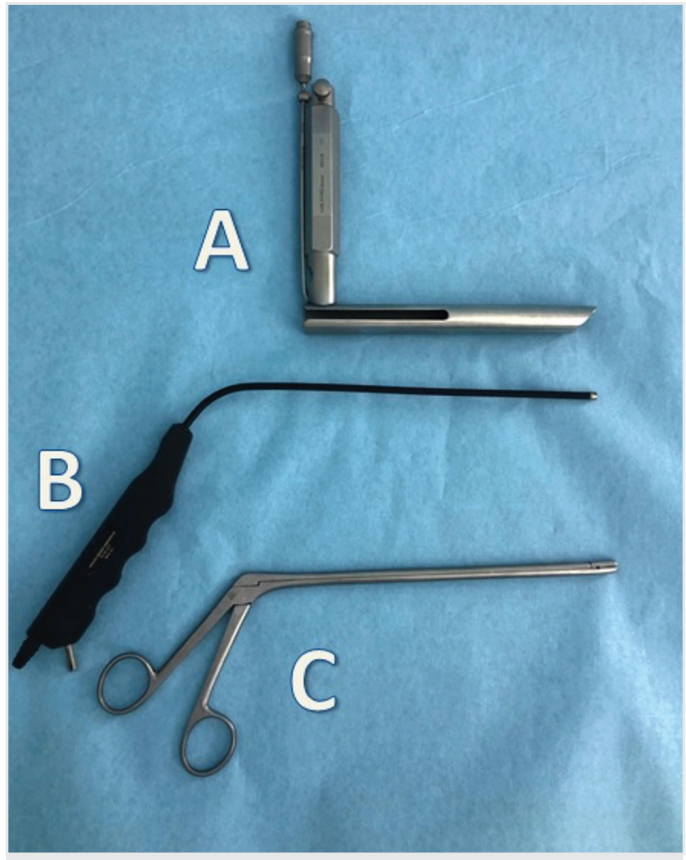

Figure 1. The SSI used in M: A) Standard mediastinoscopy, B) standard mediastinoscopy aspirator, C) standard mediastinoscopy forceps
SSI: Standard surgical instruments

Lymph node dissection; long and thin Med aspirator was used since the working area was narrower and deeper (Figure 2B).

Lymph node sampling; long and thin-tipped Med forceps were used where lymph nodes were small or unattainable with standard forceps (Figure 2C).

In some malignant or benign diseases, the mediastinal lymph node can neither be dissected with aspirator nor sampled with forceps because of the thickness of its capsule. Endoscopic scissors developed for video-assisted thoracoscopic surgery (VATS) (Figure 2D) can be used in these cases. An injection needle is placed at the tip of the forceps (Figure 2E), which then penetrates the lymph node at a depth sufficient to check the presence of any vascular formation inside or behind the capsule. The dissection was continued when there was no hemorrhage.

Bronchial artery hemorrhage may develop particularly during the dissection of the subcarinal lymph nodes and cannot be stopped by cauterization, unlike conventional hemorrhages. Therefore, VATS can be clipped with an endoclip (Figure 2F).

Statistical Analysis

Data obtained in the stud were analyzed statistically using SPSS 15.0 for Windows software. Descriptive statistics were expressed as number (n) and percentage (%) for categorical variables, and mean, standard deviation, minimum and maximum values for numerical variables. The rates were compared with chi-square test in independent groups and

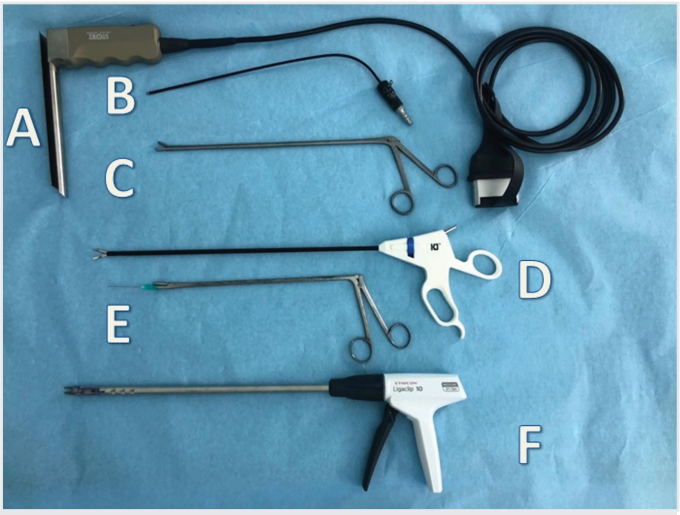

Figure 2. The NSSI used in M: A) Videomediastinoscope, B) long and thin M aspirator, C) long and thin-tipped M forceps, D) endoscopic scissors, E) forceps supported injection needle, F) endoclips
NSSI: Non-standard surgical instruments

the McNemar test in dependent groups. The statistical alpha significance level was accepted as $p<0.05$.

Results

In this study, the evaluation was made the diagnostic efficiency of using SSI and NSSI in mediastinoscopy performed in patients with mediastinal lymph nodes thought to be pathological. As sufficient tissue could be obtained from all patients for pathological interpretation, the two groups were equal in terms of diagnostic efficiency, and NSSI was found to be superior to SSI in terms of diagnosing TB (33.3% vs 2.2%) ($p<0.001$). From 1,310 operations performed between the specified datesin our clinic, 109 were Med. Two of these patients were excluded (1.8%) due to the lack of detailed operative notes, and the results of 107 patients were evaluated as follows:

Most of the patients were male (75.5%) and had malignant (82.2%) diseases (Table 1). In the mediastinal examinations of the patients with radiological and nuclear medicine methods, there were 57.9% malignant invasion, 9.3% sarcoidosis and 5.6% TB findings. PET-CT was performed in 63.5% of the patients and 67.6% of these scans had pathological (SUV_{max} >3) FDG uptake. EBUS was performed in 30.8% of the patients, of whom a diagnosis could be made in 27.3% (9 patients). While the procedure was continued vidomediastinoscopy in all the patients where SSI was used in Med, only 1 of those required videomediastinoscope due to poor vision. The regions sampled in the mediastinum were named stations and the stations were coded as 2R (right upper paratracheal region), 4R (right lower paratracheal region), 2L (left upper paratracheal region), 4L (left lower paratracheal region) and 7 (subcarinal region). During the process, 4R was sampled at the rate of 95.3%, 7 at 81.3%, and 4L at 80.4%.

During the Med procedure, it was observed that sampling was made from 3 (36.4%) or 4 (33.6%) different stations, while sampling was made from a single or all 5 stations less often (7.5%/8.4%). Complications occurred at a rate of 17.8% during the procedure (19 patients), of which 89.4% (17

Table 1. Demographic characteristics of the patients

		n	%
Gender	Male	81	75.7
	Female	26	24.3
Age (years) mean ± SD (min.-max.)		**58.0±11.2 (28-82)**	
Primary diagnosis	Malignant	88	82.2
	Non-malignant	19	17.8
Mediastinal prediagnosis	No	29	27.1
	Yes	78	72.9
	Tuberculosis	6	5.6
	Sarcoidosis	10	9.3
	Lymphoma	1	0.9
	Malignant	62	57.9
	Other	2	1.9
FDG-PET	No	39	36.4
	Yes	68	63.5
SUV_{max}	Physiological (<3)	22	32.4
	Pathological (>3)	46	67.6
EBUS-TBNA	No	74	69.2
	Yes	33	30.8
EBUS diagnosis	No	24	72.7
	Yes	9	27.3
Video mediastinoscopy	No	88	83.0
	Yes	19	17.0
Tool used	Standard surgical instrument	89	83.2
	Non-standard surgical instruments	18	16.8
Number of sampled mediastinal stations	1	8	7.5
	2	15	14.0
	3	39	36.4
	4	36	33.6
	5	9	8.4
Mediastinal stations	2R	52	48.6
	2L	15	14.0
	4R	102	95.3
	4L	86	80.4
	7	87	81.3
Complication	No	88	82.2
	Yes	19	17.8
Pathological diagnosis	Local hemorrhage	17	89.4
	Massive hemorrhage	1	5.2
	Hoarseness	1	5.2
	Malignancy	30	28.0
	Reactive	57	53.3
	Sarcoidosis	11	10.3
	Tuberculosis	8	7.5
	Other	1	0.9

SD: Standard deviation, min.: Minimum, max.: Maximum, FDG-PET: Fluorodeoxyglucose-positron emission tomography, SUV: Substance uptake value, EBUS-TBNA: Endobronchial ultrasound-transbronchial needle aspiration

patients) were minor hemorrhage and could be controlled with local hemostatic agents containing cellulose, and hemoclips when necessary. Major hemorrhage developed in 1 patient (5.2%), and the pulmonary artery hemorrhage was primarily repaired by emergency thoracotomy. Hoarseness developed in 1 patient (5.2%) and was treated conservatively. Pathological diagnoses were made of reactive hyperplasia (53.3%) and malignancy (28%), and GD such as sarcoidosis and TB were diagnosed in 7.5% and 10.3%, respectively.

With the use of SSI and NSSI when necessary in mediastinoscopy, no difference was found in terms of gender, presence of malignancy, prediagnosis, FDG-PET, and SUV involvement (Table 2). In cases where EBUS-TBNA was applied, the need for NSSI in Med performed in the absence of a diagnosis was found to be statistically significantly higher than in those without EBUS-TBNA (55.6% vs 25.8%) (p=0.013).

The sampling rate of only 1 mediastinal station was found to be statistically significantly higher in mediastinoscopies using NSSI (27.8% vs 3.4%) (p=0.004). No difference was determined between the mediastinal stations in terms of the presence of complications. Complications such as massive hemorrhage and hoarseness were not seen in cases where NSSI was used, and in only case in the other group.

In mediastinoscopies in which NSSI was used, the TB rate of pathological diagnosis was found to be statistically significantly higher than in the other group where SSI was used (33.3% vs 2.2%) (p<0.001).

Discussion

The results of this study showed no difference in the diagnostic efficiency between the use of SSI and NSSI in addition to Med in patients mediastinal lymph nodes that were thought to be pathological. The use of NSSI was seen to be superior to SSI in terms of diagnosing TB in Med performed in patients with mediastinal lymph nodes that were thought to be pathological.

The patients in the current study showed similar demographic characteristics to those of some other Med studies conducted in Turkey (Table 1) (10-12). With the introduction of minimally invasive EBUS-TBNA throughout the world, the use of Med has gradually decreased, although it remains the gold standard in invasive mediastinal staging and diagnosis (9). Since standard or extended Med is a high-risk operation (13), the effectiveness of re-mediastinoscopy due to mediastinal fibrosis is low (14) and it is no longer used in clinical practice, Med should be performed at once and effectively. The effectiveness of the procedure is directly proportional to the amount of pathological tissue taken. In a study by Fu et al. (15), videomediastinoscopy was combined with EBUS to increase the amount taken, but it was stated that a wide pretracheal dissection should be performed for the EBUS probe to move effectively. Even in M, where EBUS-TBNA or SSI is used, sufficient pathological tissue may not be obtained. The current study results confirm this as the necessity of using NSSI in extended M performed in the absence of diagnosis in cases with EBUS-TBNA was found to be statistically significantly higher than those without (55.6% vs 25.8%) (p=0.013) (Table 2).

This can be considered to be because some mediastinal lesions are too rigid and thickly encapsulated to be sampled with TBNA or SSI. Additionally, the sampling rate of only one mediastinal station was found to be statistically significantly higher in mediastinoscopies using NSSI compared with SSI (27.8% vs 3.4%) (p=0.004). This demonstrated that NSSI is generally used in lesions difficult to sample and has a high tissue sampling capability. NSSI was successful in the sharp dissection of rigid encapsulated lymph nodes, and a significantly higher rate of TB diagnosis was made compared to the cases where SSI was used (33.3% vs 2.2%) (p<0.001). In this respect, the rigidity of the capsule in benign lesions may be a sign of TB.

Some patients who do not respond to standard TB therapy and who have radiological mediastinal lymphoid hyperplasia are primarily sampled with EBUS-TBNA. If a significant diagnosis is not made and sufficient pathological tissue cannot be obtained, Med is required. In a study of 321 patients by Cetinkaya et al. (16), sampling was performed with EBUS-TBNA and the majority (92%) received a diagnosis. Diagnostic Med was subsequently performed in 7 patients who could not be diagnosed with EBUS-TBNA and accepted the surgical procedure, and of these, 3 (42.8%) were diagnosed with GD. While the efficacy of EBUS-TBNA in the diagnosis and staging of LC is good, it is not so successful in the diagnosis of some GD such as TB and sarcoidosis, probably due of the density of the tissue taken. The current study results support this view.

Since many tests will be required, it may be particularly necessary to increase the amount of tissue in the diagnosis of diseases such as multi-drug resistant-tuberculosis (MDR-TB) (17). Mediastinoscopy is more frequently preferred over EBUS-TBNA for diagnostic purposes as it has the advantage of increasing the amount of tissue sampled. The current study result of a significantly higher TB diagnosis in Med where NSSI was used, shows the importance of the amount of tissue in diagnosis.

Researchers at Duke University Center for Evidence-Based Practice reported that concerning mediastinal staging with PET, the examination had sensitivity of 74% and specificity of 85% in detecting mediastinal metastases (18). The high false-negative and false-positive rates of this method also require invasive pathological confirmation to avoid unnecessary surgery and deprivation of necessary surgery (19). In this study, there was no significant difference in terms of NSSI requirement after PET-CT (p=0.83), and there was no significant difference in SUVmax involvement. It can be concluded that PET does not provide guidance in the need for NSSI use in mediastinoscopy. According to the current study results, it can be considered that the use of NSSI is only required to increase the effectiveness of the procedure in the light of perioperative findings.

The success of accurate mediastinal staging for non-small cell lung carcinomas increases to 71.6% with invasive and non-invasive methods (20). Accurate mediastinal assessment “leads to migration of patients to true (higher) stage and less likely to misclassify” (21). Despite advances in radiological and scintigraphic imaging, as well as minimally invasive methods (EBUS-TBNA and endoscopic ultrasound-guided fine needle aspiration), mediastinoscopy remains the gold standard for staging LC and increases the efficiency of the video-mediastinoscopy technique.

There was no difference between SSI and NSSI in terms of the presence of complications. Complications such as massive hemorrhage and

Table 2. Variation of standard and non-standard instrument usage requirements in mediastinoscopy according to patient characteristics

		Instruments used in mediastinoscopy				
		SSI		NSSI		p
		n	%	n	%	
Gender	Male	68	76.4%	13	72.2%	0.765
	Female	21	23.6%	5	27.8%	-
Primary diagnosis	Malignant	74	83.1%	14	77.8%	0.735
	Non-malignant	15	16.9%	4	22.2%	-
Prediagnosis	No	28	31.5%	1	5.6%	0.022
	Yes	61	68.5%	17	94.4%	-
	Tuberculosis	4	4.5%	2	11.1%	0.265
	Sarcoidosis	9	10.1%	1	5.6%	1.000
	Lymphoma	1	1.1%	0	0.0%	1.000
	Malignant	49	55.1%	13	72.2%	0.178
	Other	1	1.1%	1	5.6%	0.309
FDG-PET	No	33	37.1%	6	33.3%	0.832
	Yes	56	62.9%	12	66.7%	-
SUV_{max}	Physiological (<3)	20	35.7%	2	16.7%	0.311
	Pathological (>3)	36	64.3%	10	83.3%	-
EBUS-TBNA	No	66	74.2%	8	44.4%	-
	Yes	23	25.8%	10	55.6%	**0.013**
EBUS diagnosis	No	17	73.9%	7	70.0%	1.000
	Yes	6	26.1%	3	30.0%	-
Number of mediastinal stations sampled	1	3	3.4%	5	27.8%	**0.004**
	2	13	14.6%	2	11.1%	-
	3	36	40.4%	3	16.7%	-
	4	28	31.5%	8	44.4%	-
	5	9	10.1%	0	0.0%	-
Mediastinal station	2R	43	48.3%	9	50.0%	0.896
	2L	13	14.6%	2	11.1%	1.000
	4R	86	96.6%	16	88.9%	0.196
	4L	74	83.1%	12	66.7%	0.117
Complication	No	73	82.0%	15	83.3%	1.000
	Yes	16	18.0%	3	16.7%	-
Complication type	None	72	80.9%	14	87.5%	**1.000**
	Local hemorrhage	15	16.8%	2	12.5%	-
	Massive hemorrhage	1	1.1%	0	0.0%	-
	Hoarseness	1	1.1%	0	0.0%	-
Pathological diagnosis	Reactive	49	55.1%	8	44.4%	0.411
	Malignancy	27	30.3%	3	16.7%	0.289
	Sarcoidosis	10	11.2%	1	5.6%	0.686
	Tuberculosis	2	2.2%	6	33.3%	**<0.001**
	Other	1	1.1%	0	0.0%	-

SSI: Standard surgical instruments, NSSI: Non-standard surgical instruments, FDG-PET: Fluorodeoxyglucose-positron emission tomography, SUV: Substance uptake value, EBUS-TBNA: Endobronchial ultrasound-transbronchial needle aspiration

hoarseness were not seen in cases where NSSI was used, although each was seen only once in the other group. Therefore, it can be considered that NSSI can be used safely when necessary, with no extra costs incurred.

Study Limitations

There are several limitations within our study. PET-CT or EBUS-TBNA were not performed in all included patients. Thus, their effect on MDR-TB has not been fully determined. More than one lymph node station was not

sampled in cases where sufficient diagnostic samples were acquired. If it had been sampled, the rate of pathological diagnosis would have increased instead of reactive hyperplasia. Microbiological evaluation for tuberculosis was not performed in the sampled lymph nodes, except those with granulomatous reaction. If it had been done, the probability of TB incidence would have increased in stations sampled with SSI.

Conclusion

Despite the small number of cases, based on our experience, it can be said that this requirement is also present in MDR-TB. It can be considered that the use of NSSI will increase the diagnostic power of Med, where there is an increasing incidence of TB and particularly MDR-TB cases. In this respect, the rigidity of the capsule in benign lesions suggests that it is a sign of TB disease, and therefore, this issue should be further investigated. The use of NSSI such as long and thin M aspirators and forceps, endoscopic scissors, injection needles, and endoclips in addition to SSI in mediastinoscopy increases the success of diagnosing TB.

Ethics Committee Approval: Approval for the study was granted by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval number: 2020-59, date: 17.12.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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Evaluation of Critical Congenital Heart Disease Screening Results with Pulse Oximetry

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ABSTRACT

Introduction: The early diagnosis and treatment of critical congenital heart diseases (CCHD), which require surgery or intervention during the 1st year of life, is an important issue. Screening of CCHD with pulse oximetry increases early diagnosis rates. Therefore, our study aimed to evaluate the results of CCHD screening with pulse oximetry among babies born in our hospital.

Methods: The results of the CCHD screening with pulse oximetry of the babies with a gestational age of ≥34 weeks that were born in our hospital between January 1, 2018, and December 31, 2020, were retrospectively evaluated.

Results: Among the 14,766 babies born during the study period, the screening results of 11,892 babies were evaluated; 5,826 of whom were female (48.9%), and 6,066 (51.1%) were male. The number of babies who passed the screening test was 11,871 (99.8%), whereas 21 (0.2%) failed. Among 21 babies who failed the screening test and were evaluated by echocardiography, 7 (33.3%) babies were found to have CCHD. Preductal and postductal saturation values were found to be significantly lower in patients with the positive screening test and in whom CCHD was detected, compared with those without CCHD.

Conclusion: Early diagnosis of CCHD before discharge is possible with pulse oximetry screening. Better prognosis and lower mortality rates are targeted with early diagnosis in these babies. Therefore, arrangements should be made for the screening of all newborn babies with pulse oximetry.

Keywords: Critical congenital heart disease, screening, pulse oximetry

Introduction

Congenital heart disease (CHD) is one of the most common congenital anomalies (1). The incidence of CHD is around 8-10 per 1,000 live births. Critical congenital heart disease (CCHD) is a disease that requires surgical intervention or catheterization within the first year of life. This group constitutes 25% of CHDs (2,3). The diagnosis of these anomalies in the prenatal period is vital in terms of reducing morbidity and mortality in the neonatal period. It was reported that early treatment of CHD with antenatal diagnosis or detected in the early postnatal period improves prognosis and decreases mortality (4-6). It is challenging to diagnose CCHD in the early postpartum period by physical examination alone. Physiological haemodynamic changes, absence of cyanosis in the early period, and absence of significant murmur are the most important reasons for delayed diagnosis. The echocardiographic examination is the gold standard in diagnosis, but it is impossible to screen every newborn with echocardiography. Oxygen saturation measurement with pulse oximetry is used for CCHD screening.

Pulse oximetry is a non-invasive device that measures the oxygen saturation in arterial blood. Changes in the absorption of red and infrared light passing through tissues by oxyhemoglobin and deoxyhemoglobin form the basis of the evaluation. Because of measuring the absorption of light through the sensor, the oxygen value in the blood is determined, and hemoglobin saturation is called oxygen saturation. Oxygen saturation measurement with pulse oximetry is an easy, painless, and reliable method (7). Additionally, with the dissemination of the CCHD screening program with pulse oximetry in the postnatal period, the rate of early diagnosis before these infants become symptomatic has increased (8,9).

Our study evaluates the pulse oximetry results of babies born in our hospital over three years.

Methods

In our study, CCHD screening test results of all healthy newborns above 34 weeks of gestation who were born in our hospital between January 1, 2018, and December 31, 2020, were evaluated retrospectively. All the babies were found to be normal in the physical examination and were rooming in with their mothers. Newborns with antenatal diagnosis, hospitalized in the intensive care unit, referred to an external center for any reason, and those with additional anomalies were excluded from the study.

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CCHD screening was performed in our hospital as follows; all newborn babies were examined before the measurement, and in case of any symptoms such as cyanosis, tachypnea, and murmur in their physical examination, these patients were considered symptomatic and evaluated in terms of echocardiographic examination. Preductal and postductal oxygen saturation were measured with the Masimo Radical 7® pulse oximeter device in babies who were asymptomatic and had no abnormal findings in the physical examination. Measurements were made from the right hand for preductal measurement and the right or left foot for postductal measurement. The test result was determined as "positive" (fail the test) and "negative" (pass the test). According to this screening result, if one or more of the following criteria were present in at least two measurements, the result was considered positive.

- Passed the test if both measurements were above 95% or above and the preductal-postductal SaO_2 difference was ≤3%.

- If any measurement was between 90 and 95% and/or the preductal-postductal SaO_2 difference was more than 3%, the test was repeated one hour later. If both measurements were 95% and above and the preductal-postductal SaO_2 difference was ≤3% on repetition, patients were considered negative (passed the test); further evaluation was performed when the result was positive.

- If any measurement was <90%, the measurement failed, and further evaluation was performed (10,11), (Figure 1).

An echocardiographic was examined on babies who failed the screening test. Additionally, cardiac anomalies detected because of the examination were evaluated.

The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 2742, date: 19.02.2021).

Statistical Analysis

SPSS (Statistical Package for Social Sciences, 23rd version, USA) program was used to analyze the findings. The distribution of variables was measured with the Kolmogorov-Smirnov test. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) in the comparison of quantitative data, Student's t-test was used for two-group comparisons of normally-distributed parameters, and Mann-Whitney U test was used for two-group comparisons of non-normally-distributed parameters. The Pearson's chi-square test, Fisher's exact, and Yates continuity correction test (Yates corrected chi-square) were used to compare qualitative data. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

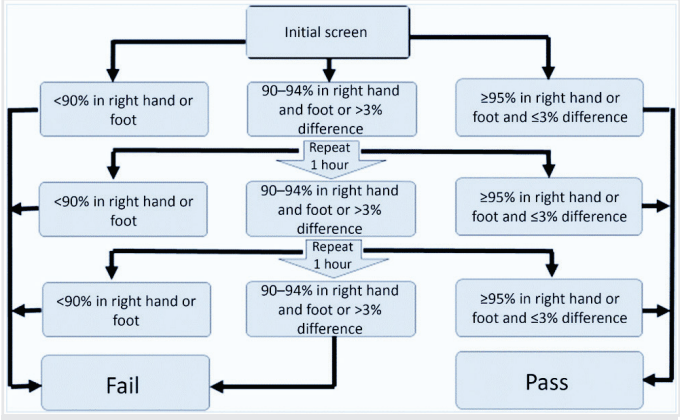

Figure 1. Neonatal congenital heart disease screening chart (10,11)
RH: Right hand, F: Foot

Results

Fourteen thousand seven hundred and sixty-six babies were born in our hospital during the study period. Screening results of 11,892 babies who met the inclusion criteria were evaluated retrospectively. Five thousand eight hundred and twenty-six (48.9%) of the cases were female, and 6,066 (51.1%) were male. While the number of infants passing the screening test was 11,871 (99.8%), the remaining failed number of infants was 21 (0.2%) (Figure 2). Seven (33.3%) out of 21 infants who failed the screening test had CCHD and underwent echocardiographic examination; patent foramen ovale (PFO) was found in 1 (0.04%), PFO and pulmonary hypertension in 1 (0.04%), and sepsis in 1 (0.04%) baby. Pulmonary atresia (28.5%) was the most common etiologic cause in those seven patients with CCHD (Table 1). The positive predictive value of the test was 33.3%. While there was no statistically significant difference in terms of gestational age and gender between the cases with the positive screening test and cases with and without CCHD, the saturation values were found to be significantly lower in infants with CCHD ($p<0.001$) (Table 2).

Discussion

In our study, 11,892 babies were screened for CCHD. While 11,871 (99.8%) of the babies passed the screening test, 21 (0.2%) babies failed. CCHD was present in 7 (33.3%) of 21 babies. The most common etiologic cause was pulmonary atresia (28.5%).

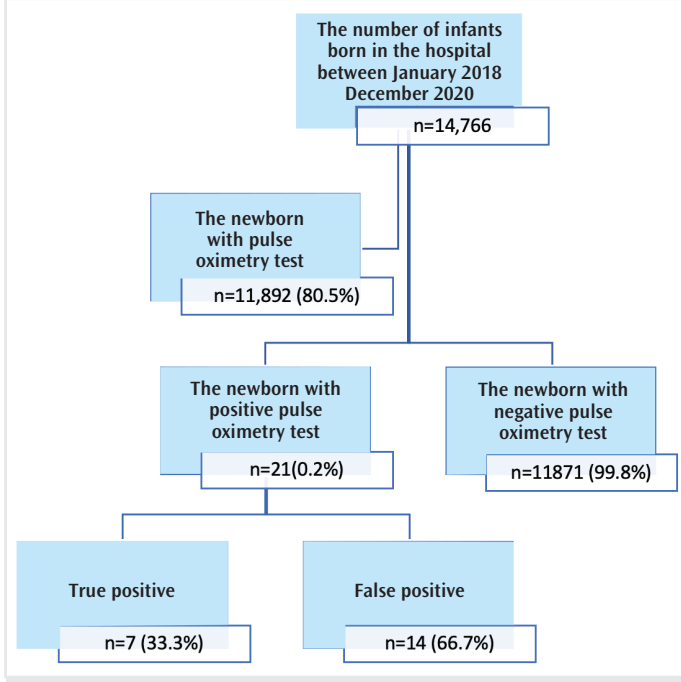

Figure 2. Screening test results of newborns screened with pulse oximetry

Table 1. Cases with positive pulse oximetry screening test and echocardiographic diagnoses

Case no	Gender	Gestation week	Preductal-postductal saturation measurement	Echocardiography
1	Male	38.14	88-89	Pulmonary atresia
2	Female	39.42	84-84	Great artery transposition
3	Male	38.28	90-91	Tricuspid atresia
4	Male	37.14	91-89	Total abnormal pulmonary venous return
5	Female	39.42	85-86	Pulmonary atresia
6	Male	37.57	87-88	Single ventricle, aortic coarctation
7	Female	38.57	91-95	Aortic coarctation
8	Female	38.28	93-92	Normal
9	Female	37.85	93-95	Normal
10	Male	39.57	94-95	Normal
11	Female	38.14	93-93	Normal
12	Female	40.42	94-92	Normal
13	Male	38.14	93-95	Normal
14	Female	39.14	91-94	Normal
15	Male	38.85	92-94	PFO, pulmonary hypertension
16	Male	39.42	91-94	Normal
17	Female	37.14	94-98	Normal
18	Female	38.85	92-90	Normal
19	Male	36.57	87-91	PFO
20	Male	40.14	91-93	Normal (early sepsis)
21	Male	39.14	91-94	Normal

Table 2. Comparison of cases with a positive screening test

Cases with a positive screening test, (n=21)		Cases with critical congenital heart disease, (n=7)	Cases without critical congenital heart disease, (n=14)	p
Gender	Female (n, %)	n=3, 43%	n=7, 50%	0.799[b]
	Male (n, %)	n=4, 57%	n=7, 50%	
Gestation week (median) (min.-max.)		38.28 (37.57-39.4)	38.85 (38.06-39.4)	0.488[a]
Preductal saturation (median) (min.-max.)		88 (85-91)	92.5 (91-93.25)	0.001[a]
Postductal saturation (median) (min.-max.)		89 (86-91)	94 (92-95)	0.006[a]

[a]Mann-Whitney U Test, [b] Fisher's exact test, min.: Minimum, max.: Maximum

Preductal and postductal saturation values of patients with positive screening tests were significantly lower in patients with CCHD than in those without.

CCHD is defined as a disease requiring surgical intervention or catheterization within the first year of life (12-16). Approximately 30% of newborns with CCHD are discharged from the hospital without being diagnosed, and these discharged newborns may present with a haemodynamic disorder, cardiovascular collapse, metabolic acidosis, and even death (17,18). Additionally, various postnatal hemodynamic changes reduce the chance of an early diagnosis of CCHD in newborn babies. It is known that one of the most important factors affecting the prognosis is the time of diagnosis (19-21). In a meta-analysis in which studies on the subject were evaluated, it was reported that the mortality risk of patients diagnosed in the antenatal or postnatal early period decreased with appropriate treatment and approach (22). Hence, it is essential to screen babies without an antenatal diagnosis for CCHD before being discharged from the hospital.

Oxygen saturation measurement with pulse oximetry is a non-invasive, easy, and applicable screening method (7,12,23,24). It is effective and reliable in critical CHD screening (25-27). The American Academy of Pediatrics and the American Heart Association have developed a CCHD screening algorithm, in which preductal-postductal saturation measurement is performed, and the difference is evaluated using pulse oximetry after the postnatal 24th hour (28,29).

In our country, since 2016, CHD screening has been performed with pulse oximetry in pilot hospitals. In our hospital, since November 2017, all babies have been screened with pulse oximetry after the 24th hour of their life or before discharge. In the last three years, 14,766 babies were born in our hospital, and 11,892 babies were screened with pulse oximetry. While 21 (0.2%) of 11,892 babies screened with pulse oximetry failed the screening, the rest (99.8%) passed. Because of the

echocardiographic examination of 21 babies who failed the screening, seven babies were diagnosed with CCHD. Two of the seven babies were diagnosed with pulmonary atresia, whereas the others were diagnosed with tricuspid atresia, aortic coarctation, single ventricle-isthmus hypoplasia, transposition of the great arteries (TGA), and total abnormal pulmonary venous return (TAPVR) anomaly (Table 1). The American Academy of Pediatrics has specified the priority disease group to be diagnosed by screening as hypoplastic left heart syndromes, pulmonary atresia, tetralogy of Fallot, total pulmonary venous return anomaly, TGA, tricuspid atresia, and truncus arteriosus (29). de-Wahl Granelli et al. (17) reported that the most common causes in cases who could not pass the screening test were TGA, pulmonary atresia, hypoplastic left heart syndromes, and aortic coarctation, respectively.

However, Riede and Schneider (24) detected the most common duct-dependent and cyanotic diseases such as TGA and TAPVD by screening (30). Dilli et al. (31) reported that 6 (0.12%) out of 34 babies with positive screening tests were diagnosed with CCHD, and the most common etiologic cause was TAPVR anomaly. In our study, the diagnoses of the cases detected by screening were compatible with the literature.

Although the measurement of oxygen saturation with pulse oximetry is useful in detecting CCHD, the false-positive rate in the literature varies between 0.14% and 0.87% (12). In a study conducted in our country in 2018, the false positivity rate was 3.7% (32), and this rate was found to be 0.12% in another study by Özalkaya et al. (33) The reason for the false-positive rate in both studies being different from the literature was associated with the scanning time. It was reported that the rate of false positivity decreased from 0.87% to 0.035% in cases screened after the postnatal 24th hour (30). In our study, the rate of false positivity was also 0.11%. We think that the false positivity rate is low because the screening time of the babies was after the postnatal 24th hour per the discharge protocol of our hospital. PFO was present in one patient, and PFO and pulmonary hypertension was present in one patient out of the fourteen false positive patients. Another patient, who was not screened and whose echocardiographic evaluation was normal, received treatment with the diagnosis of early sepsis. Scanning with pulse oximetry also enables the incidental detection of non-critical cardiac defects such as atrial septal defect, ventricular septal defect, in which right-left shunt continues, PFO who has not yet closed, and persistent pulmonary hypertension. Also, non-cardiac pathologies that may decrease the oxygen saturation value, such as sepsis, intracranial bleeding, circulatory failure, lung infection, and hereditary hemoglobinopathies, can be detected (29,34,35).

In our study, preductal and postductal saturation measurements were significantly lower in the group with CCHD among the patients with the positive screening test than without CCHD. In the literature studies conducted, no finding was found in which saturation values were compared between the two groups.

Study Limitations

The limitation of our study is that we could not include the cases whose screening test was found to be negative and had been diagnosed in the late infancy period because of its retrospective nature.

Conclusion

Early diagnosis of CCHD before discharge is possible with pulse oximetry screening. Better prognosis and lower mortality rate are aimed with early diagnosis in these babies. Therefore, necessary arrangements should be made to screen all newborn babies with pulse oximetry.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 2742, date: 19.02.2021).

Informed Consent: Retrospective study.

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Evaluation of the Relationship Between Anxiety, Obsessive-Compulsive Disorder and Clinical Parameters in Patients with Young Knee Osteoarthritis

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ABSTRACT

Introduction: In this study, we wanted to evaluate the variability relationship between the criteria used in the disease course of anxiety and obsessive-compulsive disorder (OCD) in a group of patients with knee osteoarthritis (OA).

Methods: We assessed 104 patients who were diagnosed with grade 2-4 knee OA and fifty healthy individuals. Their sociodemographic characteristics were recorded. Maudsley Obsessive-Compulsive Inventory (MOCI) was used to measure the type and extent of obsessive-compulsive symptoms, Beck Anxiety Inventory (BAI) was used to assess emotional status, Short Form-36 (SF-36) was used to assess the quality of life, visual analogue scale (VAS) was used to assess pain severity and Western Ontario McMaster Questionnaire Index (WOMAC) and Lequesne index were used to assess physical activity.

Results: BAI was higher in old patients (13.6±9.94) than in young patients (12.4±5.91) and healthy individuals (7±6.4) ($p<0.001$). A positive correlation was found between the BAI and MOCI scores and between VAS and WOMAC scores of patients with knee OA, and a negative correlation was found between SF-36 physical and mental scores in these patients.

Conclusion: Anxiety was more common in patients with knee OA. There was a relationship between OCD and clinical parameters and quality of life in patients with knee OA, but there was no significant difference when patients with knee OA were compared with healthy individuals.

Keywords: Knee, osteoarthritis, obsessive-compulsive disorder, anxiety, quality of life

Introduction

Osteoarthritis (OA) is a slowly escalating, non-inflammatory, chronic joint disease characterized by increased cartilage destruction, osteophyte formation and subchondral sclerosis observed in the load-bearing synovial (diarthrodial) joints. It is most common in the knee and hip joints. Over the past 20 years, the prevalence of knee OA has doubled, regardless of weight and patient age (1,2). When people aged 60 and over are screened, the incidence of symptomatic knee OA is 11-50%, and its importance in terms of public health increases as the incidence increases with age (3).

When the literature was searched, it was seen that different factors affect the course of the disease in people with knee OA (4,5).

Additionally, in studies that were compared with other rheumatological diseases and only with osteoarthritis, the rate of depression was found to be frequent in the osteoarthritis group and was associated with pain severity (6). Obsessive-compulsive disorder (OCD) is one of the psychiatric disorders in the group of neurotic diseases that occur with compulsions accompanied by ruminative thoughts. The fact that osteoarthritis is a long-term disease group causes its psychiatric symptoms.

OCD is one of the psychiatric disorders in the group of neurotic diseases that occur with compulsions accompanied by ruminative thoughts. The fact that osteoarthritis is a long-term disease group causes its psychiatric symptoms (7,8).

The main idea of this study was to determine the connection between anxiety, OCD levels and clinical parameters in patients with young knee OA.

Methods

Participants

We included 54 patients aged ≤50 years and 50 patients aged more than 50 years who was accepted our outpatient clinic and were diagnosed with grade 2-4 knee OA according to Kellgren-Lawrence criteria and

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50 healthy individuals as the control group. Age, gender and body mass index (BMI) were recorded. The diagnosis of knee OA was made according to the American College of Rheumatology (ACR) criteria. Patients were evaluated radiologically using the criteria of the Kellgren-Lawrence Radiographic Scale (KLRS) evaluation system (9). Radiographs (X-rays) were taken while standing and putting pressure on the knee, and anterior-posterior and lateral knee X-rays were examined.

Patients with knee OA according to the ACR criteria without any abnormal results in complete blood count, blood biochemistry, erythrocyte sedimentation rate and urine tests, did not have a neurological or psychiatric disease, did not use any anxiolytic and antidepressant drugs, did not suffer from chronic alcohol consumption and did not have clinical findings of multi-organ failure, such as liver and kidney failure, were included in the study. Patients with previous knee surgery, with a history of trauma and those with rheumatic findings in previous examinations were excluded from the study. All study group patients were diagnosed with knee OA 6 months before the study or earlier. The study was explained to the patients in our study and their consent was obtained written consent was taken from the patients. Bezmialem Vakıf University Non-Interventional Clinical Research Ethics Committee approval was received for the study (approval number: 13/234, date: 02.07.2019).

Measurement

The pain level of the patients is determined according to the visual analog scale (VAS) marker (0: no pain, 10: very severe pain) (10). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was applied to measure the functional level of the patients and morning stiffness. The WOMAC index consists of three parts and 24 items. Questions in each section receive 1 to 5 points. An increase in the score indicates that the patient's pain, morning stiffness and condition deteriorate (1: none, 2: mild, 3: moderate, 4: severe, and 5: very severe).

The Lequesne index was used to evaluate pain, especially at night, morning stiffness, pain when walking, pain when getting up from an armless chair, maximum walking distance, and activities of daily living (climbing up and down stairs, squatting, and walking, uneven ground) (2). Scores were interpreted as follows: 1-4 points, mild (grade 1); 5-7 points, intermediate (grade 2); 8-10 points, severe (grade 3); 11-13 points, very severe (grade 4) and ≥14 points, extremely severe (grade 5).

Short Form-36 (SF-36) was used to assess the patients' quality of life and health status. Developed by Ware in 1987, SF-36 includes 36 statements and two main sections (physical and mental dimensions) that evaluate eight concepts: physical function, physical role restriction, pain, vitality/fatigue, social function, emotional role restriction, mental. health and perceived general health. The scores of each sub-dimension and two main dimensions in the scale range from 0 to 100 (11). SF-36 scores positively, and higher scores indicate a higher quality of life. The Turkish version of the SF-36 was applied to patients with both OA and chronic low back pain and was found to be valid and reliable (12). The Physical Component Score (PCS) with the scores of the first four subscales and the Mental Component Score with the scores of the last four subscales were calculated to facilitate the association of the scale with many findings. data from the general population and a special calculation method (13). Thus, physical and mental quality of life scores were obtained.

Beck Anxiety Inventory (BAI) was determined to determine anxiety levels in the study group. BAI is a marker designed by Beck et al. (14). It is used to determine the anxiety level of people. It consists of 21 questions scored between 0 and 3. Ulusoy et al. (15) determined his Turkish proficiency with his work. In this scale, 0-7 points indicate very little, 5-8 points less, 16-25 points moderate and 26-63 points severe level.

The Maudsley Obsessive-Compulsive Inventory (MOCI) is designed to define obsessive-compulsive indications for both healthy and psychiatric persons. It consists of four subscales: checking, washing, doubt and slowness. A fifth subscale, "rumination", has been added to the adapted version. The calculated scores range from 0 to 37 points, and high scores indicate more obsessive-compulsive indications (16). Erol and Savasır (17) adapted the inventory to Turkish.

Statistical Analysis

Statistics were Performed Using IBM SPSS for Windows, Version 22.0 (IBM) (Corporation, Armonk, NY, USA). The continuous variables used in the study were evaluated with the Shapiro-Wilk test normality test in terms of conformance to the normal distribution. In particular, the mean and standard deviations of the data were determined. The Kruskal-Wallis test was used to determine the differences between each group for continuous variables, and the Bonferroni corrected Mann-Whitney U test was applied as post hoc for comparisons among the groups with significant differences. Chi-square test or Fisher's exact test was used to compare the categorical variables. The relationship with each other was evaluated by Spearman's rho correlation coefficient. A p-value of <0.05 was considered statistically significant.

Results

A total of 154 cases were included in the study. The clinical and sociodemographic characteristics of patients with knee OA and patients in the control group are presented in Table 1. There was no difference among KLRS scores in patients with knee OA. There was no difference in BMI between young knee OA, old knee OA and without knee OA individuals ($p=0.342$).

There was a significant difference in the WOMAC and Lequesne knee total scores between the groups, but no difference was found between young and old patients with knee OA ($p=0.33$ and $p=0.75$, respectively). Although the BAI score was higher in elderly patients with OA (13.6 ± 9.94) compared with young patients with OA (12.4 ± 5.91) and control group patients (7 ± 6.4), the overall anxiety level was higher in patients with knee OA compared with the control group ($p<0.001$). Both PCS and MCS of SF-36 were similar between both knee OA groups and lower compared with the control group ($p=0.18$ and $p=0.34$, respectively). However, similar results were obtained for mental health in all groups. In young patients with knee OA, the effect on physical roles was more prominent ($p=0.04$). There was no statistically significant difference in the total and subgroup MOCI scores between the groups (Table 1).

Table 1. Descriptive and analytical data of the groups

	Normal (n=50)		Young knee osteoarthritis (n=54)		Elderly knee osteoarthritis (n=50)		p
	(Mean ± SD)	Median (IQR)	(Mean ± SD)	Median (IQR)	(Mean ± SD)	Median (IQR)	
Age, years	42.26±5.18	43 (39-46)	43.17±5.34	45 (40-47)*	60.36±5.61	61 (55-64)§	**<0.001**
BMI (kg/m²)	29.13±5.45	30 (24-33)	30.22±5.92	29 (26-35)	31.25±5.15	31 (27-35)	0.212
Gender (n, %), females	37 (74)	-	53 (98)	-	39 (78)	-	**0.002**
Radiological scoring (KLRS)							
The right knee	-	-	2.9±0.52	3 (3-3)	2.8±0.51	3 (3-3)	0.768
The left knee	-	-	2.9±0.46	3 (3-3)	2.9±0.52	3 (3-3)	0.897
VAS	-	-	6.9±2.06	7 (5-9)	6.2±1.67	6 (5-7)	0.116
WOMAC	4±4.94	2 (0-5)	44.4±21.66	45 (26-62)*	38.6±20.4	36 (24-54)§	**<0.001**
Lequesne knee total	1.8±1.97	1 (0-3)	16.4±11.26	14 (8-23)	10.9±4.35	12 (7-14)	**<0.001**
SF-36							
Physical functioning	87.7±18.19	95 (85-100)	48.2±20.9	45 (35-65)*	41.1±23.17	40 (25-60)§	**<0.001**
Role-physical	86.7±30.86	100 (100-100)	19.2±30.55	0 (0-33)*	36.7±42.19	17 (0-67)§	**<0.001**
Role-emotional	74±37.67	100 (33-100)	38.2±45.97	0 (0-100)*	54±44.61	67 (0-100)§	**<0.001**
Vitality	57.1±19.25	55 (45-75)	43.1±19.94	45 (30-50)	47.8±19.57	48 (35-60)§	**0.002**
Mental health	68.6±14.77	68 (60-80)	61±18.82	60 (48-76)	62.1±16.43	56 (48-72)	0.052
Social functioning	81±20.55	88 (75-100)	54.1±26.24	50 (38-75)*	61.6±25.4	50 (50-75)§	**<0.001**
Bodily pain	82±15.38	90 (78-90)	40±19.74	45 (30-55)*	44.1±25.17	43 (33-68)§	**<0.001**
General health	66.9±14.46	70 (55-75)	50.1±19.52	52 (35-65)*	55.2±18.4	55 (40-65)§	**<0.001**
Physical component summary score	76.4±17.58	80 (61-91)	37.4±20.63	33 (20-55)*	45.2±24.42	42 (25-64)§	**<0.001**
Mental component summary score	74.6±11.3	77 (66-83)	51.3±15.29	52 (38-62)*	55.8±16.89	57 (44-65)§	**<0.001**
BAI	7±6.4	6 (3-9)	12.4±5.91	12 (8-16)*	13.6±9.94	12 (5-18)§	**<0.001**
MOCI							
Checking	2±1.55	2 (1-3)	2.7±2.1	3 (1-4)	2.9±2.13	3 (1-4)	0.146
Washing	4.3±2.17	4 (2-6)	4.7±2.53	4 (3-7)	4.5±2.66	4 (3-6)	0.766
Slowness	1.9±1.4	2 (1-3)	2.6±1.71	3 (1-4)	2.5±1.84	2 (1-4)	0.117
Doubling	3.2±1.36	3 (2-4)	3.5±1.61	4 (3-4)	3.1±1.6	3 (2-4)	0.328
Rumination	2.7±2.01	3 (1-4)	3.6±2.37	4 (2-6)	3.2±2.36	3 (1-5)	0.115
Total	12.7±5.37	12 (9-16)	14.8±6.97	15 (9-21)	13.9±7.67	14 (7-19)	0.257

*p<0.01 young knee osteoarthritis vs normal group, §: p<0.01 elderly knee osteoarthritis vs normal group, SD: Standard deviation, IQR: Interquartile range, OA: Osteoarthritis, BMI: Body mass index, KLRS: Kellgren-Lawrence Radiographic Scale, VAS: Visuel analog scale, WOMAC: Western Ontario and McMasters University Osteoarthritis Index, SF-36: Short Form-36, BAI: Beck Anxiety Inventory, MOCI: Maudsley Obsessional-Compulsive Inventory

There was a positive correlation between the BAI and VAS (r=0.27, p=0.004) and WOMAC (r=0.278, p=0.004) scores of patients with knee OA (p=0.004). There was a negative correlation between the BAI and SF-36's PCS (r=-0.375, p<0.001) and MCS (r=-0.455, p<0.001) scores, while there was no correlation between the BAI and Lequesne knee total score. There was a positive correlation between the MOCI total score and Lequesne knee total score (r=0.199, p=0.044), VAS (r=0.235, p=0.016) and WOMAC (r=0.306, p=0.002) scores of patients with knee OA, and there was a negative correlation between the MOCI total score and SF-36 PCS (r=-0.384, p<0.001) and MCS (r=-0.542, p<0.001) scores (Table 2).

The checking, washing, slowness and rumination subgroups and total scores of MOCI were higher in both young and old patients with knee OA. Only the doubting subgroup score was higher in the control and young knee OA groups (Figure 1, 2).

Discussion

In our study, we investigated the relationship between anxiety and disease markers in patients with knee OA. The quality of life level of the study group with knee OA was significantly lower than that of the control group (except for the mental health subgroup) in our study. However, BAI scores of the knee OA group were significantly higher than those of the control group. When the MOCI scores of each group were compared, no significant difference was found. A positive correlation was found between BAI and MOCI scores and VAS and WOMAC scores in the knee OA group. There was also a negative correlation between the BAI and MOCI and SF-36 scores.

Knee pain is very common in societies and the most common cause is knee OA. The main reason for its increased incidence is increased life

Table 2. Correlation analysis of Maudsley Obsessional-Compulsive Inventory and Beck Anxiety Inventory with VAS, WOMAC, Lequesne knee total, SF-36 physical component summary score and mental component summary score in patients with gonarthrosis

	VAS		WOMAC		Lequesne knee total		SF-36 PCS		SF-36 MCS	
	r	p	r	p	r	p	r	p	r	p
BAI score	0.278	**0.004**	0.278	**0.004**	0.098	0.323	-0.375	**<0.001**	-0.455	**<0.001**
MOCI score										
Checking	0.233	**0.017**	0.317	**0.001**	0.157	0.112	-0.297	**0.002**	-0.498	**<0.001**
Washing	0.128	0.196	0.214	**0.029**	0.187	0.059	-0.378	**<0.001**	-0.439	**<0.001**
Slowness	0.127	0.198	0.272	**0.005**	0.151	0.127	-0.223	**0.023**	-0.448	**<0.001**
Doubting	0.202	**0.039**	0.185	0.06	0.087	0.383	-0.256	**0.009**	-0.377	**<0.001**
Rumination	0.252	**0.01**	0.373	**<0.001**	0.267	**0.006**	-0.428	**<0.001**	-0.562	**<0.001**
Total	0.235	**0.016**	0.306	**0.002**	0.199	**0.044**	-0.384	**<0.001**	-0.542	**<0.001**

VAS: Visuel analog scale, WOMAC: Western Ontario and McMasters University Osteoarthritis Index, BAI: Beck Anxiety Inventory, SF-36: Short Form-36, PCS: Physical Component Summary Score, MCS: Mental Component Summary Score, MOCI: Maudsley Obsessional-Compulsive Inventory

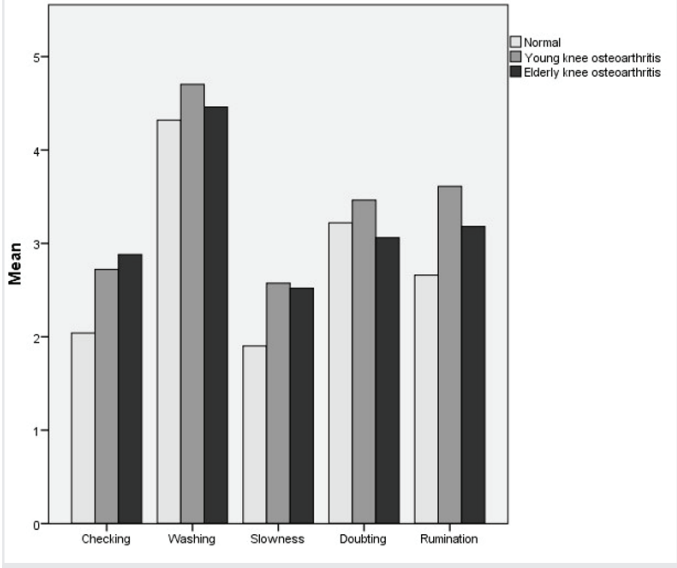

Figure 1. Maudsley Obsessional-Compulsive Inventory subscales distribution according to the group

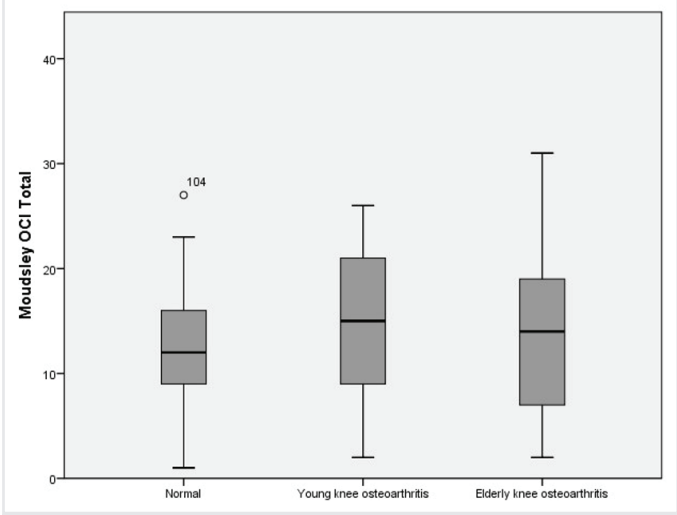

Figure 2. Boxplot of Maudsley Obsessional-Compulsive Inventory total score according to the group
OCI: Obsessional-Compulsive Inventory

expectancy, sedentary life, and increased weight gain, especially due to inactivity. Osteoarthritis, which can be seen not only in old age but also in middle age, causes socioeconomic losses. The constant pain-induced inactivity of these cases both triggers weight gain and enters a vicious circle by increasing the limitations of movement and leading to psychosocial regressions. In many studies in the literature, it has been shown that patients with knee OA have psychological problems due to limited daily activities, socioeconomic problems, and inability to participate in social life comfortably (6,18-21).

The loss of mobility and pain in patients with knee OA can cause mental deterioration, or can mental deterioration in these patients cause pain and decreased mobility in patients? Some studies recommend considering psychiatric evaluations for patients with OA because the prevalence of anxiety in these groups is high, thereby affecting the treatment process (22). Many studies in the literature have shown the two-way relationship of psychiatric disorders such as depression and anxiety with chronic pain. While depression is the most common psychiatric disease in all chronic pain cases, the most common mental symptom is anxiety. Although anxiety can increase the perception of pain, the pain itself can also cause anxiety (23-25).

Unlike the depression, anxiety can begin before the onset of pain in chronically painful patients. This makes the link between anxiety pain stronger than the link between depression and pain in a painful patient (26,27).

In a study examining patients with arthritis types other than OA, symptoms of depression and anxiety were shown to be associated with reduced mobility, pain, and treatment success (27). In this study, we evaluated the anxiety levels of young and elderly patients with knee OA and compared the findings with healthy individuals, the effect of anxiety on quality of life and the possible effect of OCD in patients with chronic knee OA. Anxiety was considered present if patients scored 8 or more on the BAI (28,29). Apart from increasing the feeling of pain, anxiety also negatively affects the quality of life. In this study, patients with knee OA had higher anxiety levels than the control group. There was a positive correlation between anxiety level and the WOMAC OA index. There was also a negative correlation between the patients' BAIs and MOCI scores and the mental and physical components of the SF-36.

Developing fear and increasing anxiety in patients support the fear-avoidance model in joint system patients. The fear-avoidance theory is based on the view that a person perceives pain in one of two ways: 1) This means that the more severe the acute pain, the more the patient does not perceive it as a threat. The person faces pain. As a result, patients recover faster. 2) Pain is perceived as threatening and the person exhibits pain-induced maladaptive behaviors such as fear, avoidance, and hypervigilance. This situation increases the functional loss in long-term follow-up and leads to more pain (30). For these reasons, patients' concerns should also be evaluated at the stage of treatment regulation.

In another study conducted with knee patients with OA over 65 years of age, a correlation was found between the proportion of joints in which pain was felt, morning stiffness, disability due to the pain threshold, and well-being. In anxiety and depression disorders, diagnosis and initiation of treatment as soon as possible may increase the response of patients with osteoarthritis to treatment (31).

Among anxiety disorders, especially OCD should be examined. OCD is the fourth most common psychiatric illness (32,33). The prevalence of subclinical OCD is observed as frequently as OCD. Both patients with OCD and patients with subclinical OCD state that their quality of life is impaired (34). Patients with OCD have an increased awareness of pain-induced stimuli (35). OCD can be considered an etiological factor in chronic pain (26).

Various questionnaires, such as WOMAC and Lequesne, are used to objectively evaluate the disease stage and treatment in patients with OA (11). In our study, the WOMAC index, in which the patient evaluated himself as multidimensional, showed low scores in the control group and high scores in the patient groups; there was no significant difference between the existing study groups in the study. However, the Lequesne index conducted in the form of interviews showed higher scores in the younger knee OA patient group. In the study by Basaran et al. (11), WOMAC observed that it was more sensitive than Lequesne in evaluating knee OA in Turkish patients and recommended this test to be performed. Scopaz et al. (35) In a study of 182 patients with knee OA, as assessed by WOMAC (self-reported function), high anxiety was associated with poor physical function.

Patient's health status, wishes and expectations reflect his/her personal and sociocultural characteristics; limitations in his/her ability to fulfill these wishes and expectations owing to his/her health status and the patient's response to these limitations and emotional status play a role in determining the health-related quality of life (36-38). SF-36 is one of the most frequently used scales for evaluating the general health status. In this study, PCS and MCS scores of SF-36 were low in both knee OA groups and were similar. In young patients, the effects on both physical and emotional roles were more pronounced, but the mental health results were similar in all groups. A limitation of this study is that the educational status and occupation of patients were not recorded because differences in these characteristics may affect the SF-36 MCS scores.

There is no study in the literature examining the quality of daily life of patients with knee pain and anxiety. However, the correlation between the physical effects of conditions such as anxiety and treatment compliance in these patients has not been examined. For these reasons, we believe that the role of mood changes in such diseases should be investigated more comprehensively.

Study Limitations

The first limitation of our current study is that it includes the situation during the study period by making an observational study by taking sections that include a certain period in a long-term disease. Another is that the drugs used and other concomitant diseases are not taken into account.

Conclusion

Anticipating risky situations that may increase the incidence of disease in knee OA diagnosed at a young age and informing the patients about this issue contributes to the preservation of joint health and increase the quality of life in the future. In our study, we found an increase in anxiety in individuals with knee OA. BAI score was higher in elderly patients with OA (13.6±9.94) compared with young patients with OA (12.4±5.91) and control group patients (7±6.4), the overall anxiety level was higher in patients with knee OA compared with the control group ($p<0.001$). However, in our study, when patients with knee pain were evaluated together with the control group, no significant difference was found between joint function and quality of life. As a result, the relationship between OCD and knee OA can be determined by more comprehensive and detailed studies.

Ethics Committee Approval: Bezmialem Vakıf University Non-Interventional Clinical Research Ethics Committee approval was received for the study (approval number: 13/234, date: 02.07.2019).

Informed Consent: The study was explained to the patients in our study and their consent was obtained written consent was taken from the patients.

Peer-review: Externally and internally peer-reviewed.

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The Effects of Immunosuppressive Therapy on Mortality in Patients Followed in Intensive Care Units with the Diagnosis of Critical Coronavirus Disease-2019 Pneumonia

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ABSTRACT

Introduction: The efficacy and safety of immunosuppressive therapy in Coronavirus disease-2019 (COVID-19) still controversial. We evaluated the effects of immunosuppressive therapy on mortality in patients followed in the intensive care units (ICU) due to critical COVID-19 pneumonia.

Methods: We compared patients followed up in the ICUs due to severe COVID-19 pneumonia who received immunosuppressive therapy with those who did not in terms of 1-month mortality, retrospectively.

Results: A total of 362 patients followed up in ICUs with a diagnosis of critical COVID-19 pneumonia were included in the study. The patients were divided into two groups as patients who received immunosuppressive therapy [n=249, 165 patients (45.5%) who received only corticosteroids, 25 patients (7%) who received only tocilizumab, and 59 patients (16.5%) who received tocilizumab + corticosteroid] and patients who did not (n=113). One hundred and ninety-two of the patients died (54.1%). There was no statistical difference between the groups in terms of 1-month mortality (p=0.38). Secondary bacterial infection was detected in 25.1% (n=91) n of the patients. The frequency of secondary infections was higher in the patients who received immunosuppressive therapy than in patients who did not receive immunosuppressive therapy (28% vs 17% respectively, p=0.03). The most common secondary bacterial infection was detected in patients who received tocilizumab + corticosteroids (n=25, 42.2%).

Conclusion: In this study, no difference in 1-month mortality was found between patients who received immunosuppressive therapy and those who did not. The frequency of secondary bacterial infections in patients who received immunosuppressive therapy was higher than in patients who did not.

Keywords: COVID-19, immunosuppressive therapy, tocilizumab, corticosteroid, mortality

Introduction

Coronavirus disease-2019 (COVID-19), caused by a new coronavirus [severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)] in December 2019, has turned into a pandemic that affects the whole world. As of the end of November 2021, the number of people infected with SARS-CoV-2 exceeded 200 million, and the number of COVID-19-related deaths exceeded 4.6 million worldwide. Although the vast majority (81%) of people infected with SARS-CoV-2 do not develop any symptoms of the disease or the disease is come around with mild symptoms, intensive care follow-up is required in approximately 5% of the patients (1,2). One of the important reasons for intensive care hospitalization is multiple organ failure caused by the "cytokine storm" caused by SARS-CoV-2. Interleukin-6 (IL-6) receptor antagonists (toculizumab), as well as corticosteroids, are the most commonly used immunosuppressive agents in the prevention and treatment of this cytokine storm.

While the routine use of corticosteroids in the management of cytokine storms in the early stages of the pandemic is not recommended, the use of corticosteroids in severe and critically ill patients is recommended at a strong level of evidence in the recently published guidelines (3,4). The efficacy and use of tocilizumab in the cytokine storm due to COVID-19 is still a matter of debate (5). While the routine use of corticosteroids and tocilizumab in the early period of the pandemic is not recommended in the COVID-19 guideline of the Turkish Ministry of Health, in the current guideline, it is recommended to start 6 mg dexamethasone or equivalent corticosteroid (30-40 mg methylprednisolone, prednisolone or prednisone) treatment per day and apply it for a maximum of 10 days in the patients who develop a need for oxygen and mechanical ventilation. It also approves the use of tocilizumab if procalcitonin is negative in patients who develop the need for oxygen and mechanical ventilation and with persistent fever signs, high or persistently elevated

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C-reactive protein (CRP) findings, evidence of ferritin values (>700 µg/L) that are above the upper limits of normal and continue to increase, and cytokine storm findings such as D-dimer elevation, lymphopenia, thrombocytopenia and neutropenia, deterioration in liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) (6,7).

In this study, we evaluated the effects of immunosuppressive therapy on mortality in patients followed in the intensive care units (ICU) due to critical COVID-19 pneumonia. We compared patients who received immunosuppressive therapy with those who did not, in terms of 1-month mortality.

Methods

Study Design, Population

Retrospectively, 362 patients diagnosed with critical COVID-19 pneumonia in the tertiary ICUs between 10 March 2020 and 1 June 2021 were included in the study. The study was approved by University of Health Sciences Turkey, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 45, date: 10.02.2022). Inclusion criteria; a) being older than 18 years old, b) being positive for COVID-19 PCR, c) having new-emergent infiltration compatible with COVID-19 pneumonia on computed tomography, d) having critical-level covid pneumonia findings (the ones with respiratory failure PaO_2/FiO_2 <300 and/or shock, multiple organ failure). Exclusion criteria; a) being younger than 18 years old, b) being pregnant or breastfeeding, c) not having findings compatible with COVID-19 pneumonia on computed tomography, d) not having critical-level covid pneumonia findings (the ones with respiratory failure PaO_2/FiO_2 <300 and/or shock, multiple organ failure). SARS-CoV-2 detection was diagnosed by next-generation sequencing or real time-polymerase chain reaction method. The patients were divided into two groups: patients who received immunosuppressive therapy (patients who received only corticosteroids, patients who received only tocilizumab, and patients who received tocilizumab + corticosteroid) and patients who did not receive immunosuppressive therapy. The groups were compared in terms of clinical outcomes and 1-month mortality.

Corticosteroid Treatment Protocol

The corticosteroid treatment was administered at ≥40 mg/day methylprednisolone for at least 10 days to patients with PaO_2/FiO_2 <300 and/or with COVID-19 pneumonia findings requiring mechanical ventilator or high flow support at the time of admission, in line with the national guideline.

Tocilizumab Treatment Protocol

Tocilizumab treatment was administered at a dose of 800 mg/day immediately or 400 mg/day for two consecutive days in cases where procalcitonin is negative in patients with PaO_2/FiO_2 <300 and/or COVID-19 pneumonia findings requiring mechanical ventilator or high flow support, persistent fever, persistently high or increasing CRP and IL-6, ferritin values that are above the upper limits of normal and continue to increase (>700 µg/L), D-dimer elevation, lymphopenia, thrombocytopenia, and neutropenia with cytokine storm findings such as deterioration in liver function tests (ALT, AST, LDH) at the moment of application in line with the national guide.

Data Collection

The demographic and clinical characteristics, laboratory findings and treatment parameters of the patients were obtained from the hospital information operating system. The Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Evaluation Score (SOFA) scores were recorded for all patients in their ICU hospitalizations. Blood, urine, and tracheal aspirate cultures (intubated patients) were taken from all patients with newly developed fever and increased procalcitonin levels. Newly developed fever and/or increase in procalcitonin values and culture positivity were accepted as the presence of secondary infection.

Statistical Analysis

The parametric test was used without a normality test due to the compatibility of the Central Limit Theorem. Non-parametric test statistics were used for laboratory measurement values with high deviations from the mean. Chi-square test and ANOVA-Tukey test were used to compare the means of two groups. Chi-square test statistics were used to evaluate the relationship between categorical variables. The exposure ratio [odds ratio (OR)] of the variables thought to be related to mortality status was given.

Results

A total of 362 patients followed up in ICUs with a diagnosis of critical COVID-19 pneumonia were included in the study. The patients were divided into two groups: patients who received immunosuppressive therapy [n=249, 165 patients (45.5%) who received only corticosteroids, 25 patients (7%) who received only tocilizumab, and 59 patients (16.5%) who received tocilizumab + corticosteroid], and patients who did not receive immunosuppressive therapy such as corticosteroids or tocilizumab (n=113). The mean age of the patients who did not receive immunosuppressive therapy was higher than patients who received immunosuppressive therapy (72.1±15 vs 67.7±13 respectively, p=0.008). The patients who did not receive immunosuppressive therapy had higher SOFA scores than patients who received immunosuppressive therapy (5.92±2 vs 4.3±2 respectively, p<0.0001). No significant difference was found between the two groups in terms of APACHE-II scores, comorbidities, and invasive mechanical ventilation support (p>0.05). ICU length of stay (11.52±9 days vs 7.9±5 days respectively, p<0.0001) and total length of stay (17.4±12 days vs 12±8 days respectively, p<0.0001) were longer in patients who received immunosuppressive therapy. Secondary bacterial infections were detected in 25.1% (n=91) of the patients. The frequency of secondary infections was higher in the patients who received immunosuppressive therapy than patients who did not receive immunosuppressive therapy (28% vs 17% respectively, p=0.03). One hundred and ninety-two of the patients died (54.1%). There was no statistical difference between the groups in terms of 1-month mortality (p=0.38). The demographic and clinical characteristics of the patients are given in Table 1.

Table 1. Demographics and clinical characteristics of the patients

Variables		Total n=362 (%)	Patients who did not receive immunosuppressive therapy n=113 (%)	Patients who received immunosuppressive therapy n=249 (%)	p
Gender	Male	220 (60.8)	68 (60.2)	152 (61)	0.88*
	Female	142 (39.2)	45 (39.8)	97 (39)	
Age (year)	Mean (SD)	69.1±14	72.1±15	67.7±13	**0.008**
APACHE-II	Mean (SD)	53.41±24	51.84±26	54.12±24	0.43
SOFA	Mean (SD)	4.81±2	5.92±2	4.3±2	**<0.0001**
ICU length of stay (day)	Mean (SD)	10.3±8	7.9±5	11.52±9	**<0.0001**
Total length of stay (ICU + clinic) (day)	Mean (SD)	15.7±11	12±8	17.4±12	**<0.0001**
Comorbidities	Yes	316 (87.3)	101 (89.4)	215 (86.3)	0.42
	No	46 (12.7)	12 (10.6)	34 (13.7)	
COPD	Yes	96 (26.5)	29 (25.7)	67 (26.9)	0.8
	No	266 (73.5)	84 (74.3)	182 (73.1)	
CAD	Yes	95 (26.2)	43 (38.1)	52 (20.9)	**0.001**
	No	267 (73.8)	70 (61.9)	197 (79.1)	
DM	Yes	138 (38.1)	47 (41.6)	91 (36.5)	0.36
	No	224 (61.9)	66 (58.4)	158 (63.5)	
CHF	Yes	65 (18)	30 (26.5)	35 (14.1)	0.004
	No	297 (82)	83 (73.5)	214 (85.9)	
CRF	Yes	53 (14.6)	21 (18.6)	32 (12.9)	0.15
	No	309 (85.4)	92 (81.4)	217 (87.1)	
Cancer	Yes	42 (11.6)	14 (12.4)	28 (11.2)	0.75
	No	320 (88.4)	99 (87.6)	221 (88.8)	
HT	Yes	205 (56.6)	63 (55.8)	142 (57)	0.82
	No	157 (43.4)	50 (44.2)	107 (43)	
Neurological disease	Yes	80 (22.1)	33 (29.2)	47 (18.9)	**0.03**
	No	282 (77.9)	80 (70.8)	202 (81.8)	
Arrhythmia	Yes	35 (9.7)	15 (13.3)	20 (8)	0.12
	No	327 (90.3)	98 (86.7)	229 (92)	
Secondary infection	Yes	91 (25.1)	20 (17.7)	71 (28.5)	**0.03**
	No	271 (74.9)	93 (82.3)	178 (71.5)	
IMV support	Yes	173 (47.8)	48 (42.6)	125 (50.2)	0.33
	No	189 (52.2)	65 (57.4)	124 (49.8)	
Death	Yes	196 (54.1)	65 (57.4)	131 (52.6)	0.38
	No	166 (45.9)	48 (42.6)	118 (47.4)	

(*: chi-square test/**: ANOVA-Tukey) p is significant at the level of <0.05. SD: Standard deviation; APACHE-II: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure evaluation, ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CHF: Congestive heart failure, CRF: Chronic renal failure, DM: Diabetes mellitus, HT: Hypertension, IMV: Invasive mechanical ventilation

The subgroup comparison of patients who received only corticosteroids, who received only tocilizumab and who received tocilizumab + corticosteroid with patients who did not receive immunosuppressive therapy is shown in Table 2. The patients who received only tocilizumab had the lowest APACHE-II scores, and the patients who received corticosteroid + tocilizumab had the lowest SOFA scores (p<0.0001). ICU length of stay (day) and total length of stay (ICU + clinic) were the longest in patients who received corticosteroid + tocilizumab and in patients who received only tocilizumab respectively (p<0.0001). The patients who received only tocilizumab had fewer comorbid diseases than the other groups (p=0.02). The most common secondary bacterial infection was detected in patients who received tocilizumab + corticosteroids (n=25, 42.2%). There was no statistical difference between the groups in terms of mortality (p=0.45).

Age (OR) 1.01, 95% confidence interval [(CI: 95%) 1.001-1.03], the presence of comorbid disease (OR: 2.23, 95% CI: 1.18-4.22), the presence of secondary bacterial infection (OR: 3.56, 95% CI: 2.08-6.08), total length

Table 2. Clinical and demographic characteristics of patients according to the type of immunosuppressive therapy they received

Variables		Total (n=362) (%)	Patients who did not receive immunosuppressive therapy (n=113) (%)	Patients who received only corticosteroid (n=165) (%)	Patients who received only tocilizumab (n=25) (%)	Patients who received corticosteroid + tocilizumab (n=59) (%)	p	Difference
Gender	Male	220 (60.8%)	68 (60.2%)	91 (55.2%)	17 (68%)	44 (74.6%)	**0.06***	NA
	Female	142 (39.2%)	45 (39.8%)	74 (44.8%)	8 (32%)	15 (25.4%)		
Age (year)	Mean (SD)	69.1±14	72.1±15	69.7±14	63.5±12	63.9±12	**0.001****	B, c<a d<b
APACHE-II	Mean (SD)	53.41±24	51.84±26	57.65±24	34.45±21	52.57±22	**<0.0001****	c<a d<b
SOFA	Mean (SD)	4.81±2	5.92±2	4.65±2	4.08±1	3.42±1	**<0.0001****	B, d<a
ICU length of stay (day)	Mean (SD)	10.3±8	7.9±5	10.5±7	12.6±15	13.8±8	**<0.0001****	a<b, d b<d
Total length of stay (ICU + clinic) (day)	Mean (SD)	15.7±11	12±8	16.05±9	22.3±24	19.11±10	**<0.0001****	a<b, d b<c
Comorbidities	Yes	316 (87.3)	101 (89.4)	148 (89.7)	17 (68)	50 (84.7)	**0.02***	NA
	No	46 (12.7)	12 (10.6)	17 (10.3)	8 (32)	9 (15.3)		
COPD	Yes	96 (26.5)	29 (25.7)	46 (27.9)	6 (24)	15 (25.4)	0.96	
	No	266 (73.5)	84 (74.3)	119 (72.1)	19 (76)	44 (74.6)		
CAD	Yes	95 (26.2)	43 (38.1)	34 (20.6)	4 (16)	14 (23.7)	**0.006***	
	No	267 (73.8)	70 (61.9)	131 (79.4)	21 (84)	45 (76.3)		
DM	Yes	138 (38.1)	47 (41.6)	61 (37)	9 (36)	21 (35.6)	0.83	
	No	224 (61.9)	66 (58.4)	104 (63)	16 (64)	38 (64.4)		
CHF	Yes	65 (18)	30 (26.5)	30 (18.2)	2 (8)	3 (5.1)	**0.003***	
	No	297 (82)	83 (73.5)	135 (81.8)	23 (92)	56 (94.9)		
CRF	Yes	53 (14.6)	21 (18.6)	25 (15.2)	-	7 (11.9)	0.11	
	No	309 (85.4)	92 (81.4)	140 (84.8)	25 (100)	52 (88.1)		
Cancer	Yes	42 (11.6)	14 (12.4)	26 (15.8)	-	2 (3.4)	**0.02***	
	No	320 (88.4)	99 (87.6)	139 (84.2)	25 (100)	57 (96.6)		
HT	Yes	205 (56.6)	63 (55.8)	97 (58.8)	11 (44)	34 (57.6)	0.57	
	No	157 (43.4)	50 (44.2)	68 (41.2)	14 (56)	25 (42.4)		
Neurological disease	Yes	80 (22.1)	33 (29.2)	40 (24.2)	3 (1.2)	4 (6.8)	**0.004***	
	No	282 (77.9)	80 (70.8)	125 (75.8)	22 (88)	55 (93.2)		
Arrhythmia	Yes	35 (9.7)	15 (13.3)	17 (10.3)	-	3 (5.1)	0.12	
	No	327 (90.3)	98 (86.7)	148 (89.7)	25 (100)	56 (94.9)		
Secondary infection	Yes	91(25.1)	20 (17.7)	42 (25.5)	4 (16)	25 (42.4)	**0.003***	
	No	271(74.9)	93 (82.3)	123 (74.5)	21 (84)	34 (57.6)		
IMV support	Yes	173 (47.8)	48 (42.6)	73 (44.3)	16 (64)	36 (61.1)	**0.04***	
	No	189 (52.2)	65 (57.4)	92 (55.7)	9 (36)	23 (38.9)		
Death	Yes	196 (54.1)	65 (57.4)	88 (53.3)	10 (40)	33 (55.9)	0.45	
	No	166 (45.9)	48 (42.6)	77 (46.7)	15 (60)	26 (44.1)		

(*: chi-square test/**: ANOVA-Tukey), p is significant at the level of <0.05. SD: Standard deviation, APACHE-II: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure evaluation, ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CHF: Congestive heart failure, CRF: Chronic renal failure, DM: Diabetes mellitus, HT: Hypertension, IMV: Invasive mechanical ventilation, NA: Not applicable, a: Patients who did not receive immunosuppressive therapy, b: Patients who received only corticosteroid, c: Patients who received only tocilizumab, d: Patients who received corticosteroid + tocilizumab

of stay (ICU + clinic) (OR: -0.95, 95% CI: 0.93-0.98), APACHE-II scores (OR: 1.02, 95% CI: 1.01-0.03), SOFA scores (OR: 1.36, 95% CI: 1.23-1.5) were statistically associated with increased mortality (p<0.05) (Table 3).

Discussion

The most important finding of our study was that there was no difference in mortality between patients who received immunosuppressive therapy and those who did not, in patients who followed up with the diagnosis

Table 3. Factors related to mortality in all patients

Variables	Odds ratio	Lower (95% CI)	Upper (95% CI)	p
Age	1.01	1.001	1.03	p<0.05
Comorbidities	2.23	1.18	4.22	p<0.05
Secondary infection	3.56	2.08	6.08	p<0.05
Total length of stay (ICU + clinic) (day)	-0.95	0.93	0.98	p<0.05
APACHE-II	1.02	1.01	0.03	p<0.05
SOFA	1.36	1.23	1.5	p<0.05

(Odds ratio) p is significant at the level <0.05. APACHE-II: Acute physiology and chronic health evaluation, SOFA: equential organ failure evaluation, ICU: Intensive care unit, CI: confidence interval

of critical COVID-19 pneumonia in the ICUs. Another important finding was that the frequency of secondary bacterial infections in patients who received immunosuppressive therapy was higher than in patients who did not receive immunosuppressive therapy and this was associated with increased mortality.

Cytokine storm syndrome is a hyperinflammatory condition characterized by increased cytokine levels and multiple organ failure. This hyperinflammatory response is shown as the most important cause of organ failure and mortality in COVID-19 patients and prevention of this hyperinflammatory response is considered one of the most important steps in the treatment (8,9). Corticosteroids, IL-6 and IL-1 inhibitors are the most commonly used agents for treating cytokine storm. However, the efficacy and safety of these drugs in the cytokine storm due to COVID-19 is still a matter of debate. In a meta-analysis involving 15,710 COVID-19 patients, it was shown that corticosteroid use does not have a positive effect on clinical recovery and mortality, and it was reported that one should be careful in terms of side effects (10). In another meta-analysis involving 20,197 COVID-19 patients, it was shown that although corticosteroid use increases the risk of secondary infection, it significantly reduces mortality (11). In the only randomized controlled study on the use of corticosteroids in COVID-19 patients, it was shown that corticosteroid use in severe COVID-19 patients reduces mortality by 35%, but there was no benefit in mild COVID-19 patients (12). In a meta-analysis including 5,776 patients evaluating the efficacy of tocilizumab use in COVID-19 patients, sufficient evidence could not be obtained regarding the clinical efficacy and safety of tocilizumab in COVID-19 patients (13). Similarly, Salvarani et al. (14) found that tocilizumab had no effect on clinical worsening in their randomized controlled study comparing patients treated and untreated with tocilizumab. Hamed et al. (15) showed that the concomitant use of corticosteroids and tocilizumab has no effect on mortality. In our study, we did not find any difference in mortality between the patients followed in the ICUs who received immunosuppressive therapy and the patients who did not receive immunosuppressive therapy. This situation may be related to the severity of the COVID-19 and the excess of comorbid diseases of the patients.

Giacobbe et al. (16) found that the use of tocilizumab and/or steroids in critically ill COVID-19 patients increases the frequency of hospital-acquired infections. van Paassen et al. (11), in their meta-analysis including 20,197 COVID-19 patients, showed that the use of corticosteroids increases the risk of secondary infections and that more antibiotics were needed in these patients. In another meta-analysis, it was reported that the frequency of secondary bacterial infections was higher in patients using tocilizumab, but this was not statistically significant (17). In our study, the frequency of secondary infections was higher in patients who received immunosuppressive therapy in ICUs, and this was associated with increased mortality. The most common secondary infection was in patients who received corticosteroid and tocilizumab together (42%).

Study Limitations

The study strengths are that the number of patients in the groups was sufficient to make an assessment and that the first and second outcomes of the treatments were evaluated on separate arms by evaluating all treatment arms separately. The most important limitation of our study was the retrospective analysis of the cases. For this reason, the groups could not be standardized and the APACHE-II and SOFA scores of the patients at admission to the ICU were different. This situation may affect the generalizability of our results.

Conclusion

In this single-center retrospective study, no difference in mortality was found between patients who received immunosuppressive therapy and those who did not, in patients followed up with critical COVID-19 pneumonia in the ICUs. The frequency of secondary bacterial infections in patients who received immunosuppressive therapy was higher than in patients who did not receive immunosuppressive therapy.

Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 45, date: 10.02.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Ö.A., İ.G.E.İ., K.C.; Concept - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Design - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Data Collection or Processing - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Analysis or Interpretation - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Literature Search - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Writing - Ö.A., İ.G.E.İ.

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Ionizing Radiation Exposure due to Medical Imaging in Hematopoietic Stem Cell Transplant Recipients

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ABSTRACT

Introduction: The study aimed to quantify the ionizing radiation exposure of patients with hematologic malignancy who underwent hematopoietic stem cell transplantation (HSCT).

Methods: This was a retrospective evaluation of the adult patients who underwent allogeneic or autologous HSCT for hematologic malignities in a single center between January 2016 and September 2020. All radiological imaging procedures involving ionizing radiation screened study participants. The study period covered both the pre- and post-transplantation phases. A typical cumulative effective dose (CED) was used to calculate the exposed ionizing radiation in units of millisieverts (mSv).

Results: A total of 120 patients (females 38.3%, mean age: 52.2±15.6 years) were included. Autologous HSCT was performed in 66 patients (55%), whereas 54 patients (45%) underwent allogeneic HSCT. Patients with acute myeloid leukemia and acute lymphoblastic leukemia comprised 53.7% and 31.5% of allogeneic HSCT, respectively. Autologous HSCT was mainly performed in patients with multiple myeloma (47%) and non-hodgkin lymphoma (34.8%). The median total CED was 11.85 mSv (interquartile range: 4.08-19.78). The median CED of allogeneic HSCT patients was significantly higher than that of the autologous HSCT group. The vast majority of the total CED (92.3%) comes from computed tomography imaging procedures. In the entire groups, 92 patients (76.7%) received a low dose (<20 mSv), whereas 26 patients (21.7%) received a moderate dose (>20-50 mSv) ionizing radiation.

Conclusion: One-third of all HSCT patients received a moderate ionizing radiation dose. Allogeneic HSCT patients had significantly higher median CED than autologous counterparts.

Keywords: Computed tomography, cumulative effective dose, ionizing radiation, radiation exposure, hematopoietic stem cell transplantation

Introduction

Hematopoietic stem cell transplantation (HSCT) is a therapeutic modality which is used in hematologic malignancies and several other disorders, including but not limited to aplastic anemia, sickle cell disease, and immunodeficiency syndromes (1). Advances in supportive therapy along with transplantation techniques have enabled a steep increase in the number of eligible patients for HSCT (2). For many hematologic malignancies, HSCT is the sole means of attaining a cure. However, despite providing a probable cure chance, HSCT has serious morbidities both in the peritransplant phase and in the long term (3). In a countless retrospective evaluation, between 2002 and 2015, the cumulative death rate among patients who underwent allogeneic HSCT for acute myeloid leukemia was 51% at five years. Although it changed according to when it occurred, the major causes of death were relapse of leukemia, graft-versus-host disease (GVHD), and infection, among others (4).

Both solid cancer and hematologic malignancy incidence increases after HSCT. One study spanning a 27-year-period reported that, among 3,372 patients who underwent HSCT, 137 patients (4%) developed a malignancy (5,6). Several risk factors impact the risk of developing a second malignancy after HSCT, such as myeloablative total body irradiation, younger age at the time of transplantation, chronic GVHD, and duration and intensity of immunosuppressive treatment (7-9). The causal association between low-dose radiation exposure from medical imaging studies and malignancies is more problematic to demonstrate. However, a large study involving 400,000 radiation workers revealed that 1-2% of deaths were from cancer was attributable to radiation exposure even at doses between 5 and 50 mSv (10).

HSCT patients undergo a host of radiological imaging procedures starting from the diagnosis of the primary malignancy for purposes of staging, preparation for HSCT, and after the transplantation for several complications. The cumulative dose of radiation exposure has been

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shown to be significantly increased in HSCT patients compared with the radiation exposure level in several solid organ transplant populations (11-14). However, there is a scarcity of knowledge regarding radiation exposure due to diagnostic imaging procedures in HSCT patients, and to the best of our knowledge, to date only one study evaluated the total cumulative radiation in patients who underwent HSCT (15). Thus, we retrospectively evaluated the ionizing radiation exposure of allogeneic and autologous HSCT patients in a single center.

Methods

This was a retrospective evaluation of the adult patients who underwent allogeneic or autologous HSCT for hematologic malignities in a single center between January 2016 and September 2020. During the specified period, we included all HSCT patients. Patients who underwent imaging procedures before admitting to our hospital were excluded because of the lack of data used to calculate the total radiation exposure.

This study approval by the İstinye University Clinical Research Ethics Committee [approval number: (2017-KAEK-120)/2/2021.G-102, date: 23.06.2021].

The necessary consent were obtained from our patients at their first admission to the hematology service so that their clinical data could be used for studies during treatment and follow-up.

All radiological imaging procedures involving ionizing radiation were detected from the patient charts and hospital radiologic imaging database system. These procedures included computed tomography (CT), direct X-rays, fluoroscopic examinations, and nuclear medicine imaging. The study period covered the time frame starting 30 days before transplantation and until the death of the patient or 60 days post-transplantation in surviving patients.

For each imaging procedure, a typical cumulative effective dose (CED) was used to calculate the exposed ionizing radiation in units of millisievert (mSv). Data reported by Mettler et al. (16) and Hart and Wall (17) were used to calculate CED for common radiology procedures such as CT and direct radiography. In case of missing and/or unavailable data, which allow the calculation of the CEDs, known minimum effective dose in mSv to calculate the total radiation dose was used by means of literature (18).

We categorized CEDs into the following groups as recommended by Nguyen et al. (13): low dose (0-20 mSv), moderate dose (20-50 mSv), high dose (50-100 mSv), and very high dose (>100 mSv).

HSCT Protocols (Conditioning Protocols)

- For autologous HCT: Multiple myeloma patients were treated with melphalan, and non-Hodgkin lymphoma (NHL) patients were treated with busulfan, etoposide, melphalan.

- For allogeneic HCT: Acute leukemias were treated with myeloablative chemotherapy (busulfan, cyclophosphamide) or nonmyeloablative therapy (fludarabine, busulfan, anti-thymocyte globulin) total body irradiation was not used in any conditioning regimen.

Statistical Analysis

To check the data in terms of distribution, Kolmogorov-Smirnov test and QQ plots were used. Non-normally distributed numeric variables were given as medians [interquartile range (IQR)]. Mann-Whitney U test was used to compare the two groups in terms of numeric data. Categorical variables were presented as numbers and percentages. To compare categorical variables, we used chi-square test. SPSS 24 (SPSS Inc., Chicago, IL) statistical software package was used for statistical analyses. Statistical significance was determined at p-value <0.05.

Results

General Characteristics of the Patients

A total of 120 patients (females 38.3%) were included in the study. The mean age of the patients was 52.2±15.6 years (minimum-maximum: 20-74 years). The most common primary hematologic diseases for which HSCT was performed were multiple myeloma (27.5%) and acute myeloid leukemia (25.8%). Of all HSCTs, autologous HSCT was performed in 66 patients (55%), whereas 54 patients (45%) underwent allogeneic HCT. Patients with AML and ALL constituted 53.7% and 31.5% of allogeneic HSCT, respectively. Autologous HSCT was mainly performed in patients with MM (47%) and NHL (34.8%).

Twenty-one (17.5%) patients had acute GVHD during the posttransplant phase. Overall, at 60 days post transplantation, 43 patients (35.8%) died. The mortality rate was significantly higher in the allogeneic HSCT group (53.7%) relative to the autologous HSCT group (21.2%) (p<0.001). The most common causes of death were infection (41.9%) and a combination of infection and GVHD (16.3%). Table 1 summarizes the general characteristics of the whole study group.

Radiologic Procedures and Cumulative Effective Radiation Dose

The median duration of the pre-transplantation phase was 122 days. During this phase, the median number of CT for each patient was 4 [(IQR), 1-6]. The maximum number of CTs for one patient was 37 in a patient with NHL; 20 before and 17 after the transplantation. The most common site for which CT was performed was thorax, followed by CT angiography. During the preparatory phase, the median number of chest X-rays was 12. During the first 60 days of the post-transplantation period, the median number of CTs and chest X-rays for one patient was 1 and 4, respectively (Table 2).

The median total CED was 11.85 mSv (IQR: 4.08-19.78). The median CED of allogeneic HSCT patients was significantly higher than that of the autologous HSCT group (Table 3 and Figure 1). The vast majority of the total CED (92.3%) comes from CT imaging procedures. Of all study patients, 40 (60.6%) had a total CED greater than 3 mSv. Only 2 patients had a total CED >50 mSv. In the entire group, 92 patients (76.7%) received a low dose (<20 mSv), whereas 26 patients (21.7%) received a moderate dose (>20-50 mSv) ionizing radiation. CED groups according to allogeneic and autologous HSCT groups are shown in Figure 2.

Discussion

The salient findings of this study can be summarized as follows: First, the median CED for HSCT recipients was 11.8 mSv. Second, only 2 of our

Table 1. Clinicodemographic characteristics of the entire study population

	Patients (n=120)
Age (years)	56.5 (41-64.8)
Sex; (n, %)	
Female	46 (38.3%)
Male	74 (61.7%)
BMI median (IQR)	26.5 (23.6-30.8)
Diagnostic; (n, %)	
Multiple myeloma	33 (27.5%)
Acute myelogenous leukemia	31 (25.8%)
Non-Hodgkin lymphoma	25 (20.8%)
Acute lymphoblastic leukemia	21 (17.5%)
Hodgkin's lymphoma	6 (5.0%)
Myelodysplastic syndrome	1 (0.8%)
Mycosis fungoides	1 (0.8%)
Plasma cell leukemia	1 (0.8%)
T-cell lymphoblastic leukemia	1 (0.8%)
The type of HCT; (n, %)	
Allogeneic HCT	54 (45%)
Autologous HCT	66 (55%)
GVHD; (n, %)	21 (17.5%)
Number of deaths; (n, %)	43 (35.8%)
Cause of death	
Infection	18 (41.9%)
GVHD + infection	7 (16.3%)
Relapse	5 (11.6%)
GVHD	4 (9.3%)
Engraftment failure	2 (4.6%)
Unknown	7 (16.3%)

IQR: Interquartile range, HCT: Hematopoietic cell transplantation, GVHD: Graft-versus-host disease

patients had a high dose, which was defined as a CED between 50 and 100 mSv. Third, the vast majority of the CED originated from computed tomographic imaging procedures. Fourth, patients who underwent allogeneic HSCT had significantly higher CED compared to patients who underwent autologous HCT.

Although recently several studies evaluated the amount of ionizing radiation exposure in various patient groups (19-22) along with the general population, some of the most vulnerable patient groups in terms of secondary cancer development, including transplant recipients, have been ignored to some extent. Some authors have even discussed the potential radiation dose for a middle-aged person just from cancer screening procedures and advised caution in this regard (23).

This relative negligence in terms of lack of studies investigating ionizing radiation exposure in transplant recipients may be due to the already increased mortality risk of these patients from more readily apparent causes such as infection and GVHD. These multiple and more palpable threats to the well-being of the transplant recipients might delegate the awareness of the harmful effects of radiation to a lower point in the list of priorities.

Table 2. Number of radiological imaging procedures involving ionizing radiation and cumulative effective doses in the whole patient group

	Patients (n=120)
Duration of the HCT preparation phase (days)	122 (64.3-174.5)
Number of procedures involving ionizing radiation	
Pre-transplantation	
Computed tomography	4 (1-6)
CT angiography	1 (1-1)
Thorax	2.5 (1-4)
Upper abdomen	0 (0-1)
Lower abdomen	0 (0-1)
Cranial	0 (0-0)
Neck	0 (0-0)
Chest X-ray	12 (7-21)
PET	
Vertebra	-
Post-transplantation	
Computed tomography	1 (0-3)
Chest X-ray	4 (2-8)
Cumulative effective dose from computed tomography (mSv)	10.50 (3.36-18.31)
Cumulative effective dose from conventional radiography (mSv)	0.84 (0.49-1.38)
Total cumulative effective dose (mSv)	11.85 (4.08-19.78)

HCT: Hematopoietic cell transplantation, PET: Positron emission tomography, mSv: Millisieverts

Several studies of solid organ transplant recipients such as heart and kidney revealed much higher doses of ionizing radiation exposure than normally allowed and that of patients who had chronic medical conditions (14,24-27). Solid organ transplantations also entail a preparatory phase during which several radiological procedures are undertaken to evaluate the disease burden and make necessary plan for the transplant procedure. However, HSCT differs from solid organ transplantation crucially; that is HSCT requires conditioning, which is carried out in some patients with the use of whole-body irradiation in addition to myeloablative chemotherapy (28). This therapeutic irradiation significantly increases the CED of a patient in a very short period. In our study, none of the patients had total body irradiation as part of the conditioning regimen. Thus, the lack of radiation in conditioning might account in part for relatively lower CED values in our patients.

Patients with HSCT have a relatively high mortality rate after the transplantation procedure (4). Secondary cancer development is as common in HCT patients as in solid organ recipients (29). Despite the high vulnerability of this special population, as far as we know, only one study to date has investigated the amount of ionizing radiation in HCT patients.

Battiwalla et al. (15) evaluated 66 allogeneic HSCT patients in a retrospective cohort study. The authors covered a period of 230 days; 30 days pre-transplantation and 200 days post-transplantation. The

Table 3. Cumulative effective doses in the allogeneic and autologous HSCT groups

	Groups (n=120)		
	Allogeneic HSCT (n=54)	Autologous HSCT (n=66)	p-value
Duration of the HCT preparation phase (days)	120 (90.8-247.8)	127.5 (46.8-173.5)	0.316*
Cumulative effective dose from computed tomography (mSv)	13.9 (9.2-22.23.0)	5.6 (0-14.1)	<0.001*
Cumulative effective dose from conventional radiography (mSv)	1.2 (0.8-1.9)	0.6 (0.4-1.0)	<0.001*
Total cumulative effective dose (mSv)	15.8 (10.2-25.0)	6.3 (0.6-14.6)	<0.001*

*Mann-Whitney U test, HCT: Hematopoietic cell transplantation, HSCT: Hematopoietic stem cell transplantation, mSv: Millisieverts

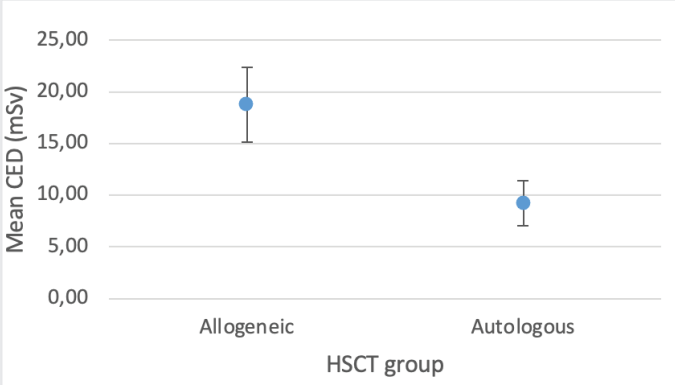

Figure 1. Simple error bars showing the mean cumulative effective dose in allogeneic and autologous hematopoietic stem cell transplantation. Error Bars: 95% confidence interval
CED: Cumulative effective dose, HSCT: Hematopoietic stem cell transplantation, mSv: Millisieverts

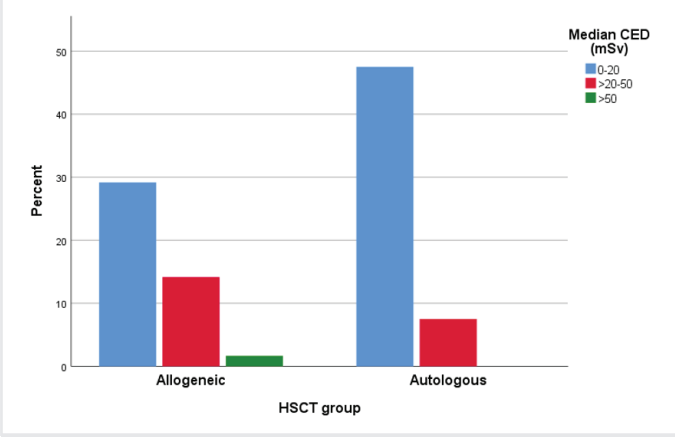

Figure 2. Clustered bar chart depicting median CED groups in allogeneic and autologous HSCT patients
CED: Cumulative effective dose, HSCT: Hematopoietic stem cell transplantation, mSv: Millisieverts

median cumulative effective radiation dose from diagnostic radiological procedures was found to be 92 mSv (range: 1.2-300). This median value is much larger than the median value of our patients [11.85 mSv (IQR, 4.08-19.78)]. Several factors can explain this discrepancy. First, we calculated radiation exposure until the 60th day after transplantation. Second, none of our patients underwent total body irradiation as part of the conditioning regimen. Third, the mortality rate in our cohort was much higher compared to the cohort of Battiwalla et al. (15) hence limiting the additional doses of ionizing radiation. The authors did not find an impact of radiation exposure on the short-term clinical outcomes. We did not evaluate the clinical outcome and radiation exposure association in our study with the presumption that radiation-induced cancer development is a late effect. We, are of course, aware of the fact that radiation exposure affects several other organ systems, including, the heart and immune system (30). Considering the increased burden of cardiovascular disease in HSCT recipients (31), new research should also explore the additional cardiac risk attained by ionizing radiation in HSCT patients.

It is well appreciated that as the dose of radiation exposure increases, the risk of secondary malignancy also increases well (32-35). Moreover, this association starts at relatively low doses of ionizing radiation exposure. Eisenberg et al. (33) reported that for every 10 mSv CED, cancer risk over 5 years showed a 3% risk increase. In a large multinational study that recruited radiation workers, Cardis et al. (10) found that workers were exposed to an average of 20 mSv ionizing radiation and there existed a positive correlation with cancer-related mortality and exposure dose. Interestingly, the cancer risk seemed to start at a dose as low as 5 mSv (36). Thus, even low-level radiation exposure might can contribute to secondary malignancy development; radiologic studies should be conducted cautiously.

Most of the total radiation dose (88%) has come from CTs in the study by Battiwalla et al. (15). Similarly, 92.3% of the total CED was due to CTs in our study. Thus, in our opinion, physicians should be particularly vigilant for the performance of repeated CT imaging in their patients if they limit the radiation exposure in their patients.

All patients in the study by Battiwalla et al. (15) underwent full-match allogeneic transplantation. However, we included both allogeneic and autologous HSCT patients in this study. Interestingly, the median CED was significantly higher in allogeneic HSCT patients compared with autologous HSCT patients. The duration of pre-transplantation phase was not different between the groups. The mortality rate was significantly higher in the allogeneic HSCT group relative to the autologous HSCT group (p<0.001). Since most of the ionizing radiation exposure comes from the pre-transplantation period, we think that the nature of the underlying hematologic diseases dictated the need for radiological procedures and thus created a significant difference between the groups in terms of median CED.

Study Limitations

First, this was a relatively small study conducted in a single center. Thus, our findings are difficult to extrapolate for other centers since conditioning regimens, and patient characteristics vary across different centers. Second, we could not obtain information regarding the exact timing of the radiological procedures. Though we knew that the imaging

procedures were certainly performed during the study period, we did not provide data with respect to the pre- or post-transplantation timing of the radiological procedures. Thirdly, during the follow-up of patients after the transplantation, we did not detect any malignancy but probably the time was probably not long enough to detect secondary malignancies.

Conclusion

This study was the second but the largest study investigating CED in patients who underwent HCT. Moreover, for the first time in the literature, we reported that patients who underwent allogeneic HSCT received significantly more ionizing radiation compared with patients who underwent autologous HCT. More studies are clearly needed to elucidate whether this increased exposure to ionizing radiation affects the future development of malignancy in HSCT recipients.

Ethics Committee Approval: This study approval by the İstinye University Clinical Research Ethics Committee [approval number: (2017-KAEK-120)/2/2021.G-102, date: 23.06.2021].

Informed Consent: The necessary consent were obtained from our patients at their first admission to the hematology service so that their clinical data could be used for studies during treatment and follow-up.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - S.H.A., A.T.; Concept - S.H.A., A.T.; Design - S.H.A., I.Y.; Data Collection or Processing - S.H.A., I.Y., A.T.; Analysis or Interpretation - S.H.A., I.Y.; Literature Search - S.H.A., I.Y., A.T.; Writing - S.H.A.

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The Effect of Postoperative Mild Varus Deformity on Functional Outcome Scores after Primary Total Knee Arthroplasty in Patients with Varus Osteoarthritis

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ABSTRACT

Introduction: This study evaluated the effect of both postoperative residual varus alignment and the amount of correction in lower limb alignment (LLA) on postoperative functional outcomes of total knee arthroplasty TKAs in patients with preoperative varus deformity.

Methods: Two-hundred and fifty-two knees of 209 patients who underwent a TKA for treating varus gonarthrosis were retrospectively reviewed in the study. Patients were then divided into the three groups according to the postoperative hip-knee-ankle angle (HKAA): the neutral group (NG) (HKAA: 183°-177°); the mild varus group (HKAA: 176.9°-174°); and the severe varus group (HKAA <174°). Patients were also categorized into the three groups based on the amount of correction in LLA; group A (<5); group B (5° to 10°), and group C (>10°). Pre- and post-operative functional outcomes were compared among the groups.

Results: There were no significant differences in the postoperative Knee Society Score (KSS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and visual analog scale (VAS) scores between the mild and NGs (p=0.99, p=0.62, and p=0.33, respectively). The severe group showed lower postoperative KSS, WOMAC, and higher VAS scores compared to other two groups (p<0.001, p<0.001, and p<0.001, respectively). No significant differences were observed in the postoperative knee flexion and extension deficits among the three groups (p=0.79 and p=0.3). Patients with correction in LLA of >10° had higher WOMAC and lower VAS scores than the other patients (p=0.008 and p=0.002, respectively).

Conclusion: Postoperative mild varus deformity is not associated with poorer clinical and functional outcomes; however, a postoperative severe varus deformity following TKA can cause a significant deterioration in postoperative clinical and functional outcomes in patients with preoperative varus osteoarthritis.

Keywords: Total knee arthroplasty, residual varus, mild varus, varus deformity, lower limb alignment, functional outcomes

Introduction

Lower limb alignment (LLA) is one of the critical determinants of successful outcomes after total knee arthroplasty (TKA), and there is a widely accepted opinion that the neutral mechanical axis of the lower limb (0°±3°) in the coronal plane after TKA contributes to good functional outcomes and to implant longevity (1,2). If the neutral alignment is not achieved postoperatively, increased load acting on the tibial insert and component may lead to earlier polyethylene wear, implant loosening, and poorer clinical outcomes (3-6). Otherwise, improvements in the design and manufacture of prostheses have potentially reduced the risk of wear and implant loosening secondary to component malposition and lower limb malalignment (7). Nonetheless, research findings have been inconsistent regarding the effect of postoperative LLA on the clinical and functional outcomes of TKAs (8,9).

In the existing literature, some studies have shown a significant association between lower limb malalignment and poor functional outcomes following TKA (5,6) whereas other studies have reported that a mild postoperative varus alignment in the coronal plane does not adversely affect postoperative outcomes (8,10). Furthermore, previous literature has found that approximately 30% of the Asian population has a constitutional varus deformity (11). Accordingly, neutral alignment after TKA may not be normal in some individuals, and functional results and patient satisfaction may be lower with neutral alignment in such patients. Moreover, a significant number of bone resections and soft tissue releases may be needed to correct the preoperative lower limb deformity back to neutral alignment during TKA (3,11). However, according to our literature review, no consensus exists to date regarding the effect of excessive alteration of the bone stock and ligament balance in the knee joint on postoperative functional outcomes following TKA.

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The aim of the present study was to evaluate the impact of both postoperative residual varus deformity and the amount of correction in LLA on postoperative functional outcomes of TKAs in patients preoperative varus deformity.

Methods

Our study is a retrospective, single center outcome study which was conducted at an education and training hospital and has institutional review board-approval. Signed informed consent form was routinely obtained preoperatively from the patients included in the study. The study was approved by the University of Health Sciences Turkey, Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 129-2021, date: 01.12.2021).

Patients who underwent primary TKA for treating varus knee osteoarthritis between January 2016 and April 2019 were retrospectively reviewed. Preoperative varus knee deformity was defined as hip-knee-ankle angle (HKAA) <177°. Inclusion criteria of our study were 1) a diagnosis of primary knee osteoarthritis, 2) preoperative knee varus deformity, 3) undergoing a posterior cruciate retaining prosthesis, 4) full medical records and radiographic images stored in the hospital Picture Archiving and Communication System (Picture Archiving and Communication System), and 5) being eager to participate in the study. The exclusion criteria of our study were 1) secondary knee osteoarthritis (rheumatologic disorder, trauma, etc.), 2) preoperative valgus knee deformity, 3) a history of previous knee surgery such as high tibial osteotomy or arthroscopic debridement, 4) concomitant chronic disease (chronic renal disease, severe heart disease, severe dementia, etc.), 5) severe preoperative flexion contracture of >20°, 6) lost to follow-up the following surgery, 7) inadequate and unacceptable radiographic imaging for the measurements, and 8) not wanting to participate in the study.

Study Population and Protocol

A total of 228 patients (271 knees) were evaluated on the basis of the above eligibility criteria. After excluding 19 knees of 19 patients (3 were lost to follow-up, 8 underwent previous knee surgery, 2 had unacceptable radiographic imaging for the radiologic measurements, and 6 had concomitant chronic disease), the remaining 252 knees (43 bilateral) of 209 patients (37 males, 172 females) were included in the study.

The study was conducted in two stages. First, to assess the impact of postoperative residual varus deformity on postoperative clinical and functional outcomes of TKAs, patients were divided into one of the three subgroups according to the postoperative HKAA: the neutral group (NG), patients with a neutral HKAA (183°-177°); the mild varus group (MVG), patients with a mild varus deformity (HKAA: 176.9°-174°); and the severe varus group (SVG), patients with a severe varus deformity (HKAA <174°). Second, to determine the impact of the amount of correction in LLA following TKA on ultimate knee functions, patients were also categorized into the three subgroups based on the amount of correction LLA following TKA; group A (<5); group B (5° to 10°), and group C (>10°). Pre- and post-operative functional outcomes were compared among the groups.

Functional Outcome Measures

The Knee Society Score (KSS) (12), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score (13), visual analog scale (VAS) (14), and knee range of motion (ROM) were calculated and measured preoperatively and been recorded in the patient files. Afterwards, the patients included in the study were called for KSS, WOMAC and VAS score calculations and ROM measurements for the final follow-up. The ROM of the knee joints were measured using a universal standard goniometer. All measurements were performed by senior orthopedic surgeons in our department.

Radiographic Outcome Measures

Varus angle was measured using HKAA, which measures the angulation between the mechanical axes of the femur and tibia (3,14), on immediate preoperative and routine postoperative 6-week follow-up orthoroentgenograms (anteroposterior full length, full weight-bearing standing digital radiography) (13) (Figure 1). All the radiographic measurements were performed by two orthopedic surgeons who were blinded to the clinical information of the patients. The measurements were recorded twice on the radiographs over a 2-week period. Intraclass correlation coefficients were used for evaluating the intra- and interobserver reliability of all radiographic assessments. The radiographic measurement was also assessed with one decimal. Orthoroentgenograms were obtained using a well-established, conventional approach that involved taking three radiographic exposures centered over the hip, knee, and ankle joints, then combining them into a single film to reduce magnification error (15).

Surgical Technique

In all patients, the skin incision was made at the midline of the knee and medial parapatellar arthrotomy was performed. After the patella

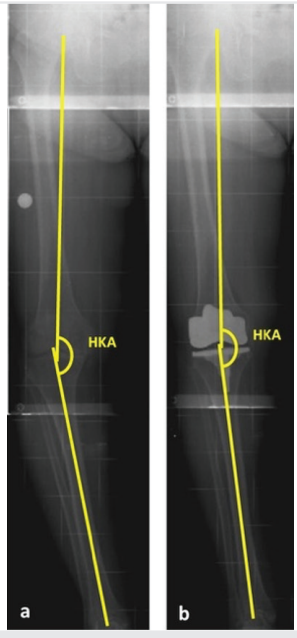

Figure 1. The measurement of hip-knee-ankle angle on full-leg radiographs (a) preoperative measurement, (b) postoperative measurement.
HKA: Hip-knee-ankle

was retracted laterally, hoffa-anterior cruciate ligament and menisci were excised. Femoral bone cuts were first performed, and then osteophytes were removed from the femoral notch. The rotation of the femoral component was identified using anatomical landmarks, as the posterior condylar axis, Whiteside's line (the anteroposterior axis), and the anatomical transepicondylar axis. The intramedullary guide was used for femoral bone cuts with a 6° of valgus angle. After femoral bone cuts and femoral component trials were performed, the proximal tibia was moved anteriorly, and surgery was continued with tibial preparation. The extramedullary tibial guide was centralized using the center of the tibial intercondylar eminence and true center of the ankle-second metatarsal as proximal and distal landmarks. All femoral and tibial components were implanted with a cemented posterior cruciate retaining TKA. None of the patients underwent patellar component implantation; peripatellar osteophytes were removed, and patellar denervation was performed.

Postoperative Rehabilitation Protocol

Postoperative rehabilitation was performed immediately, and a minimum of 90° knee flexion was obtained before discharge. Patients were scheduled for postoperative follow-up at the 3rd week for a wound check, at the 6th week, at 3, 6, 9, and 12 months, and after 1-year intervals, routinely.

Statistical Analysis

Statistical analysis was performed using SPSS ver. 21.0 (IBM Corp, 2011, Armonk, New York). The Shapiro-Wilk test was used for normality check. One-way ANOVA was used to compare the continuous variables among the three groups, and Tukey's multiple-comparison test was used for the post hoc pairwise comparisons if the values were in normal distribution. The Kruskal-Wallis test was used to compare the continuous variables among the three groups, and Tamhane's multiple-comparison test was used for the post-hoc pairwise comparisons if the values were not in normal distribution. P<0.05 was considered as statistically significant.

Results

Baseline Characteristics

Overall, of 209 patients (252 knees; 186 right side and 66 left side), were 29 males and 180 females. Their mean age was 66±7.6 years, and the mean follow-up was 56±9.7 months. The mean pre- and post-operative HKAAs were 169°±4.5° and 177°±2.3°, respectively (Table 1). The mean amount of correction in LLA following TKA was 7.1±5 degrees.

The Impact of Postoperative Residual Varus Deformity

There were 111 knees (92 patients; 12 male, 80 female) in the NG, 114 knees (102 patients; 19 male, 83 female) in the MVG, and 27 knees (27 patients; 10 male, 17 female) in the SVG. The mean age of the patients were 66.1±7.6 years in the NG, 66.4±8.0 years in the MVG, and 66.3±5.6 years in the SVG (p=0.95). The average follow-up period was 54.9±10.6 months in the NG, 57.5±8.8 months in the MVG, and 58.4±9.1 months in the SVG (p=0.21) (Table 2). Within group comparisons revealed a substantial improvement in all clinical outcomes compared to the preoperative baseline scores for all three groups.

Table 1. Demographic data of all patients

Number of patients (M/F)	209 (29/180)
Bilateral TKA (M/F)	43 (8/35)
Age (years)	66.3±7.6
The follow - up period (months)	56.4±9.7
Preoperative HKA (degrees)	169.3±4.5
Postoperative HKA (degrees)	176.5±2.3
The angle of alignment correction (degrees)	7.16±5
Preoperative extension deficit (degrees)	6.5±6.5
Preoperative knee flexion (degrees)	100.4±16.7
Postoperative extension deficit (degrees)	0.3±1.3
Postoperative knee flexion (degrees)	107.8±13.5
Preoperative KSS	32.2±8.9
Postoperative KSS	87.6±9.9
Preoperative WOMAC	27.8±9.4
Postoperative WOMAC	84.1±13.1
Preoperative VAS score	8.3±1.2
Postoperative VAS score	0.9±1.2

M: Male, F: Female, HKA: Hip-knee-ankle, KSS: Knee Society Score, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: Visual analog scale

Whereas no significant differences were determined in preoperative KSS, WOMAC, and VAS scores among the three groups, postoperative values significantly varied among the groups (p<0.001 for each outcome measure). In pair-wise comparisons of the subgroups, there were no considerable differences in all outcome scores between groups neutral and mild and groups mild and severe. Otherwise, the mean postoperative KSS and WOMAC were significantly lower and VAS significantly higher in the SVG than in the NG (p<0.001 for each score). While no significant difference was observed in the preoperative HKAA among the three groups, the mean postoperative HKAA significantly differed among the groups, which was 179°±0.9° in the NG, 175°±0.9° in the MVG, and 172°±1.2° in the SVG (p<0.001) (Table 3) (Figure 2-4).

No significant differences were observed in pre-and post-operative knee flexion ROM and extension deficits in neither between groups nor pair-wise comparisons (p>0.05 for each measure).

The Impact of the Amount of Correction in LLA

There were 79 knees (69 patients; 10 male, 59 female) in group A (<5°), 102 knees (87 patients; 13 male, 74 female) in group B (5° to 10°), and 71 knees (61 patients; 8 male, 53 female) in group C (>10°).

No significant differences were found in preoperative KSS, WOMAC, and VAS scores among the three groups (p>0.05 for each outcome measure). In the postoperative assessment, there were significant differences in WOMAC (p=0.08) and VAS (p=0.02) scores among the three groups, but no remarkable difference was observed in KSS (p=0.28) (Table 4).

In pair-wise comparisons of the subgroups, all the outcome scores of groups A and B were statistically similar. There was no significant difference for KSS in pair-wise intergroup comparison. Otherwise, the mean postoperative WOMAC was significantly higher and VAS significantly lower in group C than in the group A (p=0.006 and p=0.002;

Table 2. Comparisons of pre- and postoperative characteristics of the patients in different groups according to postoperative lower limb alignment

	Normal (n=111)	Mild varus (n=114)	Severe varus (n=27)	p-value
Age (years)	66.1±7.6	66.4±8.0	66.3±5.6	0.95
The follow-up period (months)	**54.9±10.6**	**57.5±8.8**	**58.4±9.1**	0.21
Preoperative HKA (degrees)	169.8±4.4	168.9±4.7	169.7±4.2	0.43
Postoperative HKA (degrees)	178.6±0.9	175.4±0.9	172.3±1.2	**<0.001**
The angle of alignment correction (degrees)	8.9±4.4	6.5±4.8	2.7±4.7	**<0.001**
Preoperative extension deficit (degrees)	6.7±6.4	6.2±6.7	7.0±8.0	0.42
Preoperative knee flexion (degrees)	99.8±16.9	100.1±17	104.4±14.2	0.79
Postoperative extension deficit (degrees)	0.1±0.8	0.4±1.7	0.2±1.0	0.53
Postoperative knee flexion (degrees)	108.7±13.6	107.4±13.4	105.7±13.9	0.30
Preoperative KSS	31.1±8.3	33.6±9.9	31.0±6.5	0.9
Postoperative KSS	88.8±8.9	88.7±7.3	77.9±16.0	**<0.001**
Preoperative WOMAC	27.8±9.4	27.6±9.7	28.2±7.9	0.95
Postoperative WOMAC	86.2±11.9	84.6±13.0	73.8±13.9	**<0.001**
Preoperative VAS score	8.4±1.2	8.3±1.2	8.3±0.8	0.85
Postoperative VAS score	0.7±1.0	0.9±1.2	1.7±1.4	**<0.001**

The Kruskal-Wallis test was used for comparisons. HKA: Hip-knee-ankle, KSS: Knee Society Score, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: Visual analog scale

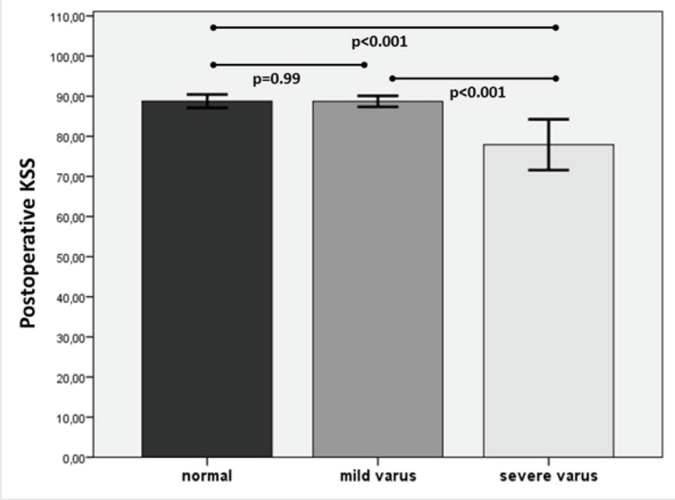

Figure 2. Graph showing differences in postoperative KSS scores between the three groups categorized according to postoperative hip-knee-ankle. The severe varus group showed significantly lower values compared with mild varus and neutral group. Values are shown as mean ± standard deviation
KSS: Knee Society score

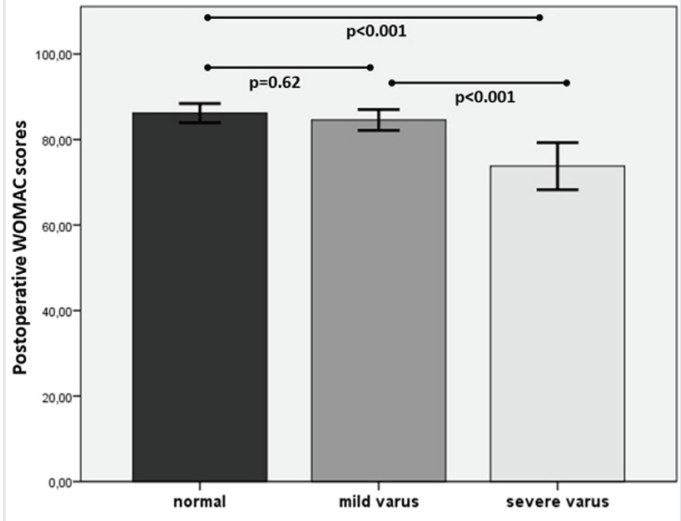

Figure 3. Graph showing differences in postoperative Western Ontario and McMaster Universities Osteoarthritis Index scores between the three groups categorized according to postoperative hip-knee-ankle. The severe varus group showed significantly lower values compared with mild varus and neutral group. Values are shown as mean ± standard deviation
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

respectively), but we could not detect any significant difference between groups C and B for WOMAC and VAS scores (p=0.09 and p=0.27; respectively). The ICCs for intra- and interobserver reliability were >0.85 (range: 0.86-0.97) for all radiographic measurements.

Discussion

The most important finding of the current study was that patients with postoperative severe varus alignment (HKA: <174°) following TKA had significantly lower functional outcomes compared to patients with postoperative neutral (HKA: 180±3°) and mild varus (174°≤ HKA: <177°) alignment. Nonetheless, similar favorable clinical outcomes were observed between patients with neutral and those with mild varus alignment. Another important finding was that the correction in LLA of >10° following TKA is associated with better clinical outcomes based on the data indicating higher WOMAC and lower VAS scores compared to patients with <10° of LLA corrections.

The neutral LLA has been considered the gold standard of TKA (15). Malalignment could cause an imbalance of contact forces on the tibial component, accelerated wear of the polyethylene insert, an increased risk of osteolysis, and further implant loosening (16). Furthermore, previous research found poorer clinical and functional results

secondary to malalignment of TKAs (5,9,17). 3° deviations from the neutral alignment were suggested as the critical point in TKA affecting the postoperative clinical outcomes (2,5). However, recent studies have reported that revision rates and clinical outcomes were similar between patients with neutral LLA and those with mild varus malalignment after TKA (18-20), supporting the findings we present here.

Salzman et al. (21) included 172 TKAs in their study and showed that postoperative residual varus alignment did not adversely affect the functional scores of TKA in patients with varus-type osteoarthritis. A study by Nishida et al. (3), which included 220 TKAs, found that postoperative mild varus and neutral mechanical alignment of the lower limb both led to excellent functional outcomes, and the researchers emphasized that postoperative mild varus LLA is acceptable following TKA for varus-type osteoarthritis. Moreover, Schiffner et al. (10) stated that leaving a residual varus alignment after TKA in patients with varus osteoarthritis leads to better functional outcomes than postoperative neutral alignment. Additionally, Vanlommel et al. (20) concluded that if the alignment is retained in the mild varus after TKA, the functional scores could be better than patients with an alignment correction to neutral. Our findings support the notion that postoperative residual varus alignment does not compromise clinical and functional outcomes following TKA as long as severe varus alignment is avoided.

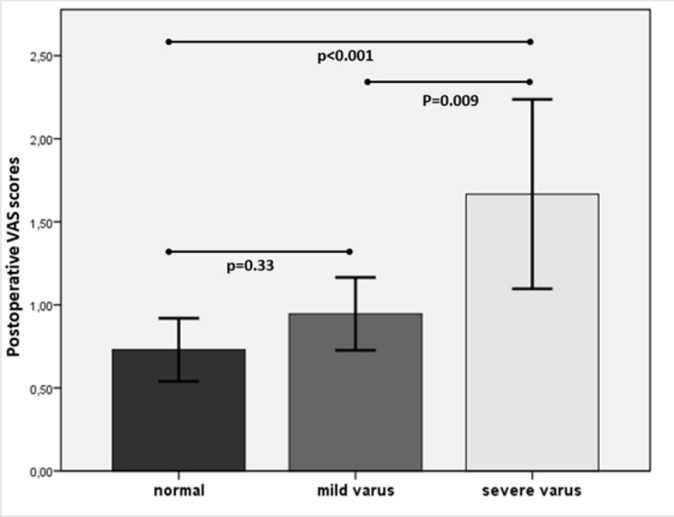

Figure 4. Graph showing differences in postoperative visual analog scale scores between the three groups categorized according to postoperative hip-knee-ankle. The severe varus group showed significantly higher values compared with mild varus and neutral group. Values are shown as mean ± standard deviation
VAS: Visual analog scale

LLA correction is also performed during TKA, and the amount of correction in LLA has been shown to be correlated with the severity of preoperative varus deformity (22). The current study has shown that the correction in LLA of >10° following TKA is associated with better clinical outcomes in terms of postoperative WOMAC and VAS scores, but not KSS. Actually, postoperative KSS showed higher trend in the patients with LLA correction of >10° but was not statistically significant. The reason for this absence of statistical difference could be that the KSS evaluates the pain, knee stability, and ROM. However, WOMAC primarily considers the knee functions according to the daily living activities. The knee ROM is taken into account once in KSS, despite several considerations in the WOMAC scoring system, as several daily activities are highly associated with knee ROM. Thus, the knee ROM affects the WOMAC score many times over KSS. In contrast to our findings, Vanlommel et al. (20) found that the amount of deformity correction has no significant impact on the clinical scores of TKAs.

Study Limitations

Our study has some limitations. First, the study had a relatively small number of TKAs, and the patients counted in the study did not have a long-term follow-up. Second, this study was a retrospective nature,

Table 3. Intergroup comparisons of postoperative clinical outcome values according to postoperative lower limb alignment

	Neutral vs mild	Mild vs severe	Neutral vs severe
Postoperative KSS	0.99	<0.001	**<0.001**
Postoperative WOMAC	0.61	0.002	**<0.001**
Postoperative VAS score	0.33	0.009	**<0.001**
Postoperative extension deficits	0.28	0.72	0.98
Postoperative knee flexion	0.73	0.84	0.56

KSS: Knee Society Score, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: Visual analog scale

Table 4. The comparisons of pre- and postoperative clinical scores for different amounts of deformity correction

	<5 degrees (n=79)	5-10 degree (n=102)	>10 (n=71)	p-value	<5° vs 5-10°	<5° vs >10°	5-10° vs >10°
Preoperative KSS	32.0±8.5	32.8±10.4	31.6±6.9	0.9	0.84	0.95	0.67
Postoperative KSS	86.2±10.3	87.9±9.1	88.7±10.4	0.28	0.48	0.28	0.87
Preoperative WOMAC	26.3±5.4	28.3±10.7	28.5±10.5	0.95	0.32	0.34	0.98
Postoperative WOMAC	81.3±12.8	83.7±15.2	87.9±8.6	**0.008**	0.43	**0.006**	0.09
Preoperative VAS score	7.9±1.2	8.7±1.1	8.4±1.1	0.85	0.63	0.78	0.89
Postoperative VAS score	1.3±1.3	0.9±1.1	0.6±1.0	**0.002**	0.06	**0.002**	0.27

The Kruskal-Wallis test was used for comparisons. KSS: Knee Society Score, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: Visual analog scale

and thus patients' data were collected from the registry. Third, the knee ROMs were measured using a hand-goniometer, a digital and calibrated goniometer could be more accurate for measurements of knee ROM with decimals. Fourth, implant survival of the patients counted in this study was not assessed. Finally, there are several factors that affect postoperative clinical outcome scores after TKA, and only postoperative LLA and correction in LLA were analyzed. The other factors such as bone resection flexion-extension-ligament balance, important clinical (e.g., BMI, comorbidities, preoperative opioid use, smoking, etc.), and psychologic (e.g., resilience, pain catastrophizing, depression, etc.) factors were not analyzed. Despite these limitations, analyzing the postoperative clinical results of the patients in the study is strength, by grouping according to both postoperative HKAA and the amount of deformity correction. Studies with long-term follow-up, homogenous patient groups, and assessing implant survival are warranted for future research.

Conclusion

Postoperative residual mild varus alignment does not compromise clinical and functional outcomes following TKA in patients with preoperative coronal-plane varus deformity. Nonetheless, postoperative severe varus deformity could cause poor clinical and functional outcomes following TKA in such patients.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 129-2021, date: 01.12.2021).

Informed Consent: Signed informed consent form was routinely obtained preoperatively from the patients included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.E., M.Er., M.Y.; Concept - M.E.; Design - M.E., M.Er.; Data Collection or Processing - M.E., M.D.; Analysis or Interpretation - M.E.; Literature Search - M.E., M.Er.; Writing - M.E., M.D., M.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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The Effect of Diagnosis and Surgical Margin Safety on the Success of Treatment in Endometriomas after Cesarean Section

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ABSTRACT

Introduction: In our study, patients who applied for abdominal wall mass and pain after cesarean section and were examined and treated and diagnosed endometriosis were evaluated in terms of age, body mass index (BMI), number of cesareans, clinical signs, size of endometriosis and surgical characteristics, as well as therapy and results.

Methods: January 2001-December 2021 in our clinic after cesarean section, surgery due to a painful mass in the abdominal wall and pathologically diagnosed endometriosis cases were retrospectively investigated. Age, number of cesareans, clinical signs, size of endometriosis and surgical characteristics and therapy results were recorded. Four patients were diagnosed with endometriosis with a tru-cut biopsy. All patients underwent primary mass excision.

Results: A total of 14 patients were identified. The average age of the patients was 35.9 and the average BMI was 26.81. All patients were admitted with a painful mass at the cesarean site. Only four patients had multiple cesarean sections. Ultrasonography and abdominal computed tomography were evaluated. Desmoid tumor, foreign body reaction, granuloma, abscess and endometriosis were identified in their preliminary diagnosis. Endometriosis was established by tru-cut biopsy in four patients. Primary mass excision was performed for all the patients. In one patient, prolene mesh repair was performed, while in other patients primary repair was performed. In all patients, pathological diagnosis was reported as endometriosis ekstarna.

Conclusion: The diagnosis of endometriosis should be kept in mind when diagnosing patients with pain and/or mass complaints at the site of surgery after cesarean section.

Keywords: Endometriosis, desmoid tumor, hematoma, abdominal pain

İntroduction

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity (1). It has been reported that the incidence of endometriosis in women of reproductive age is around 5-15% (2). Endopelvic endometriosis; it develops more frequently in different structures such as ovaries, uterosacral ligaments, pelvic peritoneum, recto-uterine pouch, cervix, vagina and round ligament. It is rarely observed in extrapelvic structures such as the abdominal wall, urinary and gastrointestinal tract, skin, brain and lungs (3,4). Many theories have been proposed regarding the development of endometriosis. These theories include retrograde menstruation, metaplasia, venous-lymphatic metastasis, and mechanical implantation into the incision scar during surgery. The most common operations leading to endometriosis include hysterectomy, cesarean section, amniocentesis and episiotomy (5). The most common finding is palpable painful mass at the cesarean scar site during menstruation (6). The patient's history and physical examination are the most valuable steps for diagnosis. Various examination methods such as ultrasonography (USG), computed tomography (CT), magnetic resonance, Doppler sonography and fine needle biopsy can be used as advanced examinations (7,8). Surgical resection of endometriosis externa remains the treatment of choice to prevent recurrence of the disease. The resection of a mass with a surgical margin of at least 10 mm is accepted as the best clinical practice (9,10).

Methods

This study was conducted in accordance with the recommendations of the Declaration of Helsinki governing biomedical research in humans. The study was approval by the İstanbul Atlas University Non-Interventional Scientific Research Ethics Committee (approval number: E-22686390-050.01.04-8485, date: 28.09.2021). Informed consent was obtained from the patients regarding the study.

Between January 2001 and December 2021, patients with a history of cesarean section, who were operated for mass in the pfhanensteil incision area, and whose pathological diagnosis was endometriosis were retrospectively analyzed. Age, BMI, clinical complaints, history of physical examination findings, diagnostic features, treatments and post-

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operative follow-ups and pathological features of the patients were evaluated.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24.0 for Windows (IBM, Armonk, NY). Continuous variables are presented as mean ± standard deviation, whereas categorical variables were shown as numbers and percentages

Results

A total of 14 patients were included in the study. The mean age of the patients was 35.9 (28-44). BMI indexes were found to be 26.81 kg/m^2 on average.

Most patients 71.43% (n=10) were admitted to the hospital with a painful mass with a cyclic course that became evident during menstruation at the site of the old cesarean section, while the remaining 28.57% (n=4) presented to the hospital because of palpable stiffness. Four patients had a history of more than one section. A hard painful mass was detected in the section area as an examination finding in all patients. It was stated that all the masses were single and isolated and adhered to the surrounding tissue. The masses were also evaluated with radiological diagnostic tools such as USG and CT. While only USG was performed in four patients, only CT was performed in 10 patients. In one patient, both USG and CT were performed.

The diameter of the masses was found to be 3.48 (1.4-6.0) cm radiologically. Radiological preliminary diagnoses were endometrioma, desmoid tumor, foreign body reaction, granulation tissue, abscess, and hematoma (Figure 1). Four patients were diagnosed with endometriosis by tru-cut biopsy. All patients were operated through the old phanensteil incision scar.

A firm mass limited to the abdominal wall, fixed to the surrounding tissue, was detected in all patients. The masses were excised with a margin of at least 10 mm in all patients (Figure 2). While repair was performed with prolene mesh in one patient due to the size of the defect, primary repair was performed using non-absorbable sutures in all other patients. The mean tumor diameter detected per operatively was 4.53 (2.5-6.5) cm. The mean hospital stay was 1 day in patients who had no post-operative problems. The pathological diagnosis of all patients was defined as endometriosis externa (Figure 3).

No recurrence was observed in the follow-up of the patients for 1 year or more. One patient was operated after USG and CT was performed due to the development of 2 cm mass with suspected recurrence in the operation area. A totally subtracted pathological evaluation was reported as fibrosis.

Discussion

Endometriosis implants that develop in the subcutaneous tissue of surgical scars most commonly occur after gynecological and obstetric procedures, including cesarean section, hysterectomy, cystectomy, tubal

Table 1. Patients with endometriosis in the abdominal wall

Patients no	Age	BMI	Radiological findings on the abdominal wall	
1	36	27.92	CT	4 cm mass on the left sides. Endometriosis?
2	37	27.99	CT	4x3x2.5 cm mass on the left side. Desmoid tm, granülation?
3	28	23.53	USG	35x21x32 mm hypoechoic solid mass on the left side.
4	38	26.72	USG	28 mm heterogeneous hypoechoic mass in the fatty tissue on the left side.
5	37	22.76	USG	25x20 mm well-sircumscribed hypoechoic heterogeneous mass on lift side. Endometrioma.
6	35	32.15	CT	21x19x23 mm mass on the right side and surrounded by dirty tissue. Desmoid tm, abscess, hematoma?
7	28	30.48	CT	26x21x22 mm mass on the right side and suspect contrast uptake. Endometrioma?
8	43	23.95	USG	35x17 mm mass on the midline. Endometriosis, desmoid tm?
9	36	29.74	CT	35x19 mm solid mass on the left side and mild contrast uptace. Endometriosis, desmoid tm?
10	42	30.8	USG	30x22 mm mass on the midline. Endometriosis?
11	44	24.26	CT	3.5 cm solid mass on the right side. Desmoid tm, endometriosis?
12	33	23.94	CT	6x3 cm mass on the left side. Endometriosis?
13	38	28.63	CT	4 cm hipoecoic mass on the right side. Endometriosis?
14	28	22.59	CT	13x14x14 mm mass with irregular edges on the left side. Endometriozis ?
Average	**35.93**	**26.82**		
Stiffness and pain in the abdominal wall were found in all patients as presenting complaints.				
Endometriosis externa was found on pathological diagnosis in all patients				
Mesh was used with primary repair in only a patient.				
Primary repair was sufficient in all other patients.				
All the patients were discharged after one day of hospitalization.				
The smallest one was 1.4 cm, the largest was 6 cm/diagnosed by CT in 9 patients and by USG in 5 patients				

BMI: Body mass index, CT: Computed tomography, USG: Ultrasonography

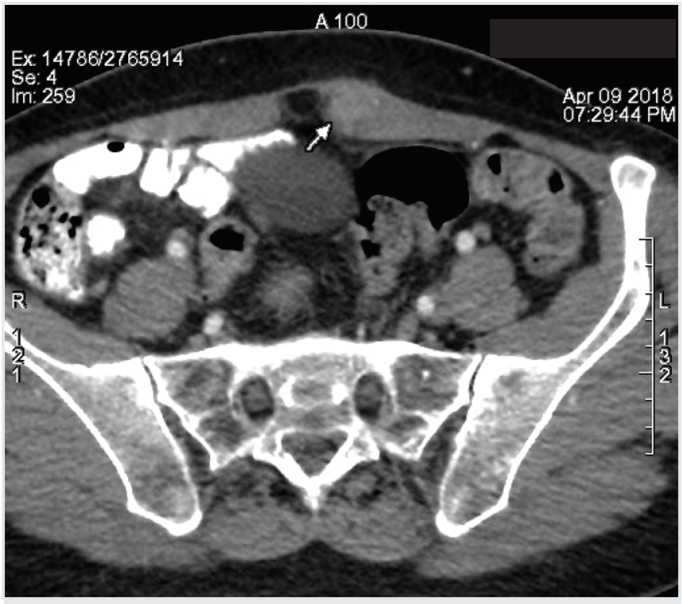

Figure 1. Endometrial mass on computed tomography scan

ligation, and amniocentesis (11). Cyclic or noncyclic pain was noted as the main symptom, reported by more than 80% of patients in the cohorts of Uçar et al. (9) in Turkey, and Zhang and Liu (12). In our study, all the patients applied because of mass in the cesarean section, and 71.43% (n=10) n of them presented with prominent mass and pain during their menstrual period. Ultrasound and CT, particularly clinical examination, are the most reliable and cost-effective imaging techniques for the diagnosis of endometriosis externa. Incisional hernia, hematoma, abscess, cyst, or lipoma should be considered in the differential diagnosis (13,14). In appropriate cases, tru-cut biopsy can be performed for pathological diagnosis. It has been shown that approximately 26% of patients may have deep infiltration (12). In our study, USG, CT and tru-cut biopsy methods were used in the diagnosis of endometriosis externa. In the differential diagnosis, endometrioma, desmoid tumor, foreign body reaction, granuloma, abscess, and hematoma were found.

Local wide surgical excision with a margin of at least 10 mm is considered good clinical practice as the first choice for treating patients with endometriosis externa (7,9,10,15). Depending on the size of the defect, repair of the formed defect can be done using primary repair or prolene mesh (15). In our study, prolene mesh was used in one patient and primary repair was performed in 13 patients using nonabsorbable sutures. In a study by Francica (16), the mean lesion size was 41 mm for large endometriomas and 18.2±5.17 mm (range: 7-26 mm) for small endometriomas. Tumor size can be difficult to diagnose; According to Gajjar et al. (17) gave a variation of the palpation score of 50x40 mm, but later using ultrasound found that the nodules had three dimensions of 18x17x17 mm. Additionally, in a study investigating the location of the tumor according to the midline, left localization was found to be more common (18). In our study, the mean tumor diameter was found to be 3.48 (1.4-6.0) cm radiologically, and 4.53 (2.5-6.5) cm in per-operative measurement. It was determined that the placement was more on the left (n=8).

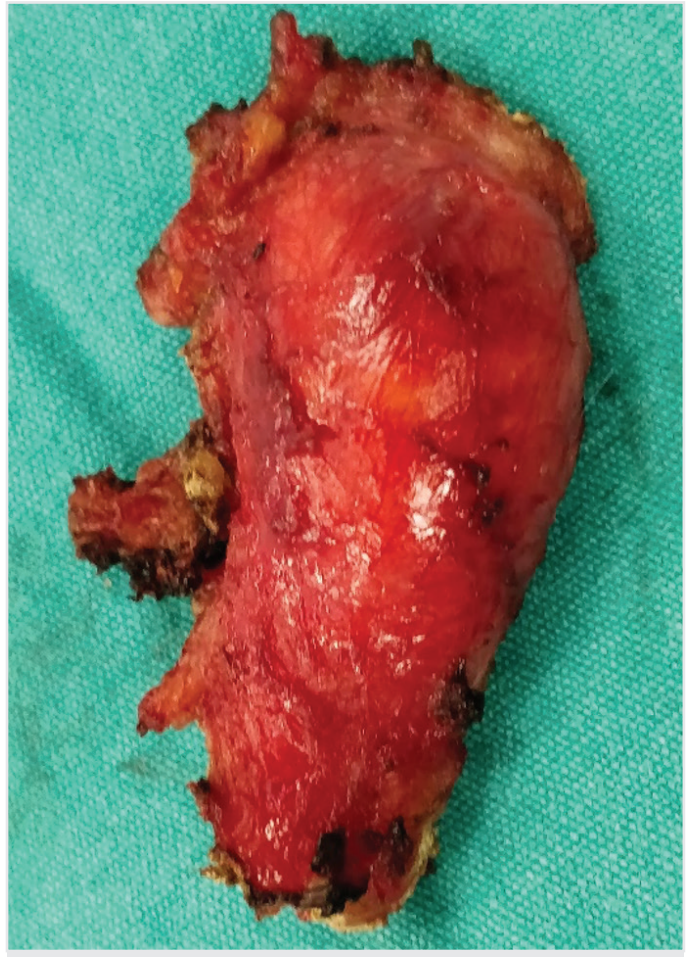

Figure 2. Excision material

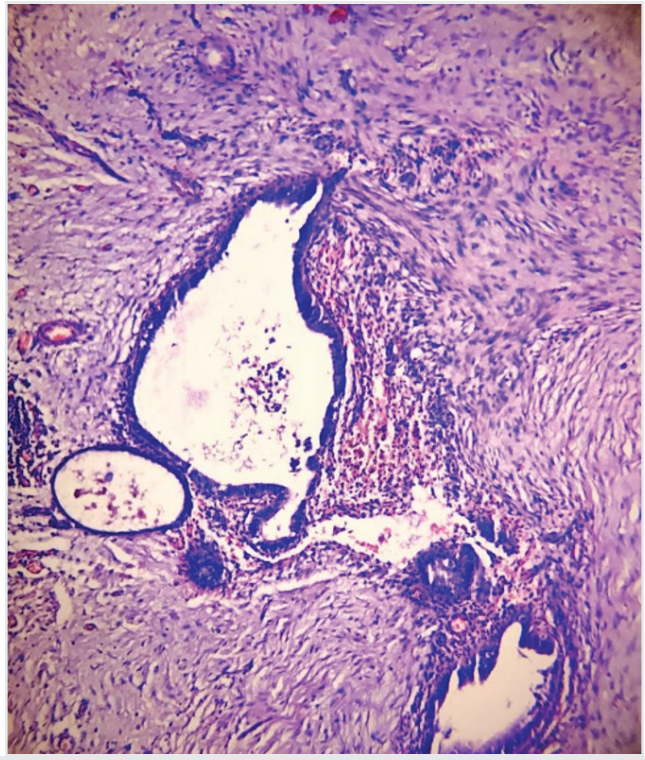

Figure 3. Hematoxylin and eosin staining 40x10 endometriosis

Study Limitations

This research, however, is subject to several limitations. The first is that the study included a limited number of patients. The second is that it is a retrospective study, so there is a problem in the documentation of the patients.

Conclusion

Endometriosis externa should be considered in the foreground in patients who complain of painful mass during menstruation at the scar sites after cesarean section, and total excision of the mass with a safe margin should be considered for treatment after differential diagnosis.

Ethics Committee Approval: The study was approved by the İstanbul Atlas University Non-Interventional Scientific Research Ethics Committee (approval number: E-22686390-050.01.04-8485, date: 28.09.2021).

Informed Consent: Informed consent was obtained from the patients regarding the study.

Peer-review: Externally peer-reviewed.

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Validation of the Classification of Intraoperative Complications for Gastrointestinal Surgery

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ABSTRACT

Introduction: In recent, a new classification system for intraoperative adverse events (iAEs) was proposed, called "the Classification of Intraoperative Complications (CLASSIC)." Our aim was to evaluate the relationship between CLASSIC and the grade of postoperative complications (PostC) in gastrointestinal oncological surgery.

Methods: Demographics, preoperative laboratory parameters, grades of iAEs, grades of PostC, and intraoperative pH and lactate levels were evaluated in patients who underwent gastric and colorectal surgery.

Results: A total of 95 patients were included in this study. Mean age was 60±14, 57 male vs 38 females. There was no significant relationship between the grade of iAEs and PostC in terms of demographics and the presence of intraoperative acidosis. Preoperative albumin level was inversely proportional to the grade of iAEs. There was no relationship between the grade of iAEs and the grade of PostC (p=0.563). The actual rates of high-grade PostC in patients with low-grade iAEs and high-grade iAEs were 10% and 18%, respectively. Additionally, the length of stay was higher in patients with high-grade iAEs (p=0.018).

Conclusion: CLASSIC may be a predictive of the grade of PostC in patients who undergo gastrointestinal surgery. High-grade iAEs is a valuable predictor of increased hospital stay.

Keywords: Colon cancer, complication, gastric cancer, gastrointestinal cancer, intraoperative, postoperative

Introduction

Intraoperative complications are one of the most confusing issues in the surgical literature. Several sources of evidence have previously been reported regarding the effects of intraoperative adverse events (iAEs) on the postoperative course of a surgical patient (1-4). However, a common language related to the severity of iAEs has not been provided up to recent years. This gap have was most evident in donor operations with living donor-related liver transplantation in which donors are equally healthy in the preoperative period (5). Kaafarani et al. (6) and Rosenthal et al. (7) reported two different classification systems for iAEs. The system proposed by Kaafarani et al. (6) generally includes undesirable injuries in general surgical operations. The accepted definition of iAE by Kaafarani et al. (6) was "an inadvertent injury that occurred during the operation" (8). It was validated during the construction of the system and the correlation of the severity of PostC with high grades of iAEs was put forward.

Rosenthal et al. (7) proposed a system named the "Classification of Intraoperative Complications (CLASSIC)" to define the grades for iAEs for all types of surgical operations. In contrast to Kaafarani et al. (6) classification, the CLASSIC system graded all types of complications, including anaesthesia-related complications. However, this had not been validated until our recently published study in which we included patients who had undergone hepatopancreatobiliary surgery (9).

In this study, we examined the validity of the CLASSIC system in patients who underwent gastric and colorectal resections. For this purpose, the relationship between the grade of iAEs according to the CLASSIC system (7) and the grade of postoperative complications (PostC) according to the Accordion Severity Classification of Postoperative Complications (ASCPC) (10) were evaluated.

Methods

Patients undergoing gastric or colorectal resection between December 2015-2018 were included in the study protocol. The demographics, biochemical characteristics, preoperative features, iAEs, intraoperative parameters and postoperative course of the patients were considered. Unexpected adverse events during surgery were also evaluated and included in the grading of iAEs, such as injury of untargeted organs or vessels; additional organ resection (e.g., cholecystectomy, splenectomy); technical problems (e.g., malfunction of equipment), anaesthesia-related adverse events, arrhythmia, oliguria or anuria. Moreover, atelectasis,

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wound infection, anastomotic leak, intra-abdominal fluid collection, bleeding, other respiratory complications, delayed gastric emptying, mechanical intestinal obstruction, organ failures, and readmission in the first 30 days after surgery were recorded.

The CLASSIC was used to grade iAEs, which is proposed by Rosenthal et al. (7). Five grades, from 0 to 4, are included in the system. Intraoperative complications were divided into two groups to prevent a confusing statistical analysis and to provide easily understandable results. According to the CLASSIC system, grade 0 is defined as the patients with ideal intraoperative course; grade 1 is defined as a minor deviation from the ideal intraoperative course without the need for additional treatment or intervention; grade 2 is defined as a major deviation from the ideal intraoperative course; grade 3 is defined as the need for additional treatment or intervention; grade 4 is defined as intraoperative death. Grade 0 and grade 1 iAEs were collected in the first group (low grade iAEs). Grade 2, grade 3, and grade 4 iAEs were collected in the second group (high-grade iAEs).

PostC were graded according to the ASCPC proposed by Strasberg et al. (10) PostC were also divided into two groups. The first group includes "low-grade PostC" (patients with no, mild, or moderate complications). The second group includes "high-grade PostC" (patients with severe complications or mortality). All of the preoperative, intraoperative parameters, and the grades of PostC were compared between the groups.

Ethics Committee approval was obtained from University of Health Sciences Turkey, Istanbul Training and Research Hospital for the study (approval number: 2529, date: 02.10.2020). Written consent was obtained from the patients in our study.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., IBM Corporation, Armonk, NY, USA) software. The distribution of variables was measured with the Kolmogorov-Smirnov test. Normally-distributed continuous variables were analyzed with Student's t-test and expressed as mean ± standard deviation. Variables not normally distributed were analyzed with Mann-Whitney U test and expressed as median and minimum-maximum range. The chi-square test and Fisher's exact test were used in the analysis of categorical variable.

Results

Descriptive statistics of demographic and clinical measurements of a total of 95 patients who underwent gastric or colorectal resection due for malignant diseases were evaluated (Table 1).

In 14 patients, minor iAEs (grade 1) observed during surgery, such as controllable hypotension, transient arrhythmia, and simple, controllable bleeding from laceration on the splenic and pancreatic capsule. In 26 patients with high-grade (grade 2 or 3) iAEs, injury of the adjacent organ(s) were seen, such as ureteral injury requiring primary anastomosis with double-J catheter insertion in two cases, bladder injury requiring primary suturing in three cases, and injury of the gallbladder requiring cholecystectomy in one case. Additionally, vascular injury was seen in the same group of patients, including injury to the splenic artery, aberrant left hepatic artery, and sacral venous plexus. The other adverse events that complicated the operative process were technical failures such as inappropriate formation of esophagojejunostomy due to malfunction of a circular stapler, or anaesthesia-related adverse events including severe hypo- or hypertension or resistant arrhythmia.

Table 1. Descriptive statistics of demographic and clinical measurements of the patients (n=95)

Age (mean ± SD) (years)	60.49±14.54
Gender (n, %) (male)	57 (60.00%)
Colorectal resections	65 (68.42%)
Gastric resections	30 (33.68%)
Intraoperative complications* (n, %)	
Grade 0	55 (57.89%)
Grade 1	14 (14.73%)
Grade 2	25 (26.31%)
Grade 3	1 (1.05%)
Grade 4	0 (0.00%)
Postoperative complications (n, %)**	
No complication	27 (28.42%)
Grade 1	24 (25.26%)
Grade 2	26 (27.36%)
Grade 3	7 (7.36%)
Grade 4	4 (4.21%)
Grade 5	6 (6.31%)
Grade 6	1 (1.05%)

*: According to the CLASSIC (7), **: According to Accordion Severity Classification of Postoperative Complications (10), SD: Standard deviation

PostC of any grade was seen in 68 patients (71%). Operation-related postoperative mortality was observed in a 73-year-old female patient who underwent low anterior resection for rectal malignancy. Postoperative enterocutaneous fistula-related abdominal sepsis caused death. High-grade (grades 4-6) PostC was seen in 26 patients (27%).

Outcomes of the patients are summarized in Table 2. Preoperative albumin level (p=0.047) and postoperative hospital stay (p=0.018), were significantly lower at low-grade iAEs than at high-grade iAEs. High-grade PostC rates were 10% in patients with low-grade iAEs and 18% in patients with high-grade iAEs. There was no significant difference between the groups (p=0.563).

Discussion

The classification of PostC first proposed by Clavien et al. (11) and its modifications (10,12,13) is widely accepted in the surgical literature. The need for a classification system for iAEs has been mentioned in previous studies, especially regarding donor surgery in living-donor liver transplantation (5,14). Hence, the first reported classification for iAEs was related to donor hepatectomy in 2005 (15). However, it was not limited to intraoperative complications and was complicated for clinical use. Therefore, it has not been widely accepted in the literature. In the last two years, Kaafarani et al. (6) and Rosenthal et al. (7) proposed two different classification systems to define and classify iAEs to provide reliable intraoperative patient care. Defining the predictive value of the

Table 2. Comparison of the patients according to the grade of iAEs

	Low-grade iAEs (n=69)	High-grade iAEs (n=26)	p
Demography			
Age (years)	61.28±14.73	59.41±12.29	0.748[a]
Gender (male) (n, %)	34 (49.27%)	3 (11.53%)	0.817[b]
Preoperative findings			
ASA score (n)	-	-	0.225[b]
1	24 (34.78%)	7 (26.92%)	-
2	35 (50.72%)	12 (46.15%)	-
3	10 (14.49%)	7 (26.92%)	-
Malignant lesion	41 (78.84%)	6 (100.00%)	0.583[b]
Hemoglobin (g/dL)	11.75±1.72	11.69±2.31	0.842[a]
Creatinine (mg/dL)	0.97±0.36	0.73±0.26	0.106[a]
Albumin (g/dL)	3.78±0.54	3.52±0.74	**0.047**[a]
AST (U/L)	18 (9-34)	22 (11-43)	0.181[c]
ALT (U/L)	17 (3-160)	16 (5-46)	0.904[c]
LDH (mg/dL)	222.76±60.23	232.68±98.39	0.554[a]
INR	1.04±0.13	1.13±0.21	0.167[a]
Intraoperative findings			
Operation time (minute)	155 (80-345)	165 (75-320)	0.175[c]
Transfusions (U)	0 (0-2)	0 (0-2)	0.161[c]
pH	7.32±0.30	7.39±0.12	0.273[a]
Lactate (mmol/L)	1.19 (0.39-7.00)	1.35 (0.92-4.16)	0.381[c]
Ca^{++}	1.04±0.16	1.00±0.13	0.291[a]
Postoperative findings			
PostC grade* (n)	-	-	0.563[d]
High-grade PostC	7 (10.14%)	4 (15.38%)	-
Low-grade PostC	62 (89.85%)	22 (84.61%)	-
Hospital stay (d)	7 (5-27)	9 (6–38)	**0.018**[c]
Intraoperative mortality (n)	0 (0.00%)	0 (0.00%)	-
Postoperative mortality (n, %)	1 (1.44%)	0 (0.00%)	0.998[d]

*: According to Accordion Severity Classification of Postoperative Complications (6), [a]: Student's t-test, [b]: chi-square test, [c]: Mann-Whitney U test, [d]: Fisher's exact test, ALT: Alanine aminotransferase, ASA: American Society of Anesthesiologists, AST: Aspartate aminotransferase, INR: International normalization ratio, iAEs: Intraoperative adverse events, PostC: Postoperative complications

grade of iAEs for postoperative course was not listed in the aims. The proposed classification by Kaafarani et al. (6), however, was validated for general surgery patients in the same study, which made it superior to the work of Rosenthal et al. (7). Nevertheless, it was generally related to injuries of non-targeted organ(s) in the planned operation and excluded the anaesthesia-related complications that were the shortcomings in Kaafarani et al. (6) classification. Conversely, in the CLASSIC system, the grades are described with more general phrases, and the system was proposed for all types of surgical operations and included anaesthesia-related complications, which make it potentially more useful. However, the main limitation of the Rosenthal et al. (7) study was the lack of validation of the system, which was the main goal of our study for gastric and colorectal operations.

The question of which group of patients should be selected to measure the validity of a proposed classification system for iAEs is critical, as to study a selected or mixed group of patients would directly affect the results. It is our contention that if the number of patients is limited, a special group of surgical operations with similar features should be selected to provide reliable conclusions. For this purpose, we first studied the patients who underwent hepatopancreaticobiliary surgery (9). We found a positive relationship between the grade of iAEs and the severity of PostC in this special group of patients (9). In this study, we determined the validity of the CLASSIC system in another group of surgical operations, gastric and colorectal resections, using a similar methodology.

The CLASSIC system is limited to iAEs. However, the presence of iAEs and the preoperative condition of the patient has predictive value for early postoperative morbidity and mortality in both gastric and colorectal resections (16-18). Therefore, patient-dependent factors and the biochemical parameters related to basic organ functions were recorded to be able to include the effect of these factors. Preoperative features and basic laboratory findings were similar in patients with both low-grade and high-grade iAEs. A unique exception was the preoperative albumin level, which was significantly lower in patients with high-grade iAEs (p=0.047). Although the difference was statistically significant, actual values of preoperative mean albumin levels were 3.7±0.5 and 3.5±0.7 in patients with low and high-grade iAEs, respectively.

There have been no reported data about the validation of the CLASSIC system in this group of patients. Therefore, it is impossible to compare the present results with those of previous studies. The grades of iAEs in gastric and colorectal surgery patients were not significantly correlated with the grades PostC. In contrast, a significant relationship was found between the grades of iAEs and PostC in patients who underwent hepatopancreatobiliary surgery in our recently published study conducted (9). However, although the difference between the groups was not statistically significant, the actual rates of high-grade PostC were 10% and 18% in patients with low grade and high-grade iAEs, respectively. Note that this result could be the product of the insufficiency in the number of cases. Additionally, the other considerable result of this study is the significantly longer hospital stay in patients with high-grade iAEs. Therefore, the proposed classification system, CLASSIC, has some degree of a relationship with the postoperative course in patients who underwent gastric and colorectal resections when, the hospital stay and the actual rates of the grades of PostC were considered.

Intraoperative acidosis and blood lactate level are new parameters being used as surrogates for the adverse events occurring during surgery and to predict the postoperative course in major abdominal operations (1,2). The main argument for these studies was the potential relationship between iAEs and metabolic state of the patient during surgery. However, there was no considerable difference in pH and lactate level between the two groups in the current study, which means that CLASSIC does not reflect the perioperative metabolic state of the patient. Acidosis is a useful marker for tissue hypoperfusion that can be due to excessive blood loss, major transfusions, long operation time, hypothermia, or inappropriate fluid administiration during surgery (19). However, the metabolic state of the patients cannot reflect the technical

(e.g., reconstruction of an unreliable anastomosis) or mechanical (e.g., injury of adjacent organs or resection of untargeted organs) adverse events that can also disturb the postoperative healing process (20). Two important parameters were also ignored in the CLASSIC system: 1) History of previous abdominal surgery and depending adhesions, and 2) recognition time of an intraoperative inadvertent injury, which were expressly considered by the team who proposed Kaafarani et al. (6) classification system (8). We believe that the CLASSIC system would be a more reliable predictor of postoperative course, if it was to be modified to combine these pe rspectives.

Study Limitations

There are some limitations related to this study. The first and the most important point is the relatively small number of patients; the effects of this limitation were previously discussed in this article. However, there have been no published data regarding the validation of the CLASSIC system in this group of patients. We believe that this is an important contribution to our previous study regarding the validity of the CLASSIC system (9). This study is also limited to the area of gastric and colorectal resections. Although the CLASSIC system was proposed for all types of surgical interventions, the nature of diseases and surgical manipulations should be considered during the evaluation of the clinical value of this system. For this purpose, we divided the operations according to the target organs and diseases. Finally, the retrospective nature of the study was another limitation.

Conclusion

The grade of iAEs according to the CLASSIC system (7) could be related to the grade of PostC according to ASCPC (10) in patients who underwent gastric and colorectal resections. Importantly, our findings indicate that high-grade iAEs can be a valuable indicator for a longer hospital stay in the same group of patients.

Ethics Committee Approval: Ethics Committee approval was obtained from University of Health Sciences Turkey, Istanbul Training and Research Hospital for the study (approval number: 2529, date: 02.10.2020).

Informed Consent: Written consent was obtained from the patients in our study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.M.S., E.K., U.O.I., S.D., C.T.; Concept - M.M.S., E.K.; Design - M.M.S., E.K.; Data Collection or Processing - M.M.S., U.O.I., S.D., C.T.; Analysis or Interpretation - M.M.S., E.K., U.O.I., S.D., C.T.; Literature Search - M.M.S., E.K., U.O.I., S.D., C.T.; Writing - M.M.S., E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Importance of Informed Consent in Clinical Practice

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ABSTRACT

Introduction: This study aims to determine the experiences and opinions of physicians on informed consent practices, to research their awareness of their legal responsibilities, and to provide solutions to the problems encountered in practice.

Methods: This research is a descriptive field study. One hundred and eighty-four physicians working in a state hospital in İstanbul participated in this study between January 15 and February 15, 2018. The questionnaire form was used as a data collection tool. After the participants were informed about the purpose and method of the research, their consent was obtained, and they were asked to fill in the questionnaire forms. The analysis of the data was performed using the SPSS 18.00 program. The significance level was accepted as $p<0.05$.

Results: One hundred and eighty-four physicians working in a state hospital in İstanbul participated in this study. 69% (n=127) of the physicians participating in the study were male and 31% (n=57) were female. 35.3% (n=65) of the participants were from the 30-39 years old age group. 96.7% (n=178) of the physicians in the study stated that they personally informed their patients before the surgical interventions. 83.7% (n=154) of the physicians think that the lawsuits filed against the physicians due to medical malpractice affect the health services provided by the physicians to their patients.61.4% of the participants (n=113) think that they have not received enough education in their medical education processes regarding the rights and obligations of the physicians.

Conclusion: Considering the current situation in Turkey, the informed consent process is not yet at the level it should be. Since human rights are in the process of development in the world, informed consent and many more patient rights will gain importance with studies on this subject. Therefore, training, and studies should be increased to inform physicians and patients about informed consent and to make them a behavioral model physicians.

Keywords: Informed consent, physician, patient rights

Introduction

Informing patients and obtaining their consent are both legal and ethical requirements within the framework of contemporary medical practice. Before any medical practice, it is one of the basic rights of patients to be informed about their diseases in accordance with their sociocultural background so that they can provide their informed consent. This process is an important element of the current medical approach in legal and ethical terms as a requirement of the principle of respecting the autonomy of the individual and the responsibility of the physician (1,2).

In the third section of the Patient Rights Regulations, which entered into force in Turkey on August 1, 1998, the right of patients to obtain information about their own health status is regulated. According to the regulations, patients have the right to request verbal or written information about the possible causes of the disease and how it will progress, by whom, how and for how long the medical intervention will be performed, alternative treatment methods, benefits and risks of treatment, possible complications and consequences in case of refusal of treatment (3).

Previous studies on informed consent have noted that patients who were adequately informed in the preoperative period and had a detailed preparation for surgical intervention had a more successful process (4-6).

Recently, the concept of informed consent has begun to be further discussed in legal and medical circles in Turkey. Moreover, the awareness of both healthcare professionals and patients on this issue has increased. This process has also led to lawsuits against physicians for allegations that the patient was not adequately informed, or that the information obtained did not provide the appropriate conditions. Compared to the past, there are many more cases concerning only alleged deficiencies in the application of the right of informed consent.

With advanced technological applications becoming frequently used in the field of medicine, physicians have become able to perform riskier

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interventions. Additionally, the expectations of patients from these applications have increased. Physicians face more complaints due to these high expectations and increased awareness. If physicians are familiar with the legal regulations in their fields, manage the informed consent process correctly, show sufficient care, and spend sufficient time on patients in the process, the problems in this area will be minimized.

The aim of this study is to determine the experiences and opinions of physicians on informed consent practices, to research their awareness of their legal responsibilities, and to provide solutions to the problems encountered in practice.

Methods

This research is a descriptive field study designed to determine the experiences and opinions of physicians on informed consent practices and to investigate their awareness of their legal responsibilities.

One hundred and eighty-four physicians working in a state hospital in İstanbul participated in this study between January and February 2018. The questionnaire form was used as a data collection tool. After the participants were informed about the purpose and method of the research, their consent was obtained, and they were asked to fill in the questionnaire forms.

The questionnaire form consisted of four parts. The first part consists of 6 questions about the sociodemographic characteristics of the participating physicians. The second part consists of 11 questions about the physicians-way of obtaining informed consent, whether they received training on informed consent and their opinions on the legal consequences of informed consent. The third part consists of 8 questions about the attitudes of physicians during the informed consent process. The fourth and final part consists of 9 statements about their views on informed consent.

The study was approved by the Acıbadem Mehmet Ali Aydınlar University Local Ethics Committee (approval number: 2018-1-37, date: 11.01.2018).

Statistical Analysis

Data were analyzed using the SPSS 18.0 package program. Statistical analyses were conducted with frequencies, percentages and the χ^2-test. A p-value less than 0.05 was accepted as significant.

Results

One hundred and eighty-four physicians working in a state hospital in İstanbul participated in this study between January and February 2018. 69% (n=127) of the physicians participating in the study were male and 31% (n=57) were female. The age groups of the participants were analyzed in five groups- 25-29, 30-39, 40-49, 50-59, and 60+ years old. Thirty-39 years old age group was the largest group. 35.3% (n=65) of the participants were from the 30-39 years old age group. Of the physicians participating in the study, 72.8% (n=134) were specialists, 25.5% (n=47) were residents and 1.6% (n=3) were general practitioners. The years of work experience of the participants were analyzed in four groups-0-10, 11-20, 21-30, and 30+ years. Participants were most commonly within the 0-10-year group, with 41.8% (n=77), in terms of working time in the profession. The sociodemographic characteristics of the participants are in Table 1.

96.7% (n=178) of the physicians in the study stated that they personally informed the patients before the surgical interventions. The behavior of the physicians when having patients sign the consent form is shown in Table 2.

The views of the physicians on the implementation of the informed consent procedure are shown in Table 3.

52.2% (n=96) of the physicians believe that obtaining informed consent from the patients before surgical interventions will protect the

Table 1. Sociodemographic characteristics of the physicians participating in the study

	n	%
Gender		
Male	127	69
Female	57	31
Age		
25-29	51	27.7
30-39	65	35.3
40-49	47	25.5
50-59	17	9.2
60+	4	2.2
Title		
Specialist	134	72.8
Resident	47	25.5
General practitioner	3	1.6
Years of work experience		
0-10	77	41.8
11-20	59	32.1
21-30	23	12.5
30+	7	3.8
Specialty		
Department of surgical sciences	96	52.2
Department of medical sciences	85	46.2
Department of basic sciences	2	1.1

Table 2. The behavior of the physicians about having patients sign the consent form

	n	%
Please mark the appropriate option for you below		
I read the consent form out loud to patients, patients sign it themselves.	50	27.2
I have patients read the consent form, patients sign it themselves.	107	58.2
I have nurses read the consent form out loud to patients, patients sign it themselves.	2	1.1
I have patients sign the consent form without having it read.	12	6.5
I have relatives of patients sign the consent form instead of patients themselves	1	0.5
Other hospital staff have the consent form signed	9	4.9

Table 3. The views of physicians on the implementation of the informed consent procedure

	n	%
Do you think the informed consent procedure is implemented correctly in Turkey? If not, what do you think is the reason for this?		
I think the procedure was implemented correctly.	34	18.5
I don't think informed consent procedure was implemented.	64	34.8
Reasons:		
Adverse working conditions		
Insufficient number of existing health personnel	48	26.1
Healthcare professionals not showing the necessary diligence	41	22.3
Not having enough information about informed consent	31	16.8
patients not caring informed consent	25	13.6

healthcare personnel from medical practice errors. 83.7% (n=154) of the physicians think that the lawsuits filed against the physicians due to medical malpractice affect the health services provided by them.

13.6% (n=25) of the physicians participating in the study have a lawsuit or an investigation filed against them regarding alleged medical malpractice. When asked what they would do if they took action that would fall within the scope of medical malpractice, 51.1% (n=94) of the physicians gave the answer-I will immediately report this situation to the hospital management-For the same question, 25.5% (n=47) of the physicians answered-I share this situation with the patient- 12% (n=22) of them answered as "I only share this situation with my close friends/ family- and 7.6% (n=14) of them answered-I do not share this situation with anyone-

61.4% of the participants (n=113) think that they have not received enough education in their medical education processes regarding the rights and obligations of the physicians. The attitudes of the surgeons toward the content of informed consent are shown in Table 4. The agreement of the physicians with the statements about informed consent is shown in Table 5.

Table 4. The attitudes of the surgeons toward the content of informed consent

	n	%
Before the surgery, I informed the patient in detail about the disease that caused the patient to undergo surgery		
Yes	89	97.8
No	2	2.2
Before the surgery, I inform the patient about the problems he/she may encounter in case of not having surgery		
Yes	90	98.9
No	1	1.1
If the patient agrees to undergo surgery, I inform him/herest about the possible risks of the surgery		
Yes	87	95.6
No	4	4.4
Before the surgery, I informed the patient about the available alternative treatment methods		
Yes	82	90.1
No	9	9.9
Before the surgery, I inform the patient about how long he/she will stay in the hospital after the surgery, the issues to be careful about after the surgery, and when he/she will return to his/her normal activities after the surgery		
Yes	85	93.4
No	6	6.6
Before the surgery, I introduce the surgical team to the patient		
Yes	7	7.7
No	84	92.3
I use medical terminology while informing the patient		
Yes	14	15.4
No	77	84.6
I inform the patient about the risks that are very unlikely to occur		
Yes	62	68.1
No	29	31.9

Discussion

Informing patients in accordance with their sociocultural background and then obtaining their consent for medical intervention is a basic patient right, which is included in national and international regulations (1,2). Nowadays, the awareness of patients in this field and their expectations from physicians have increased with the developing technology. This has led the physicians to face legal problems recently in Turkey.

It is very important that physicians are adequately knowledgeable about their legal rights and obligations. Since obtaining informed consent is a legal obligation and a condition for the respect of the autonomy of patients, physicians must be familiar with the law. Additionally, physicians should know about the content of informed consent and when and from whom it should be obtained. Therefore, physicians should be educated about their legal responsibilities-both during their medical education and while practicing their profession (7). In the study, 61.4% (n=113) of the physicians stated that they did not receive sufficient education regarding the rights and obligations of the physicians in the medical education process. In another study, when physicians were asked about the adequacy of the education they received regarding their rights and obligations, 85.9% of them stated that education was inadequate (6). In the study by Yaşar Teke et al. (8), this rate was found to be 82.4%. As seen in the studies conducted, physicians generally do not find the education they receive in this field sufficient. If physicians had sufficient knowledge in this field, this would enable them to fulfill their legal obligations, and this will be in the interest of patients. With the provision of graduate and post-graduate training, the concept of informed consent has become more known. Physicians have begun to make more efforts to inform patients about their diseases, to provide the conditions for obtaining their consent based on the information provided, and to manage this process correctly.

In our study, 83.7% (n=154) of the participating physicians are of the opinion that the lawsuits brought against the physicians due to medical malpractice affect the health service provided by them. Physicians may turn to defensive medicine practices under the pressure of medical malpractice (9,10). In the study of Yıldırım et al. (11), when

Table 5. The agreement of the physicians with the statements about informed consent

	n	%
Obtaining informed consent before a surgery is a legal right		
I agree	175	95.1
I do not agree	4	2.2
I have no idea	2	1.1
Obtaining informed consent is an indicator of respect for the patients' autonomy		
I agree	171	92.9
I do not agree	6	3.3
I have no idea	5	2.7
It is correct to obtain informed consent from the patients before every surgery		
I agree	175	95.1
I do not agree	4	2.2
I have no idea	3	1.6
The physician makes the best decision in planning the treatment of the patients, including the surgeries		
I agree	102	55.4
I do not agree	57	31
I have no idea	23	12.5
Physicians should inform the patients about even the smallest risks that may occur during surgery		
I agree	119	64.7
I do not agree	36	19.6
I have no idea	23	12.5
The consent given by the patient when he/she just comes to the hospital remains valid for all medical interventions to be applied to that patient		
I agree	68	37
I do not agree	89	48.4
I have no idea	24	13
The patient has the right not to get information from the physician if he/she requests		
I agree	69	37.5
I do not agree	83	45.1
I have no idea	25	13.6
Even if the patient has information about the health problem he/she has, the physician should provide information		
I agree	142	77.2
I do not agree	24	13
I have no idea	15	8.2
If the physician believes that the patient will be adversely affected if the patient is informed, she may not inform the patient, in this case, this information was retained with the relatives of the patient		
I agree	76	41.3
I do not agree	85	46.2
I have no idea	21	11.4

the participants were asked what impact the concern of being sued for malpractice would have on healthcare, 66.7% of them stated that it would be harmful. When the physicians were asked whether they behaved recessively in the intervention due to the concern of malpractice, 69.7% of them answered yes (11). This situation actually does not benefit the patients. It is critical to conduct studies to minimize errors in the health system and to organize vocational training and meetings regarding the legal processes in practice.

The physician must inform the patient about the disease, its treatment process of the disease and treatment options. This information should be made in a clear, understandable language and in accordance with the sociocultural background of the patient. Whether the patient understands this information should be checked and their consent should be obtained. During the informed consent process, the physician and patient should be actively involved in the process and patient should decide with his/her free will. In our study, 96.7% (n=178) of the physicians stated that they personally informed the patients before the surgical intervention. In the study of Turla et al. (12), 64.7% of the physicians stated that they obtained consent from their patients before all professional practices. In the study of Jukic et al. (13), just 38% of the physicians stated that they were completely informed about the process of obtaining consent. In our study, 94% of the physicians stated that they informed patients in detail about diseases that caused patients to have surgery before the operation, 96.2% of them stated that they informed patients about the problems they might encounter in case of not having surgery, 94% of them stated that they inform patients about the possible risks of the surgery if the patients agree to have surgery, 85.3% of them stated that they informed patients about the available alternative treatment methods before the surgery, 90.8% of them stated that they informed the patients about how long they will stay in the hospital after the surgery, the points they should be careful after the surgery and when they will return to their normal activities after the surgery. However, 10.9% of the physicians stated that they introduced the surgery team to the patients before surgery, and 15.8% of them stated that they used medical terminology while informing the patients. Nowadays, the awareness of physicians has increased due to the discussions of the issue on different platforms and the legal problems encountered. It can be observed that they care about informing their patients personally and in detail. However, it also appears that there are deficiencies in terms of introducing the surgical team and explaining them in an understandable language without using medical terminology.

In the study, although the participating physicians stated that they informed patients in person and in detail, only 18.5% of them believed that the informed consent procedure was implemented correctly in Turkey. An insufficient number of existing health personnel (26.1%), adverse working conditions (34.8%), healthcare professionals not showing the necessary diligence (22.3%) and patients not caring informed consent (13.6%) are mentioned as possible reasons for this. In a study conducted on healthcare professionals, 47.6% of the interviewees partially agreed that the process of informed consent was applied correctly. In the same study, the reason why informed consent was not implemented at the desired level was attributed to the insufficiency of the number of personnel (33.6%) and adverse working conditions (23.8%). Furthermore, it was seen that 56.6% of the participants considered consent as an assurance of proof, and 62.2% of them shared the opinion that the responsibility for obtaining informed consent belongs to the whole

team (11). In the study by Turla et al. (12), 84.3% of the physicians spent less than 10 min to inform their patients. Among the reasons for this, it was stated that the number of personnel was insufficient.

Study Limitations

Our study has no limitations.

Conclusion

Considering the current situation in Turkey, the informed consent process is not yet at the level it should be. Since human rights are in the process of development in the world, informed consent and many more patient rights will gain importance with further studies on this subject. Therefore, training and studies should be increased to inform physicians and patients about informed consent and to make this a behavioral model for physicians. It is critical to define the problems regarding informed consent, which is one of the basic elements of patient rights, and to develop strategies for solving these problems. The awareness of healthcare professionals about informed consent should be increased, and continuous educational activities should be emphasized to make standard practice a behavioral model.

Ethics Committee Approval: The study was approved by the Acıbadem Mehmet Ali Aydınlar University Local Ethics Committee (approval number: 2018-1-37, date: 11.01.2018).

Informed Consent: Informed consent was obtained.

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The Relationship Between the Presence of Severe Acute Respiratory Syndrome-Coronavirus-2 during Pregnancy and Neonatal Hearing Loss

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ABSTRACT

Introduction: In this study, we investigated the maternal severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection's effect on newborn hearing loss.

Methods: Thirty-nine newborns whose mother's SARS-CoV-2 real time-polymerase chain reaction test was positive at the time of parturition were included in this study. Another 39 newborns who were born from healthy pregnancies were selected as the control group. Neonates with risk factors for hearing loss determined by the American Academy of Pediatrics Joint Committee on Infant Hearing 2007 and those with ear pathology were excluded. The newborn hearing screening was done with auditory brainstem response (ABR) test. Second ABR test (ABR-2) was performed on newborns who failed the 1st test (ABR-1). The third ABR test (ABR-3) was performed on newborns who failed the second ABR test (ABR-2). The screening results were analyzed statistically.

Results: In the control group, a total of 6 (15.4%) newborns failed ABR-1, five newborns in one ear (3 right, 2 left), and one newborn in both ears. In the study group, a total of 14 (35.9%) newborns failed ABR-1, 11 newborns from both ears and 3 (2 right, 1 left) newborns from one ear. ABR-1 results were significantly worse in the study group's neonates ($p=0.038$). In addition, the rate of involvement of both ears was higher in the study group ($p=0.018$; $p<0.05$). 1 (16.7%) newborn in the control group and 2 (14.3%) newborns in the study group failed the ABR-2 in both ears. There was no statistically significant difference according to the ABR-2 test ($p=0.681$; $p>0.05$). All babies passed the ABR-3.

Conclusion: There was a significant relationship between neonatal hearing loss and maternal SARS-CoV-2 infection. This hearing loss is usually bilateral and temporary.

Keywords: SARS-CoV-2, hearing loss, maternal-fetal relations, neonatal screening*, auditory brainstem response

Introduction

Coronavirus disease-2019 (COVID-19), emerged in the Wuhan district of China in December 2019, was declared as a pandemic by the World Health Organization (WHO) (1). As of 26 July 2021, 194,835,316 approved cases and 4,175,129 deaths related to COVID-19 have been reported (2). COVID-19 is caused by a new member of the Coronaviridae family identified as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). SARS-CoV-2 is a single-stranded RNA virus which affects the entire population and pregnant women (3,4).

Angiotensin-converting enzyme (ACE) plays a crucial role in the renin-angiotensin system. ACE-2 is a transmembrane peptidase that is a homologue of ACE and presents in the heart, lungs, kidney, intestine, and other organs (5,6). ACE-2 also functions as an intracellular inlet point for SARS-CoV and SARS-CoV-2 (7).

Previous studies reported that, ACE-2 production increases in the kidneys, uterus and placenta during pregnancy, also this enzyme presents in the fetal lung and brain tissue (8). Although pregnancy is not an increased risk of contracting SARS-CoV-2 infection, it has been reported that SARS-CoV-2 infection is more severe in pregnant women. The need for intensive care and invasive ventilation and mortality rates were higher in pregnant women (9,10). A study conducted on mice showed that the virus involves the uterus and placenta during pregnancy (11). Studies that investigated the transmission of SARS-CoV-2 from pregnant mothers to their newborn reported different results. However, Wang et al. (12) reported a SARS-CoV-2 infected neonate whose COVID-19 positivity was confirmed by pharyngeal swab PCR-36 hours after birth, born from a COVID-19-positive pregnant.

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It is known that intrauterine infections can cause congenital or acquired, acute or late-onset, unilateral or bilateral, conductive or sensorineural, permanent or temporary types of hearing loss. Various pathogens such as toxoplasma, rubella, cytomegalovirus (CMV), herpes, and syphilis can cause congenital sensorineural hearing loss (SHL) after intrauterine infection (13). Viruses, the most common cause of non-genetic congenital hearing loss, can damage hearing cells, auditory organs, auditory pathways, and auditory centers by direct or host-mediated immune reactions (14).

The auditory brainstem response (ABR) test is an essential diagnostic tool for detecting audiometric thresholds in infants and other patients for whose hearing thresholds are difficult or impossible to determine. The ABR test can be performed with various stimuli. While ABR with click stimulus is the gold standard method in newborn hearing screenings, tone burst ABR has become the gold standard for estimating frequency-specific hearing thresholds in infants under five to six months (15,16).

There are limited studies in the literature about congenital hearing loss associated with SARS-CoV-2, which is shown to be transmitted vertically, is neuroinvasive and neurodegenerative, and has a relationship with SHL in adults (17,18). In this study, we investigated the presence and features of SHL in newborns of COVID-19 infected pregnant.

Methods

This prospective controlled study was conducted at İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Obstetrics and Gynecology between January 2021-July 2021 on pregnant women and their newborns with the approval of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: E-83045809-604.01.02-67990, date: 07/04/2021).

Populations, Inclusion and Exclusion Criteria

All pregnant women who were included in this study, were applied İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Obstetrics and Gynecology for delivery. As an institutional rule, all patients were tested for SARS-CoV-2 with PCR before hospital administration. Pregnant women whose naso/oropharyngeal swab PCR results during the hospitalization procedure were positive for COVID-19 and their newborns were included in the study as the study group. Healthy pregnant women and their newborns were randomly chosen as the control group.

Pregnant women who have a chronic disease, multiple pregnancies, gestational diabetes, pregnancy-related disease such as preeclampsia, symptoms of COVID-19 (such as anosmia, myalgia, cough, dyspnea), previous history of COVID-19, received COVID-19 treatment, did not accept cesarean delivery and had insufficient mental capacity was excluded from the study. In addition, neonates who have risk factors for hearing loss as specified by the American Academy of Pediatrics Joint Committee on Infant Hearing 2007; such as hypoxia, a family history of hereditary SHL, prenatal infection such as rubella, craniofacial abnormalities, parturition weight under 1500 g, hyperbilirubinemia that requires exchange transfusion, ototoxic treatments, intensive care unit stay more than five days; APGAR scores of 0-4 at the 1st or 0-6 at the 5th minute of parturition and stigmata or other findings associated with a congenital syndrome and neonates with ear pathologies were excluded (19).

Sample Size and Sampling Technique

The minimal subject size was calculated according to the study by Celik et al. (18). The minimal subject size was 78 with 80% confidence interval and 5% tolerable error assumptions. All COVID-19-positive pregnant women (study group) who met the study criteria during the study period were included in this study. An informed consent form was obtained from all subjects.

Procedures and Data Collection

Study Design

Day 0 (birth): Combined naso/oropharyngeal swabs were collected from pregnant women before delivery by the same physician. To reduce the risk of transmission, COVID-19 PCR-positive pregnant women's delivery were performed by cesarean section within the first 24 hours after their admission. Pregnant women whose COVID-19 PCR tests were negative and delivered by cesarean section were included as a control group to ensure the standardization.

Day 1 (initial hearing evaluation): Neonates that included in this study were taken for ontological examination 24 hours after birth to the same institution's otorhinolaryngology department and audiology department. Automates Auditory Brainstem Response (AABR) screening test results of neonates with normal ear examination and tympanogram (type A) were included in the study. Newborns who passed the AABR test (ABR-1) considered having normal hearing. Newborns who failed their AABR test (ABR-1) were called 10 days later for the second evaluation.

Day 10 (second hearing evaluation): AABR test (ABR-2) was performed by the same specialist audiologist. Newborns who passed the AABR test (ABR-2) considered having normal hearing. Newborns who failed their AABR test (ABR-2) were called 20 days later for a third evaluation.

Day 30 (third hearing evauation): AABR test (ABR-3) was performed by the same specialist audiologist. Newborns who passed the AABR test (ABR-3) considered having normal hearing.

Collection of Swab Samples and PCR Tests

The swabs were taken from the oropharynx and nasopharynx, respectively, with the same stick by an expert otorhinolaryngologist. RT-qPCR kit (Bio Speedy, Turkey) targeting the RNA-dependent RNA polymerase (RdRp) gene was used to detect SARS-CoV-2.

Hearing Screening Test

Hearing screening tests were performed using AABR (Madsen Accuscreen Pro, GN Otometrics, Denmark) device after birth in the institution's audiology department by the same, 10 years experienced, audiologist. According to the Republic of Turkey Ministry of Health's Neonatal Hearing Screening Protocol, the first hearing screening test must be performed within the first 72 hours after birth before discharge from hospital. The second ABR test was performed within 7-15 days after delivery, and the third ABR test was completed within 15-30 days (before

the 30th day). All tests were carried out in a soundproof room with a noise value not exceeding 35 dbA (20). The neonates with normal type A tympanogram and acoustic reflex test who failed the AABR tests were considered to have SHL and referred for further evaluation.

Statistical Analysis

The minimal subject size was estimated using the G* Power program version 3.1 (21). The statistical analysis was performed with SPSS 22 (IBM SPSS Statistics, USA). Normal distribution and homogeneity of data were analyzed with the Kolmogorov-Smirnov and Levene's tests, respectively. The comparisons of two independent groups were performed using the Mann-Whitney U test and chi-square test or Fisher's exact test. Hearing screening results were compared with the chi-square test between the neonates whose mothers' COVID-19 PCR was positive and neonates whose mothers' COVID-19 PCR was negative. The statistical significance level was set as $p<0.05$.

Results

Thirty-nine SARS-CoV-2 PCR-positive pregnant women and 39 healthy pregnant women were included in the study. No deaths were observed in the pregnant women and their babies included in the study. The mean age of the COVID-19-negative pregnant women (group 1) included in the study was 27.77+3.55 (minimum: 22; maximum: 34) years, while the mean age of the COVID-19-positive group (group 2) was 28.53+3.68 (minimum: 22; maximum: 36) years. The mean weeks of delivery were 38.43+1.14 (minimum: 28; maximum: 41) and 37.77+2.61 (minimum: 36; maximum: 41), respectively. The birth weights of the newborns were 3407.56+610,98 gr (minimum: 2650 gr; maximum: 4610 gr) and 3504.36+408.6 gr (minimum: 2225 gr; maximum: 3900 gr), respectively. The pregnant women included in the study and newborns of these pregnant women were statistically similar according to their demographic characteristics ($p<0.05$) (Table 1).

In the control group, 6 of 39 (15.4%) newborns; five newborns in one ear (3 right, 2 left) and one newborn in both ears failed the first ABR test (ABR-1). In the study group, 14 of 39 (35.9%) newborns; 11 newborns from both ears and 3 (2 right, 1 left) newborns from one ear, failed ABR-1. According to the ABR-1, the number of newborns who failed the test in the study group was statistically significantly higher ($p=0.038$; $p<0.05$) (Table 2). In addition, the number of newborns who failed the ABR-1 test in both ears was significantly higher in the study group ($p=0.018$; $p<0.05$) (Table 3).

In the second ABR test (ABR-2) performed on newborns who could not pass the first ABR-1 after 10 days. One newborn (16.7%) in the control group and 2 newborns (14.3%) in the study group could not pass the test in both ears. According to the ABR-2, no statistically significant difference was found between the groups ($p=0.681$; $p>0.05$). The third ABR test (ABR-3) was performed on babies who could not pass the second ABR test 20 days later and all babies passed ABR-3.

Discussion

In this study, the rate of failing the ABR-1 test was found to be statistically significantly higher in newborns of pregnant women with COVID-19 compared to newborns of healthy pregnant women. In addition, the rate of failing the ABR-1 test bilaterally was statistically significantly higher in newborns of pregnant women with COVID-19 compared with newborns of healthy pregnant women. However, it was found that this difference disappeared in the second and third control ABR tests performed on those who did not pass the test. The data obtained in our study showed that temporary SHL developed in newborns of pregnant women with COVID-19.

Viral infections, which have a definite relationship with congenital SHL, are (toxoplasmosis, rubella, CMV, herpes, and syphilis) infections, especially CMV (22-25). It is known that the vertical transmission of SARS-CoV-2 infection, which was declared a pandemic by the WHO in 2019, is low in pregnant women (26,27). There has been no study in the literature aimed at isolating the virus in the ear of the fetus. However, the locations where the virus is isolated in adults were the cerebrospinal fluid, middle ear, and mastoid bone, which were anatomically close to the inner ear and auditory tract (28-30). In addition, there are findings of extensive brain involvement in autopsy studies in COVID-19 patients (31,32). This situation led to the hypothesize that the inner ear may be affected by COVID-19 and that this virus, which can affect the inner ear, may develop SHL in newborns of pregnant women with COVID-19.

There are two studies in the literature examining the presence of SHL in babies of pregnant women with COVID-19 (17,18). In a retrospective study by Alan and Alan (17), babies of healthy pregnant women and babies of 236 pregnant women infected with SARS-CoV-2 were evaluated with the ABR test, and the rate of SHL in the first ABR was statistically significantly higher in the babies of pregnant women who had COVID-19. However, this difference disappeared in the second ABR test performed on newborns (17). The rate of failing in the first ABR was found to be statistically significantly higher in pregnant women who had COVID-19 in the second trimester compared in those who had it in the third trimester (66.6% and 38.7%, respectively; $p=0.014$). In their study, the period of infection and the symptoms of the disease of mothers who had COVID-19 infection differ. In addition, there is no

Table 1. Examination of the characteristics of the subjects

Parameter		COVID-19 (-) pregnant (control group)	COVID-19 (+) pregnant (study group)	p
Maternal age		27.77+3.55 (28)	28.53+3.68 (28)	0.399*
Birth week		38.43+1.14 (38)	37.77+2.61 (38)	0.413*
Birth weight		3407.56+610.98 (3420)	3504.36+408.62 (3500)	0.384*
Gender	Male	24 (61.5%)	22 (56.4%%)	0.645**
	Female	15 (38.5%)	17 (43.6%)	

*: Mann-Whitney U test ($p>0.05$), **: Pearson chi-square ($p>0.05$). COVID-19: Coronavirus disease-2019

Table 2. Evaluation of first ABR test results

First ABR test	COVID-19 (-)	COVID-19 (+)	p
ABR pass	33 (84.6%)	25 (64.1%)	**0.038***
ABR refer	6 (15.4%)	14 (35.9%)	

*Pearson chi-square test, value: 4.303; p<0.05. COVID-19: Coronavirus disease-2019, ABR: Auditory brainstem response

Table 3. Evaluation of affected ear laterality of newborns who did not pass the test

Affected ear	COVID-19 (-)	COVID-19 (+)	p
Unilateral	3 (21.4%)	5 (83.3%)	**0.018***
Bilateral	11 (78.6%)	1 (16.7%)	

*Fisher's exact test (p<0.05), Coronavirus disease-2019

standardization in the treatment of pregnant women with COVID-19, and 25.4% of the pregnant women included in their study were given hydroxychloroquine, which was reported to be ototoxic and may cause malformation in newborns when used during pregnancy (33,34). In a cross-sectional study by Celik et al. (18), the Transient Evoked Otoacoustic Emissions (TEOAE) test was performed on the babies of 73 healthy and COVID-19-infected pregnant women who passed the bilateral ABR test before and hidden SHL was investigated. As a result of the study, SHL at high frequencies (3-4 kHz) was found in the babies of pregnant women with COVID-19. It has been found that when the contralateral ear is suppressed, SHL in babies with COVID-19 becomes more pronounced and all frequencies are affected. High-frequency SHL in these infants has been associated with the efferent system involvement. However, there was no correlation between the SHL detected in these babies and pregnancy trimesters. In accordance with the study of Alan and Alan (17), this study also differs in terms of the duration of COVID-19 infection and the patients' symptoms (18). When both studies are evaluated together, the SHL caused by COVID-19 infection is temporary, according to the AABR test. This SHL is especially high frequencies according to the TEOAE test results.

Unlike these studies mentioned, the standardization of this study is unique. The pregnant women who were asymptomatic at the time of admission and had a positive COVID-19 PCR test were included in our prospective study for standardization since the severity of the COVID-19 infection is closely related to the symptoms. In addition, no COVID-19 treatment was given to the pregnant women before delivery, and all pregnant women in the study and control groups were delivered by cesarean section to prevent the newborns from being affected by the delivery method and to minimize the risk of transmission to healthcare personnel.

The mechanism of development of SHL after viral infection is still in the theoretical phase. Prominent among these hypotheses are virus-induced degeneration in inner ear structures, apoptosis of the cells of the auditory tract, microcirculation disorders, and immune response-mediated SHL (35). The cytokines responsible for this immune response that causes SHL due to viruses are interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (36,37). In the immune response seen in COVID-19, an increase in IL-1, IL-6, and IL-10 is observed, and drugs that suppress these cytokines, which also have prognostic features, are used to treat the disease (38). This similarity in primary cytokines shows that the microcirculation disorder caused by the virus and the immune response may be responsible for SHL seen in newborns of pregnant women with COVID-19. Transient activation in the cochlear immune response results in spontaneous recovery in SHL (39,40). The temporary nature of SHL in newborns in this study may be explained by the transient nature of microcirculation disorder and immunity seen in COVID-19 and the fact that the infection occurred in mothers at the latest stage of the pregnancy, right before delivery.

Study Limitations

Although this study has outstanding aspects compared to the studies in the literature, it has some limitations. The hearing test data of our research are nominal, the diagnostic ABR for determining the thresholds, and the additional OtoAcustic Emissions tests were not used in our study, which causes us not to obtain numerical data, thus limiting this study. Secondly, only the common conditions were excluded that may lead to conductive hearing loss, so all of the hearing loss detected in this study was accepted as SHL. Another limitation is that only asymptomatic pregnant women with positive SARS-CoV-2 PCR tests were included in this study to optimize the standardization. For this reason, the possible effects of the virus at the earlier stages of pregnancy or symptomatic COVID-19 infection's effect on newborn hearing during pregnancy could not be investigated.

Conclusion

The COVID-19 pandemic is affecting the entire population and the healthcare system at all stages. It is an unavoidable fact that this pandemic can also affect pregnant women. Babies of pregnant women with COVID-19 may develop pathologies related to the characteristics of the virus and disease. In this study, we examined the newborns of pregnant women with COVID-19 in terms of SHL. We demonstrated the presence of a temporary SHL in these babies with an objective methodology with optimal standardization. However, studies with larger sample size are needed to be performed order to determine this relationship further.

Ethics Committee Approval: The study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: E-83045809-604.01.02-67990, 07/04/2021).

Informed Consent: An informed consent form was obtained from all subjects.

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Comparison of the Effectiveness of Anesthesia Methods on Percutaneous Kyphoplasty: Erector Spinae Plane Block Versus Local Anesthesia

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ABSTRACT

Introduction: Currently, local or general anesthesia is commonly applied in patients undergoing percutaneous kyphoplasty (PKP) procedures; however, the best anesthesia method for PKP remains elusive. This study examined the efficacy of erector spinae plane block (ESPB) in comparison with local anesthesia in terms of postoperative analgesia requirement and pain scores, in patients undergoing kyphoplasty.

Methods: The files of 42 patients who underwent kyphoplasty were retrospectively reviewed. PKP procedure was either under local anesthesia (controls, n=20) or using ultrasound-guided ESPB (ESPB group, n=22). Postoperative analgesia requirement and pain scores assessed by visual analog scale (VAS) were recorded and compared.

Result: All control patients (100.0%) required postoperative analgesia, whereas only five patients (22.7%) in the ESPB group required postoperative analgesia ($p<0.001$). At all time-points, ESPB group had significantly lower VAS scores ($p<0.001$ for 0, 2, and 6 hours). At two hours, all patients in the ESPB group had 0 VAS score.

Conclusion: ESPB as a sole anesthesia technique for kyphoplasty procedures is a promising method that may reduce the need for perioperative analgesia and provide superior postoperative pain management, thus allowing pain-free discharge.

Keywords: Erector spinae plane block, percutaneous kyphoplasty, local anesthesia, pain management, postoperative pain

Introduction

Vertebral compression fractures (VCF) may occur due of osteoporosis, trauma, hemangioma, or metastasis in cancer patients (1). Recently, the aim of vertebral fracture treatment is to alleviate pain, prevent new fractures, and achieve spinal stability (2). Prolonged bed rest, analgesic, and corset treatment may lead to systemic complications in elderly patients with VCF (2). Surgical management of VCF in patients with neurological deficits is associated with increased length of hospital stay as well as morbidity and mortality (3). Consequently, minimal invasive procedures such as vertebroplasty, kyphoplasty (KP), and lordoplasty have been developed in recent years in an attempt to obtain anatomical and functional restoration of the vertebrae, to achieve earlier symptomatic relief, to allow earlier return to social life, and to significantly reduce morbidity and mortality (4). KP involves the use of inflatable balloons within bone to restore vertebral body height and low-pressure cement injections into the volume obtained through the use of the balloon (1). Today, local or general anesthesia are commonly applied in patients undergoing percutaneous KP (PKP) procedures, which are carried out in prone position, potentially increasing the risk of cardiopulmonary complications due to anesthesia and poor airway management. General anesthesia may be associated with life-threatening problems, particularly among the elderly with comorbidities. On the other hand, local anesthesia alone fails to provide adequate analgesic activity (1). Anesthesia management effectively controlling anxiety and pain without any interventions to maintain respiratory and cardiac functions may represent a more appropriate approach (1), although the best anesthesia method for PKP remains controversial. Ultrasound-guided erector spinae plane block (ESPB) is an inter-fascial plane block involving injecting local anesthetic into the fascial plane. The injection occurs deep in the erector spinae muscle reaching the tip of the transverse process of the vertebra. Therefore, the local anesthetic diffuses not only into the cranio-caudal fascial plane but also into the paravertebral and epidural spaces anteriorly, and intercostal space laterally at several levels (5). This method provides both intraoperative and postoperative analgesia. To the best of our knowledge, use of ESPB in KP to achieve analgesia was reported in only one previous case report, with no comprehensive studies examining the utility of this approach in this procedure (6). Thus, this study was undertaken to examine the efficacy of ESPB in comparison

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with local anesthesia in terms of the need for intra-operative and post-operative analgesia requirements and pain scores, in a group of patients undergoing KP.

Methods

Patients who underwent percutaneous KP between June 2019 and November 2021 at our institution were included in this retrospective study. The procedure had been performed either under local anesthesia (controls) or using ultrasound-guided ESPB (ESPB group). Written informed consent was obtained from each patient. This study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval number: 09.2021.101, date: 07.01.2022). The study was conducted in accordance with the Declaration of Helsinki.

Anesthesia management: In addition to standard monitoring, all patients were monitored the analgesia nociception index (ANI) to objectively evaluate perioperative pain. Two ANI electrodes were placed on the sternum and at the level of the left nipple, and ANI was continuously displayed throughout surgical procedure. All patients received nasal oxygen with a rate of 2 liters per minute. Following ESPB or local anesthesia, the procedure was initiated when ANI ≥50. In the local anesthesia group, sedation with 1-2 mg midazolam and 50-100 mcg fentanyl was administered, when necessary.

ESPB: In the ESPB group, ESPB was performed bilaterally in the prone position by the same experienced anesthesiologist before the procedure. The procedure was performed under ultrasound guidance using a linear probe (6-13 MHz) with in-plane technique. C-arm fluoroscopy was used to identify the fracture level. A 22G block needle (100 mm, B-braun, Germany) was inserted 3 cm lateral to the spinous process (either at the right or left side). The needle was advanced in cranio-caudal direction and 1-2 mL saline was injected to separate the erector spinae muscle from the transverse process. Then, 20 mL 0.25% bupivacaine and 50 mg 0.2% lidocaine were injected, and the needle was removed. The same procedure was performed on the contralateral side. Thus, totally 100 mg bupivacaine and 100 mg of lidocaine were injected. No additional analgesics were used during the procedure.

Local anesthesia: In the control group, following the identification of fracture level using C-arm fluoroscopy, 100 mg prilocaine plus 25 or 50 mg bupivacaine were injected into 20 mL solution in the prone position for infiltration anesthesia before the procedure.

Surgical technique: Injection site was identified with the aid of fluoroscopy. First, the trocar was advanced from the skin to the pedicle and then to the vertebral body under fluoroscopy guidance. The working cannula was placed, then the balloon was placed using a catheter and inflated within the collapsed vertebra, thus a space was made for cement. Then, the vertebral body was filled with cement through the working cannula under fluoroscopy guidance.

Postoperative pain management: Pain was assessed using 0 to 10-point visual analog scale (VAS): 0, no pain; 6, severe pain; 10, worst imaginable pain. Self-assessed VAS scores of all patients were recorded upon termination of the procedure and at 2 and 6 hours. Patients received 1 gr i.v. paracetamol when the VAS score was 2 or 3; whereas they received 1.5 mg/kg i.v. tramadol when VAS ≥4. Patients were discharged eight hours after the procedure.

Statistical Analysis

SPSS version 21 software was used for data analysis. Both hypothesis tests and graphical method were used to test the distribution of continuous variables. Student's t-test for independent samples or Mann-Whitney U test was used to test between-group differences in continuous variables. Pearson's chi-square test was used to compare categorical variables. Two-sided p values <0.05 were considered as an indication of statistical significance.

Results

Table 1 shows patient characteristics. The two groups were similar in terms of mean age as well as sex and vertebral site distribution (p>0.05; for all). In the control group, six of 20 patients (30.0%) required sedation. All control patients (100.0%) required postoperative analgesia, whereas only five patients (22.7%) in the ESPB group required postoperative analgesia (p<0.001).

Changes in Postoperative VAS Scores

Figure 1 shows changes in VAS scores within 6 hours of the procedure. At all time points, ESPB group had significantly lower VAS scores (p<0.001

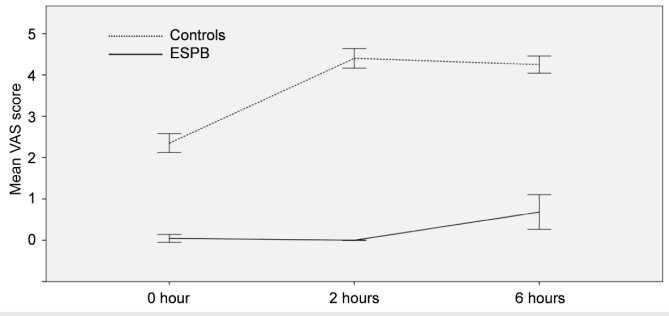

Figure 1. Changes in mean postoperative visual analog scale scores over time (immediately after the procedure, at 2 hours and at 6 hours). Upper dotted line, control group; lower straight line, erector spinae plane block group. Error bars indicate 95% confidence intervals for the mean
ESPB: Erector spinae plane block, VAS: Visual analog scale

Table 1. Patient characteristics

Characteristic	All patients (n=42)	ESPB group (n=22)	Controls (n=20)	p
Age, mean ± SD	62.2±15.0	61.7±14.0	62.8±16.3	0.791*
Female sex	29 (69.0%)	14 (63.6%)	15 (75.0%)	0.426[ı]
Vertebral site				
Thoracic	21 (50.0%)	11 (50.0%)	10 (50.0%)	1.000[ı]
Lumber	21 (50.0%)	11 (50.0%)	10 (50.0%)	
Postoperative VAS scores, median (range)				
VAS - 0 hour	0.5 (0-3)	0 (0-1)	2 (2-3)	<0.001[δ]
VAS - 2 hours	0 (0-5)	0 (0-0)	4 (4-5)	<0.001[δ]
VAS - 6 hours	2.5 (0-5)	0 (0-0)	4 (4-5)	<0.001[δ]

Unless otherwise stated, data presented as n (%). *Student's t-test for independent samples, [ı]: chi-square test, [δ]: Mann-Whitney U test, SD: Standard deviation, VAS: Visual analog scale

for 0, 2, and 6 hours, Table 1). At two hours, all patients in the ESPB group had 0 VAS score.

Discussion

Our results suggest that bilateral ESPB is a promising method for perioperative pain control in patients undergoing KP. To our knowledge, use of ESPB in KP procedures has not been reported before, except for a case report. In that case report, 30 cc of 0.05% bupivacaine was administered bilaterally under ultrasound guidance at T5 level as the primary anesthesia method in an elderly patient with chronic obstructive pulmonary disease and comorbidities who could not lie in the supine position due to intractable back pain. In addition, the patient received mild perioperative sedation with propofol infusion. The patient required no additional local anesthesia during the procedure, and was discharged home with no pain symptom. The authors of that case report suggested that ESPB provided a good level of patient comfort (6). In contrast with that case report, our patient did not require additional sedation during the procedure following bilateral ESPB. Vertebral augmentation procedures are associated with significant pain since they involve the insertion of needles of varying calibers into the vertebral body. If local anesthesia is preferred, a good level of anesthesia should be achieved to prevent needle malposition with consequent spinal cord or nerve injury (7). Several previous reports have suggested that ESPB offers a successful block strategy for managing acute and chronic pain. It has also been found to be effective for analgesia at the cervical, thoracal, and abdominal levels (8). In addition, ESPB at T4-T5 level was reported to provide effective postoperative pain management in video-assisted thorax surgery, pneumothorax surgery, open thoracotomy, and breast surgery (9-12). Other reported uses in analgesia management include costal fractures, post-thoracotomy syndrome, and chronic shoulder pain (13-15). In some other studies, low-thoracic ESPB for perioperative analgesia in patients undergoing lumbosacral spinal surgery was associated with reduced postoperative opioid need and postoperative pain scores (16,17). Similarly, in our study, VAS scores were lower in the ESPB group at postoperative 6 hours. Postoperatively, only five patients in the ESPB group required opioids, as compared to all in the other group. Opioid use is associated with relatively milder side effects such as vomiting or hypotension, as well as more severe effects, including loss of consciousness and respiratory depression (18). In the study by Apan et al. (1) comparing general anesthesia with segmental epidural anesthesia in patients undergoing percutaneous KP, the latter method was found to be more advantageous compared to general anesthesia in terms of postoperative analgesia and recovery. Hannallah et al. (19) administered low dose spinal anesthesia in conjunction with mild sedation for high-risk patients undergoing KP. Although adequate analgesia could be achieved, some of the pain control could be attributed to the concomitant administration of intravenous fentanyl and propofol. In another study, experience with spinal anesthesia was reported in 11 patients undergoing KP. Despite the administration of local anesthesia, pain was reported in four patients, and problems with the baricity of the preferred local anesthetic were seen, with hemodynamic instability (20). As compared to general anesthesia, although regional anesthesia may provide superior analgesia and may allow better maintenance of cardiovascular and respiratory reserves, adjustment of the baricity of the local anesthesia is also an important consideration since hemodynamic stability is impaired during KP when hyperbaric lidocaine is used in the prone position. This may lead to a number of adverse effects such as hypotension, vomiting, and nausea. Also, the anesthetic effect may not reach the desired segments, or may reach higher levels, potentially leading to cardiac or respiratory arrest (21). In a retrospective cohort study, a single dose ketamine administration in elderly patients with comorbidities undergoing KP, postoperative narcotic use and VAS scores at 6 hours was not reduced, and only a reduction in intraoperative narcotic use was noted. Intraoperative epidural block did not affect postoperative narcotic usage, and postoperative narcotic use was comparable across patient groups with or without epidural anesthesia (22). A prospective randomized study by Nitta et al. (23) showed no effect of intraoperative ketamine infusion on postoperative analgesia. In another prospective and randomized study, remifentanil and dexmedetomidine were compared in KP patients (24). Although propofol and remifentanil are frequently preferred because of their rapid and short acting effects, they may also be associated with hypoxemia and oxygen desaturation. Dexmedetomidine has both sedative and analgesic effects, with much less pronounced respiratory depression. However, they could not provide adequate analgesia when used as a single agents in KP (24). Mohr et al. (25) reported that oxycodone and midazolam were useful and well-tolerated agents for sedative and analgesic effects in KP. On the other hand, analgesics may aggravate oxygenation and increase right ventricular afterload due to hypercapnia (7). In our study, patients receiving ESBP did not require perioperative local anesthesia or sedative use. On the other hand, six patients in the local anesthesia group required sedation due to pain sensation. Intraoperative pain can lead to increased platelet aggregation, reduced fibrinolysis, and elevated thromboembolic risk due to stress (26). Furthermore, pain sensation may have marked effects on the psychological health of the patients with the emergence of negative emotions such as fear and anxiety, as well as distracting the surgeons with potentially reduced surgical quality (26). Similarly, Mao et al. (26) reported severe pain and intolerance among patients undergoing percutaneous KP during balloon dilatation and cement injection, and therefore these authors administered vertebral anesthesia in addition to traditional local anesthesia and found significant pain reduction without any side effects throughout the procedure. Poor perioperative pain management is associated with increased morbidity and mortality and reduced patient satisfaction, particularly among subjects with comorbidities. In patients with underlying cardiovascular conditions, pain may increase mortality via arrhythmias, hypertension, and cranial hemorrhage (26). Surgeons may prefer to operate an awake patient to be able to directly assess any neural injury. Although a lack of general anesthesia has certain advantages such as reduced risk of cardiopulmonary complications, lower medical costs, earlier discharge and early mobilization (27), Fang et al. (28) failed to observe any effect of the type of anesthesia on percutaneous KP. In our unit, surgeons did not seem to experience any problem during KP procedures in patients receiving an ESPB. In addition, these patients could be discharged at postoperative 8 hours without pain. Most authors agree that ESP block may offer certain advantages compared with traditional techniques akin to neuraxial anesthesia. Firstly, this is an easy technique, given the ultrasound guidance for

inserting the needle into the target location. Secondly, the technique is associated with a low risk of complications, since the site of administration is distant from significant anatomical structures such as the major vasculature and pleura. For this reason, ESPB has been proposed as a part of multimodal analgesia (29). So far, only a few complications of ultrasound guided ESPB has been documented. The first of these reports was published by Selvi and Tulgar (30), who observed motor weakness associated with ESPB in a patient following cesarean section. In our retrospective analysis, no ESPB-related complications were found in our patient groups that received ESPB for any indication. High-quality studies with larger sample sizes have clearly established the safety of ESPB (18).

Study Limitations

Our study included a small sample size and a retrospective design. Also, a questionnaire could have been used to assess surgeon satisfaction.

Conclusion

Our results suggest that ESPB as a sole anesthesia technique for kyphoplasty procedures is a promising method that may reduce the need for perioperative analgesia and provide superior postoperative pain management, thus allowing pain-free discharge. Further studies with a larger number of patients will shed more light on its role in this setting.

Ethics Committee Approval: This study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval number: 09.2021.101, date: 07.01.2022).

Informed Consent: Written informed consent was obtained from each patient.

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Endoscopic Procedures for Upper Gastrointestinal Tract Lesions and a Brief Review of Literature

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ABSTRACT

Introduction: We evaluated the efficacy, safety, short- and long-term results of balloon, bougie dilatations and self-expandable metallic stent (SEMS) procedures in benign and malignant obstruction of upper gastrointestinal tract (UGIT) in the last 6 years of the tertiary referral center.

Methods: This study is a retrospective review of all patients who underwent bougie, balloon dilatation and SEMS procedures because of benign or malignant lesions of UGIT from January 2014 to 2020 in a tertiar referral center. The demographics of patients, indications, technical and clinical success, complications and surveillance records were collected from the hospital database system.

Results: In the last 6 years, a total of 530 procedures, including 209 SEMS (152 SEMS placement, 57 SEMS removal), 297 bougie dilatation (Savary-Gilliard), 20 balloon dilatation and 4 percutan endoscopic gastrostomy procedures, were performed for 140 patients in our clinic. Eighty-nine patients were male and 51 patients were female and the median age of the patients was 59.6 years. The technical success rate with SEMS was 98% and the clinical success rate was 93.5% when it was provided for oral intake and purpose. The complication rate was 12% (n=64), immediate and early complication rates were 7.16% (n=38), and the late complication rate was 4.9% (n=26).

Conclusion: Serial dilatation with a balloon or bougie and SEMS can be successfully applied to UGIT fistulas and strictures without increasing complication rates.

Keywords: Endoscopic balloon and bougie dilatation, self-expandable metallic stent, upper gastrointestinal strictures

Introduction

Obstructions due to benign or malignant lesions or external compression of upper gastrointestinal tract (UGIT) cause symptoms such as nausea, vomiting, difficulty in swallowing, impaired oral intake and weight loss (1). Bougie or balloon dilation and self-expandable metallic stent (SEMS) procedures are used to remain the luminal patency for due to a carcinoma which narrows and completely obstructs the UGIT directly or externally. They are also used in benign conditions such as gastroesophageal reflux disease, peptic injury, esophageal webs, radiation damage, caustic injury and anastomotic stricture. Ingestion of caustic material or postoperative cicatrization or stricture of the esophagus and stomach are difficult complications to treat (2).

Endoscopic balloon and bougie dilatations are the gold standard treatment options used in peptic esophageal strictures (3). Although there is no difference between the two techniques in terms of success, recurrence and complication rates, 40% of patients require recurrent dilatations due to recurrence symptoms and dysphagia (4-6).

Endoscopic balloon dilation is a minimally invasive procedure with reliable, short- and long-term results and acceptable complication rates, particularly in caustic injury and chron-induced UGIT strictures (7,8). Perforation rates have been reported to be up to 0.4% due to recurrent dilatations (9). Therefore, stents are also used for iatrogenic perforations due to endoscopic procedures or for the purpose of bridging up for patients who are planned for palliative or definitive surgery, in cases such as trachea-esophageal fistula (TEF) and gastrointestinal fistula after RT or surgery and achievement of hemostasis in refractory variceal bleeding (10). Although surgical procedures have serious complications, such as wound infection, bleeding, anastomotic leakage, and dumping syndrome, it should be performed if the repeated stenting and dilatation fail (11-14). Despite the advantages of stents, this procedure has some disadvantages such as stent obstructions, bleeding, pain, fistulas, or stent-related complications (15). In the esophageal cancer group, up to %50 of patients have advanced stages and the SEMS is a reliable alternative to surgical procedures, such as feeding gastrostomy, jejunostomy, by-pass surgery. Endoscopic or oncological procedures such as balloon or bougie dilatation, chemoradiotherapy, ethanol injection, brachytherapy,

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endoluminal laser ablation and photodynamic therapy also used for palliative purposes (16-18).

This study aimed to evaluate the efficacy, safety, technical and clinical success with short- and long-term results of our experience with patients who have been successfully treated with balloon and bougie dilatations and SEMS procedures for the benign and malignant scatrization, stricture and fistula for UGIT considering current literature.

Methods

This study is a retrospective review of all patients who underwent bougie and balloon dilatation and SEMS procedures because of benign or malignant lesions of UGIT at a referral center from January 2014 to 2020. The demographics of patients, indications, technical and clinical success, complications, and surveillance records were collected from the hospital database system.

Technical success was defined as successful dilation of the stenosis, placement of the stent in the correct position for the purpose, and successful passage of the endoscope through the stenosis. Clinical success was defined as providing of the short- and long-term passage, closure of the fistula tract, and oral intake of the patient. In the long term, passage and stent patency were evaluated in patients who underwent stenting and dilatation. Complications were defined as perforation, bleeding and stent migration.

Dilatation or type of stent, width, length were chosen on the basis of preoperative clinical, radiologic, fluoroscopic, or endoscopic findings. Dilatation was performed initially by Savary-Gilliard 7 to 9 mm dilators over a guidewire and if necessary, the stent was deployed through the guidewire under the control of endoscopy or fluoroscopy. Stent positioning was confirmed by an endoscope or X-ray after deployment.

Covered stents were used for benign strictures or fistulas and were removed at the end of the 6th week and non-covered stents were used under benign conditions and removed after 4th week in accordance of instutional policy. The degree of dysphagia and clinical success was evaluated by Cowling's scoring system before and after the procedure (Table 1) (19). Oral intake was initiated according to the patient's tolerance, within the first 24 hours with liquids and then progression to semisolid.

Complications such as perforation bleeding and stent migration during the procedure are described as procedural, complications seen in the first 24 hours were defined as immediate, complications seen in the first 72 hours were defined as early and complications seen after 72 hours, such as food impaction, migration, perforation, stent-related fistula have defined as late complications (20,21).

The local ethical committee approval was obtained from University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2640, date: 25.12.2020). Well written detailed informed consent was obtained from all patients included in this study. Data were collected from a hospital database system under the control of administration. Funding This study was conducted according to with the Declaration of Helsinki.

Statistical Analysis

Descriptive statistical methods, such as mean ± standard deviation and/or median (minimum-maximum) and frequency and percentage, were used for data evaluation. The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS®) software package for Windows, version 17.0 (SPSS Inc. Chicago, Illinois, USA).

Results

In the last 6 years, a total of 530 procedures were performed, including 209 SEMS (152 SEMS placement, 57 SEMS removal), 297 bougie dilatation (Savary-Gilliard), 20 balloon dilatation and 4 percutan endoscopic gastrostomy (PEG) procedures in 140 patients. Eighty-nine patients were male and 51 patients were female and the median age of the patients was 59.6 years.

In our series, 62 patients had esophageal tumors; 83 sessions of bougie dilatation, 4 sessions of balloon dilatation and 69 SEMS placement were performed. 17 sessions of bougie dilatation were performed in 13 patients due to proximal and distal esophageal web.

Fifty-one bougie dilatations and 13 SEMS procedures were performed in a patient with caustic material-related esophagus and gastric injury. Thirty-nine bougie dilatation and 17 SEMS procedures were performed in another patient with HSV esophagitis-induced stricture and TEF.

Five times balloon dilatations were performed in 4 patients for achalasia. Three times balloon dilatations were performed in 2 patients with stenosis following Nissen fundoplication.

There were 22 patients who underwent surgery and/or radiotherapy (RT) for hypofarenx and larynx cancer and 4 patients with RT-related stenosis. 73 bougie dilatation and 27 SEMS were performed in these cases.

Eleven patients underwent 11 SEMS procedures, 10 bougie dilatations and 1 PEG procedure due to the lung cancer related mediastinal invasion, esophageal compression and TEF.

Thirteen patients who underwent surgery for gastric cancer and gastric localized gastro-intestinal stromal tumor developed stricture of esophago-jejunostomy anastomosis and 3 of them, which considered inoperable, underwent 12 dilatation and 14 SEMS procedures. Eight balloon dilatations were performed in 6 patients due to pyloric stenosis and duodenal apical stenosis.

Stenting and dilation procedures failed in 8 patients (5.8%). When cowling dysphagia score was compared with pre- and post procedure, 3 patients receiving RT to the cervical region and 1 patient receiving RT due to lung tumor were achieved to feed with bougie dilatation followed

Table 1. Cowling dysphagia scores

Score	Oral intake	Before the procedure (n)	After the procedure (n)
0	Able to normal diet	25	136
1	Semi-solid only	10	0
2	Liquid diet only	37	0
3	Complete dysphagia	68	64

by PEG procedure. Demographic information of the patients and interventions for lesions are summarized in (Table 2, 3). Complications are summarized in (Table 4).

In 3 patients, the stent could not be placed where it should be, and the procedure was repeated and the stent was properly placed. The technical success rate of passage through SEMS was 149 out of 152 (98%). The clinical success rate was 93.5% when oral intake and purposeful oriented were examined.

Balloon dilatation failed in 5 patients with duodenal apical stenosis and pyloric stenosis and these patients underwent surgery. Overgrowft developed in 9 patients on average 232.5 days. In 3 patients ingrowft developed and re-stenting procedure was performed.

Discussion

Endoscopic interventions such as balloon or bougie dilatation are recommended for treating benign peptic structures (3). SEMS is generally recommended for palliative or definitive purposes in benign conditions and patients with short life expectancy and when recurrent dilatation failures (22,23).

In our previous series, the overall complication rate was 26% (n=19), the immediate and early complication rates were 9.6% (n=7), and the late complication rate was 16.4% (n=12) (24). In this series, the overall complication rate was 12% (n=64), the immediate and early complication rates were 7.16% (n=38), and the late term complication rate was 4.9% (n=26). When these results are compared, we have seen that despite the increasing number of complicated procedures, our complication rates have decreased considerably with increased experience in the last 2 years.

Seventeen SEMS and 39 bougie dilatations were performed in the patient with HSV-induced esophagitis and 13 SEMS procedures were successfully performed in the patient with caustic material-induced injury.

These two patients had been followed up for 5 years because they did not want surgery and bougie dilatation was performed at intervals of 3-4 weeks and treatment was continued with intermittent SEMS procedures if it failed or needed. Our experience with these two patients; No matter how difficult the strictures, multiple SEMS and bougie dilatations can be used multiple times and persistently without increasing complications in the treatment of benign strictures.

Table 2. Esophageal lesions

Pathology	Operability		Stent placement (n)	Stent removal (n)	Balloon dilatation (n)	Perfo-ration (n)	Over-growft (n)	Mig-ration (n)	Mal-position (n)	Failure (n)	Bleeding (n)	HGAS (n)	EJAS (n)	TEF (n)	EGF (n)	PEG (n)
	Yes (n)	No (n)														
Hypofarenx cancer	-	2	-	-	3	-	-	-	-	-	-	-	-	-	-	1
Larynx (Ca)	18	2	28	23	64	-	1	3	1	2	-	3	1	4	-	1
Esophageal cancer (cervical)	-	3	1	-	8	1	-	-	-	-	-	-	-	-	-	1
Esophageal cancer (middle)	15	11	28	5	72	-	2	2	-	-	-	9	-	-	1	-
Esophageal cancer (distal)	5	16	28	1	6	-	7	1	-	1	-	1	-	1	-	-
EGJC	1	10	13	-	5	-	1	-	-	-	-	-	-	-	-	-
Lung cancer	-	11	10	2	9	-	-	2	-	-	-	-	-	1	-	1
RT-induced stricture (tyroid Ca)	-	-	-	1	5	-	-	1	-	-	-	-	-	-	-	-
Proximal esophageal web	-	-	-	-	14	-	-	-	-	-	-	-	-	-	-	-
Schatzki's ring	-	-	-	-	4	-	-	-	-	-	-	-	-	-	-	-
Achalasia	-	-	-	-	5	-	-	-	-	-	-	-	-	-	-	-
Nissen fundoplication stricture	1	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-
Caustic injury	-	1	13	11	51	-	-	-	-	-	-	-	-	1	-	-
HSV Esophagitis	-	1	17	13	39	-	-	-	-	-	-	-	-	1	-	-

*EGJC: Esophago-gastric junction cancer, HGAS: Hypopharingo-gastostomy anastomosis stricture, TEF: Tracheo-esophageal fistula, EJAS: Esophago-jejunostomy anastomosis stricture, EGF: Esophago-gastrostomy fistula, EJF: Esophago-jejunostomy fistula, PEG: Percutan endoscopic gastrostomy

Table 3. Gastric lesions

Pathology	Operability		Stent placement (n)	Stent removal (n)	Balloon dilatation (n)	Overgrowft (n)	Migration (n)	Malposition (n)	Failure (n)	EJAS (n)	EJF (n)
	Yes (n)	No (n)									
GIST	2	-	1	-	6	-	1	-	-	2	-
Gastric cancer	11	3	13	1	6	1	1	1	-	7	1
Pylor stenosis	-	1	-	1	8	-	-	-	5	-	-

*GIST: Gastrointestinal stromal tumor, EJAS: Esophago-jejunostomy anastomosis stricture, EJF: Esophago-jejunostomy fistula

Table 4. Complications of endoscopic procedures

Complications	Immediate (5.84%) (n)	Early (1.32%) (n)	Late (4.9%) (n)
Perforation	2	-	-
Hemorrhage	15	-	-
Malposition	6	-	-
Migration	-	5	6
Food Impaction	-	-	4
Over/ingrowft	-	-	12
Fistula	-	2	4
Failure	8	-	-
*Retrosternal pain	-	128	-

We have also evaluated esophageal and gastric strictures separately, and we believe that balloon dilatation fails, especially in gastric localized strictures and duodenal apical stenosis and surgical treatment should be performed for these patients.

Caustic induced damage is more difficult to treat than other benign strictures and requires multiple dilatations (25,26). In a study examining the effectiveness of multiple balloon dilatations in caustic induced gastric outlet obstructions, a clinical success rate of 97.3% was reported (27).

In a cohort study examining the results of balloon dilatation in patients with crohn disease-associated upper GIT stricture, multiple use of balloon dilatation to the same stenotic segment was shown to be safe and effective and did not increase the complication rate (28). Although this study was conducted in a specific patient group such as crohn disease, it was shown that multiple dilatations can be successfully performed without increasing the complication rates.

When the partial and full-covered SEMS (FC-SEMS) are compared according to migration rates, it is reported as 36% versus 12% (9,29). The most common complication in our patients was pain that responded to analgesics, especially after stenting and which was reported 16.2% rate in the literature (27).

Iatrogenic esophageal perforations are life-treating complications of endoscopic procedures and FC-SEMS placement and drainage are the treatment option. We encountered 2 cases and one of them was improved with FC-SEMS.

Pharyngo-esophageal strictures (PES) is a frequent cause of dysphagia in head and neck cancer patients. Although the exact prevalence is unknown, several retrospective series estimates that upper cervical stricture is present in 1% to 23% of the cases. The initial approach to PES is endoscopic dilatation, with a reported success rate ranging from 76% to 96% (30,31).

What do our results contribute to the literature? Especially with the experience has obtained from 2 patients, we found that stent and bougie dilatations can be performed in series without major complications in benign strictures and the most successful segments for bougie dilatations are hypopharingo-gastrostomy and gastro-enterostomy anastomosis strictures.

In addition, we demonstrated that multiple stent and dilatation procedures, which we performed especially in 2 patients, could be performed safely in the long term, and were not an alternative to surgery, and were mandatory because of the unwillingness of the patients for surgical treatment. However, these procedures have shown that multiple bougie dilatation and stenting can be performed safely in such patients.

Study Limitations

This study has several limitations that should be acknowledged. First, we didexperienced of intra-lesionar steroid injection, which reported that the success rates were significantly increased when was applied with dilatation, especially in refractory benign strictures and caustic-induced injury (32). Also, we have no experience with the method that sphincterotoms or needle-knife radial incisions combined with balloon dilatation, used for refractory pyloric stenosis (33-35).

Conclusion

Balloon or bougie serial dilatation and self-expendable metallic stent can successfully treat fistulas and strictures without increasing complication rates and can eliminate the need for emergency or definitive surgery.

Ethics Committee Approval: The local ethical committee approval was obtained from University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2640, date: 25.12.2020).

Informed Consent: Well written detailed informed consent was obtained from all patients included in this study.

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