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Aims and Scope

The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Turkey, Istanbul Istanbul Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (January, March, June, September and November).

The aim of the Medical Bulletin of Haseki is to publish original research papers of the highest scientific and clinic value on general medicine. Additionally, educational material reviews on basic developments, editorial short notes and case reports are published.

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The Medical Bulletin of Haseki

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The Effects of Intraoperative Oxygen used at Different Concentrations on Oxidative Stress Markers: A Randomized Prospective Study

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Abstract

Aim: In the case of hypoxia, despite the definite benefit of oxygen (O_2) administration, there is controversial evidence regarding the risk/benefit balance of high concentration O_2 inhalation during surgery as a precaution in those not previously hypoxic. The purpose of this study was to determine the effect of inspiratory O_2 (FiO_2) administered at different concentrations on oxidative stress during general anesthesia.

Methods: This randomized prospective study was conducted from February to May 2021. According to intraoperative FiO_2, the patients were divided into two groups: 50% FiO_2 (group 1) and 30% FiO_2 (group 2). Blood samples taken before preoxygenation and at the end of surgery were used to assess arterial partial O_2 pressure (PaO_2), total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI).

Results: The study was completed with 40 patients. Intragroup plasma TOS, OSI, and PaO_2 levels increased significantly at the end of surgery (group 1 p=0.003, 0.003, <0.001, and group 2 p=0.002, 0.044, 0.002) and TAS levels decreased (p<0.001 in both groups) were found. Because of intergroup surgery, TAS, TOS, and PaO_2 levels were higher in group 1 than in group 2 (respectively p=0.002, 0.002, <0.001).

Conclusion: Since the use of high concentrations of O_2 (50%) causes a significant increase in oxidative stress, we think that it is important to use lower concentrations of O_2 in the intraoperative period in suitable patients. More research is urgently needed on perioperative O_2 therapy.

Keywords: Inspiratory oxygen concentrations, oxidative stress index, total antioxidant status, total oxidant status

Introduction

Oxygen (O_2) is the most common drug that's used during general and regional anesthesia. High concentrations of O_2 are applied to prevent tissue hypoxia, especially during the induction and extubation phases of general anesthesia (1,2). It is known that the application of high concentrations of O_2 in the perioperative period can cause various complications (3-7). In the case of hypoxia, despite the definite benefit of O_2 administration, there is controversial evidence regarding the benefit/risk balance of high concentration O_2 inhalation during surgery as a precaution in those not previously hypoxic (3-9). Morkane et al. (10) reported that the amount of O_2 administered intraoperatively to adult patients undergoing major surgery varies greatly [inspiratory O_2 (FiO_2): 25-100%]. The intraoperative administration of O_2 differs widely in clinical practice.

In the plasma, reactive O_2 species (ROS) formed by the partial reduction of O_2 molecules, antioxidant components that inhibit the harmful effects of ROS also exist. The ratio of total oxidant status (TOS) to total antioxidant status (TAS) is the oxidative stress index

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(OSI), which is an indicator of oxidative stress (11-14). ROS are produced because of normal metabolism in cell organelles, particularly mitochondria, or for reasons such as ischemia-reperfusion, aging, radiation, high O_2 pressure, inflammation, and exposure to chemical agents (14-16). In a meta-analysis involving more than 16,000 patients, it was reported that liberal O_2 therapy in adults increases mortality and that supplemental O_2 administration with peripheral O_2 saturation (SpO_2) above 94-98% may also have adverse consequences (17). It has been reported (in laparoscopic surgery) that screening for TAS, TOS, and OSI in procedures with ischemia-reperfusion injury can be used as biochemical parameters in routine, in order to not only prevent oxidative injury but also provide a better treatment option (14). It is known that hyperoxia is a risk factor that increases patients' morbidity and mortality in intensive care units (18). Additionally, it has been reported that excessive ROS production can cause considerable organ damage in both *in vivo* and *in vitro* experiments via oxidative stress (19). The mechanism of action of oxidative stress related to high FiO_2 in inducing the formation of ROS in patients undergoing surgery hasn't been understood yet (20). Additionally, the methods to predict the benefit-risk balance of hyperoxia in such patients are not well identified yet. Currently, there is limited data describing intraoperative O_2 administration by anesthetists. The purpose of this study was to determine the effect of FiO_2 administered at different concentrations on oxidative stress during general anesthesia.

Materials and Methods

Compliance with Ethical Standards

Our study was conducted in the Zonguldak Bulent Ecevit University operating room from February to May 2021, after the approval of the Zonguldak Bulent Ecevit University Non-Invasive Clinical Research Ethics Committee (protocol number: 2021/01, ClinicalTrials.gov Identifier: NCT05099523) and the obtaining of written consent from the patients. The consolidated standards of reporting trials flow diagram was used for patient enrollment (Figure 1) (21).

Patient Population

A total of 40 patients over 18 years old who had American Society of Anesthesiologists (ASA) status I-II, under elective conditions, and under general anesthesia that lasted over 1.5 hours (h) were included in the study. The exclusion criteria were the existence of any cardiovascular, metabolic, severe hepatic, or renal diseases; malignancies; pregnancy; and the usage of drugs with antioxidant properties such as vitamin E-C, acetylcysteine in the last 48 hours, and patients requiring intraoperative 100% O_2 inhalation.

Application of General Anesthesia and Monitoring

The heart rate (HR), non-invasive mean arterial pressure (MAP), and SpO_2 of the patients taken onto the operating table were monitored. In all non-premedicated patients, vascular access was established with a 20-gauge (6) granule and saline infusion was initiated. Allen's test was performed for arterial blood gas analysis of the patients breathing room air, and if possible, a 20 G granule was placed in the radial artery, and the patency of the granule was maintained by intraoperative intermittent heparinization.

In the preoxygenation phase, 100% O_2 was applied to all patients for a duration of 3 minutes, and anesthesia induction was performed with propofol, fentanyl, and rocuronium. In our study, randomization was achieved by the sealed envelope method. According to their intraoperative FiO_2 ratio, the patients were divided into two groups: group 1 was for those with 50% FiO_2, and group 2 with 30% FiO_2. During the maintenance of anesthesia, remifentanil infusion was applied to all patients, and by selecting the automatic gas control mode of the same anesthesia device, ventilation was achieved in accordance with 2% sevoflurane, tidal volume of 8 mL kg^{-1}, and end-tidal carbon dioxide of 35-45 mmHg. During tampon insertion into the nose, the study was terminated by the halt of anesthetic gases. Then, manual ventilation was performed at a flow rate of 8 lt min 1 with 100% O_2, and the patients who started spontaneous respiration were extubated after reversal with neostigmine and atropine (0.05 and 0.01 mg kg 1, respectively).

In our study, it was planned that iv 5-10 mg ephedrine would be administered when MAP decreased more than 20% compared to control, iv 0.5 mg atropine when HR decreased below 50 beats per min, and in the case of SpO_2 below 93%, FiO_2 was planned to be increased to 100% O_2.

Data Management

Hemodynamic measurements in our study were recorded at 5-minute intervals before preoxygenation and after anesthesia induction until the end of surgery. Two different types of blood samples taken from all patients via radial artery cannula before preoxygenation (T0) and at the end of surgery (O_2 just before the concentrations were changed, T1) were transferred to the biochemistry laboratory of our hospital for a short time in a cold environment with the aim of studying their arterial partial O_2 pressure (PaO_2) with TAS, TOS, and OSI values. Samples on which oxidative parameters would be studied were separated by centrifugation at 4000 rpm, 45 minutes after the vessel puncture, and then stored at -20 °C until testing.

Measurement of Oxidant and Antioxidant Stress Markers

TAS and TOS were measured using commercially test kits (Rel Assay Diagnostics kit; Mega Tip, Gaziantep, Turkey) according to the manufacturer's instructions and using their reagents and equipment. The results of the TAS were expressed as mmol of Trolox Eq L^{-1}, whereas the results of the TOS were expressed as μmol H_2O_2 Eq L^{-1}. OSI was calculated using the formula OSI= [(TOS, μmol H_2O_2 Eq L-1)/(TAS, μmol Trolox Eq L-1) × 100] (22,23).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 23.0 (IBM SPSS Inc. Chicago, IL, USA) program. Compliance with the normal distribution was evaluated using the Shapiro-Wilk test. The chi-square test was used to compare categorical variables according to the groups. To evaluate the effects of the group and time main effectors and of their interactions on HR, MAP, and SpO_2 values, the generalized linear model method was used, and Bonferroni correction was used for multiple comparisons. In the comparison of normally distributed data based on the groups, the Independent two-sample t-test was used, and the Mann-Whitney U test was used to compare the non-normally distributed data. The paired two-sample t-test was used to compare the normally distributed data according to time within the group, and the Wilcoxon signed-rank test was used to compare the non-normally distributed data. Analysis results were presented as mean quantitative data ± standard deviation.

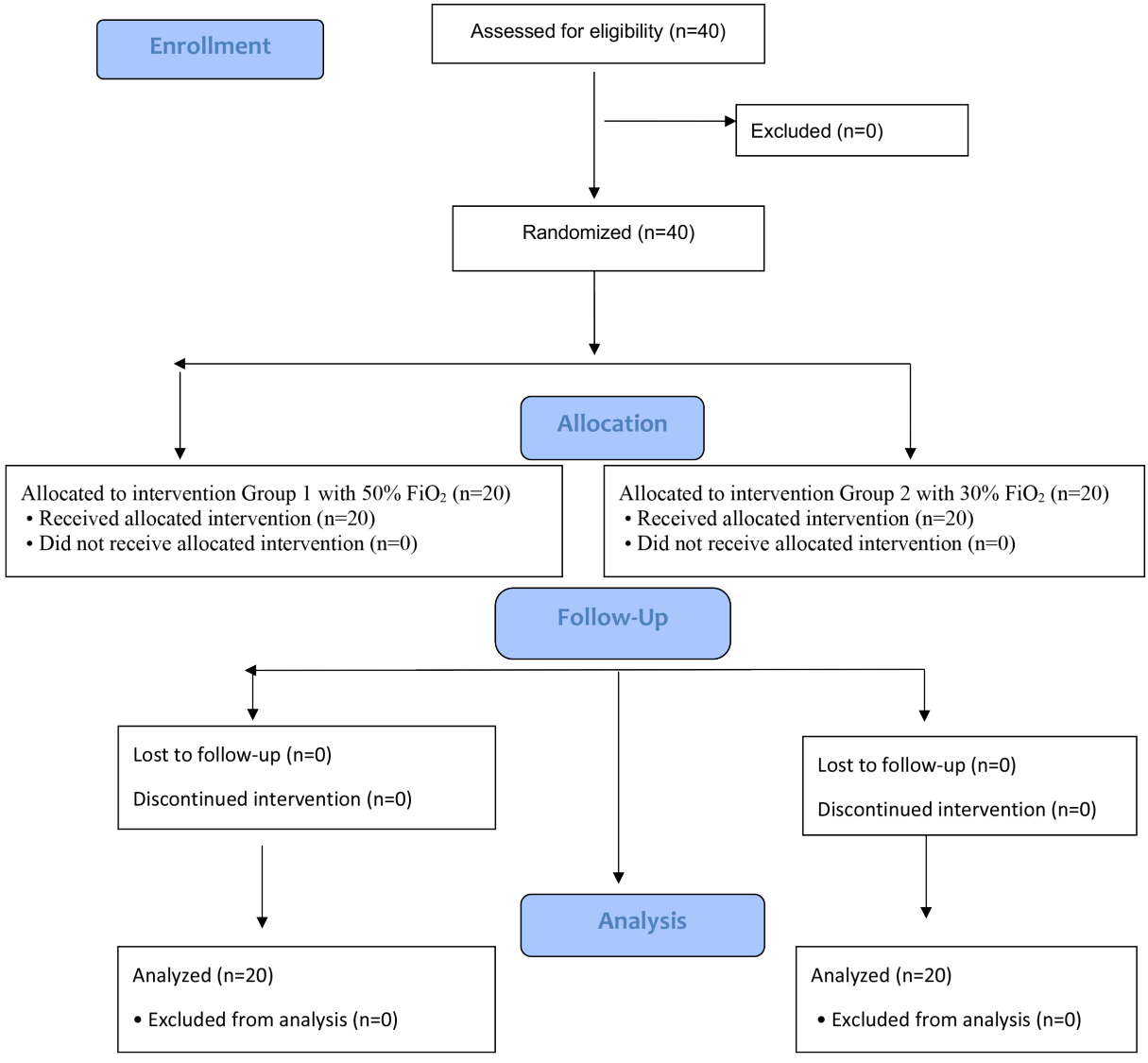

Figure 1. CONSORT flow diagram of the study

The planned sample size required to detect 95.9% test power (1-β), 95% confidence (1-α) and effect size d=1.16 was 9 people per group. We included 20 patients in each group to compensate for patient dropouts (18). A p-value of <0.05 was considered statistically significant.

Results

Our study was completed with 40 patients. Demographic characteristics, ASA risk classes, and the duration of surgery and anesthesia of the patients were similar (Table 1).

In all patients, hemodynamics were stable during the procedure, and the HR, MAP, and SpO_2 levels of the patients did not show significant differences between and within the groups. We did not have any patients who were desaturated and therefore excluded by increasing the O_2 concentration.

Before preoxygenation and at the end of surgery, TAS, TOS, OSI, and PaO_2 levels are summarized in Table 2.

Discussion

It was observed that intraoperative O_2 used at 30% and 50% concentrations caused a significant increase in post-surgical plasma TOS, OSI, and PaO_2 levels, while decreasing TAS levels compared with the levels before preoxygenation in both groups. Changes in postsurgical plasma TAS, TOS, and PaO_2 levels were found to be higher in the FiO_2 50% group.

During the induction and extubation of anesthesia to prolong the desaturation development time when unexpected difficulties arise in airway management, 100% O_2 application is widely used (1,2,6). The World Health Organization recommends the use of intraoperative high FiO_2 to prevent surgical site infections (24). However, while many anesthesiologists use high FiO_2 only during anesthesia induction and extubation, relatively low FiO_2 is used for anesthesia maintenance. The fact that intraoperative high FiO_2 was demonstrated to be associated with postoperative major respiratory complications and 30-day mortality limits intraoperative high O_2 application (7,20). Although there are many studies on the subject, the results regarding the optimal FiO_2 to be administered intraoperatively are still controversial (6,10,24). In daily anesthesia practice, FiO_2 rate appears to be determined according to the preference of patients or routine application regimen rather than evidence-based guidelines (6,25). A recent Cochrane systematic review reports that the evidence to support the routine use of high FiO_2 during anesthesia in humans is insufficient (20). Park et al. (26) investigating the effects of the reduction FiO_2 on postoperative gas exchange during microvascular decompression surgery, demonstrated that the reduction of FiO_2 from 1.0 to 0.3 during anesthesia induction and extubation, and from 0.5 to 0.3 in the intraoperative period, improved postoperative PaO_2/FiO_2 rate.

In the literature, it has been stated that oxidative stress in animals exposed to high concentrations of O_2 is increased (27,28). Chongphaibulpatana et al. (27) in their study conducted in dogs to determine the effects on oxidative stress markers, reported that O_2 application at 3 different concentrations (40%, 60%, and 100%) during general anesthesia with sevoflurane lasting 3 hours caused no significant difference between the 3 groups; actually, 100% O_2 application did not change the level of oxidative stress. However, Kumar et al. (28) speculated that antioxidant enzyme activity may exist differently among species. Although they are the main antioxidant enzymes in humans, the activity of some antioxidant enzymes didn't appear to increase in rabbits exposed to O_2.

Table 1. Demographic data concerning with patients

	Group 1 (n=20)	Group 2 (n=20)	p-value
Female/Male	8/12	10/10	0.525
Age (year)	28.40±8.60	28.80±9.59	0.890
Weight (kg)	70.90±15.34	71.95±15.18	0.829
ASA (I/II)	12/8	11/9	0.749
Operation time (min)	168.75±58.86	175.35±52.62	0.711
Anesthesia time (min)	182.75±60.76	188.65±53.21	0.746

Data are presented as mean ± standard deviation or number (n)
Group 1: FiO_2 50%, Group 2: FiO_2 30%
min: Minute, ASA: American Society of Anesthesiologists

Table 2. Comparison of oxidative stress parameters and PaO_2 levels

	Group 1 (n=20)	Group 2 (n=20)	p-value
TAS (mmol Trolox equiv/L)			
T0	1.38±0.37	1.07±0.43	**0.019**
T1	1.09±0.39	0.69±0.37	**0.002**
P*	**0.003**	**0.002**	
TOS (μmol H_2O_2/L)			
T0	4.48±1.32	3.81±1.05	0.123
T1	6.08±1.98	4.49±1.14	**0.002**
P*	**0.003**	**0.044**	
OSI (arbitrary unit)			
T0	0.34±0.11	0.41±0.18	0.267
T1	0.66±0.40	0.93±0.66	0.332
P*	**<0.001**	**0.002**	
PaO_2			
T0	98.34±13.48	104.36±26.26	0.561
T1	214.60±35.43	146.90±43.88	**<0.001**
P*	**<0.001**	**<0.001**	

Group 1: FiO_2 50%, group 2: FiO_2 30%
p: comparison between groups
p*: comparison in-group
TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, PaO_2: Arterial partial oxygen pressure, T0: Before preoxygenation; T1: The end of surgery (just before the alteration of O_2 concentrations)

The anesthetic agents used in general anesthesia and the duration of anesthesia, along with the stress of surgical trauma, are important factors that disrupt the immunological and antioxidant barrier systems of the body (5,14,26,28,29). In the inspired O_2 concentration, its effects on ROS and antioxidant capacity have been demonstrated in many studies (3-5,13,14,20,28,29). It has been reported that the antioxidant capacity decreases after exposure to intraoperative 50% O_2 in adult patients undergoing colorectal surgery (30). Baysal et al. (14), in their study investigating the oxidant and antioxidant status in laparoscopic surgeries in pediatric patients, reported that after exposure to intraoperative 50% O_2, post-surgical TAS levels decreased, while TOS and OSI levels increased. They concluded that ROS is produced during the laparoscopic procedure, possibly because of the ischemia-reperfusion phenomenon induced by inflation and deflation of the pneumoperitoneum, thus resulting in the consumption of plasma antioxidants.

During anesthesia induction and extubation in our clinic, 100% O_2 is used, and FiO_2 in 50% concentration is often used in anesthesia maintenance. In our study, the fact that TAS increased statistically and TOS decreased in both groups at the end of surgery suggests that our findings are consistent with the literature. While in our study, the oxidant/antioxidant and PaO_2 levels of the FiO_2 50% group were higher than those of the FiO_2 30% group at the end of surgery, no difference was found with regard to OSI levels. Since the initial TAS level was higher in the FiO_2 50% group, we think that there is no difference in OSI levels between the groups. The fact that the duration of anesthesia was approximately 3 hours, the surgery was minimally invasive, and the hemodynamics were stable, suggests that our results may be responsible for unpredictable findings on oxidative stress markers. Thus, the clinical implications and appropriate pathophysiological mechanisms of the findings of this study require further clarification by larger-scale studies.

Study Limitations

Our study has several limitations. First, patients with serious comorbidities were not included. Therefore, it is difficult to know whether there is a beneficial effect of decreasing intraoperative O_2 concentration in patients at high risk. Additionally, studies investigating longer O_2 exposure durations of oxidative stress markers need to be evaluated. Despite its limitations, our study is a valuable study because it makes us think that we should be more sensitive in the use of intraoperative O_2 and it is one of the few studies that contribute to the literature by showing that O_2 is an effective factor in the increase in oxidative stress markers.

Conclusion

Since the use of high concentrations of O_2 (50%) causes a significant increase in oxidative stress, we consider that it is important to use lower concentrations of O_2 in the intraoperative period in suitable patients. More research is urgently needed on perioperative O_2 therapy.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Zonguldak Bulent Ecevit University Non-Invasive Clinical Research Ethics Committee (protocol number: 2021/01, ClinicalTrials.gov Identifier: NCT05099523)

Informed Consent: Written informed consent was obtained from patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.K., B.G.A., H.A., Design: G.K., B.G.A., H.A., M.C., Data Collection and/or Processing: G.K., E.B., M.C., Analysis and/or Interpretation: B.G.A., H.A., Literature Research: G.K., B.G.A., Writing: G.K., B.G.A., H.A., M.C.

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Original Article

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Classification of Breast Cancer on the Strength of Potential Risk Factors with Boosting Models: A Public Health Informatics Application

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Abstract

Aim: The diagnosis of breast cancer can be accomplished using an algorithm or an early detection model of breast cancer risk via determining factors. In the present study, gradient boosting machines (GBM), extreme gradient boosting (XGBoost) and light gradient boosting (LightGBM) models were applied and their performances were compared.

Methods: The open-access Breast Cancer Wisconsin Dataset, which includes 10 features of breast tumors and results from 569 patients, was used for this study. The GBM, XGBoost, and LightGBM models for classifying breast cancer were established by a repeated stratified K-fold cross validation method. The performance of the model was evaluated with accuracy, recall, precision, and area under the curve (AUC).

Results: Accuracy, recall, AUC, and precision values obtained from the GBM, XGBoost, and LightGBM models were as follows: (93.9%, 93.5%, 0.984, 93.8%), (94.6%, 94%, 0.985, 94.6%), and (95.3%, 94.8%, 0.987, 95.5%), respectively. According to these results, the best performance metrics were obtained from the LightGBM model. When the effects of the variables in the dataset on breast cancer were assessed in this study, the five most significant factors for the LightGBM model were the mean of concave points, texture mean, concavity mean, radius mean, and perimeter mean, respectively.

Conclusion: According to the findings obtained from the study, the LightGBM model gave more successful predictions for breast cancer classification compared with other models. Unlike similar studies examining the same dataset, this study presented variable significance for breast cancer-related variables. Applying the LightGBM approach in the medical field can help doctors make a quick and precise diagnosis.

Keywords: Breast cancer, boosting algorithm, gradient boosting algorithm, XGBoost algorithm, LightGBM algorithm

Introduction

Breast cancer, one of the most frequently diagnosed tumors in women worldwide, has become the second-largest cause of cancer-related deaths. Breast cancer is a serious global health problem: it is the most commonly diagnosed cancer worldwide, with an estimated 2.26 million cases in 2020, and the leading cause of cancer death among women. With the developments in medical treatment, the 5-year survival rate has reached 91%, and the 10-year survival rate has reached 86% (1). According to the World Health Organization, the global incidence of breast cancer is increasing rapidly due to advances in lifestyle, reproductive factors, and life expectancy. 58% of all breast cancer fatalities occur in middle-and low-income nations. While breast cancer survival rates are typically 80% in rich countries, they decrease to 60% in the middle- and 40% in low-income countries due to a lack of early screening programs, which results in incurable diagnoses in 80% of late-stage tumors (2).

Breast cancer is a leading cause of morbidity and death worldwide, and its prevalence is increasing daily. According to Global Cancer Statistics 2020 data, the incidence of breast cancer in Turkey was calculated as

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10.6% (22345 individuals, both genders, all ages). In the same report, it is reported that approximately one out of every four women (24.4%) in Turkey is diagnosed with breast cancer, and 4.7% (5452 individuals) die of breast cancer in the second rank in terms of mortality rates (3). From a public health perspective, breast cancer incidence is most commonly associated with age, among other risk factors. The incidence of breast cancer increases rapidly at the age of 40-50 toward the end of the active reproductive age and decreases slightly after menopause around the age of 50. The relatively low incidence and mortality of breast cancer causes it to be the most prevalent type of cancer (4).

Breast cancer is thought to be a genetically varied and physiologically diverse illness. Disparities in gene expression are linked to long-known clinical and phenotypic differences. Previous research on breast cancer has revealed five distinct subtypes [luminal A (estrogen receptor (ER +); luminal B (ER +); HER2 overexpression; normal breast-like and basallike] that are associated with varying clinical outcomes. Early detection and classification of breast cancer development allows patients to obtain proper treatment. The basal-like subtype is typically ER and HER2 negative (i.e. not amplified) and resembles breast myoepithelial cells. The basal-like subtype has been associated with BRCA1-associated carcinomas and has the highest proliferation rates and poor clinical outcomes (5,6).

The diagnosis of breast cancer can be accomplished using an algorithm or an early detection model of breast cancer risk via determining factors. This model is used to detect breast cancer risk and is a preventive action that uses machine learning to classify the risk of breast cancer associated with variable predictors, making it easier to classify.

Machine learning is a type of artificial intelligence that allows computers to learn without being explicitly programmed. Machine learning is an area of artificial intelligence technology that employs algorithms to synthesize the underlying relationship between data and information (7). The scientific field of machine learning concerns how computers learn from data; it is also a type of artificial computer intelligence that enables computers to learn automatically and without human involvement or aid (8). Machine learning has been used in cancer detection and diagnosis. Using machine learning algorithms, tumors and other malignancies have been identified, classified, detected, and distinguished. In other words, machine learning has mostly been used to assist in diagnosing and detecting cancer (9,10). Scientific studies on the application of machine learning methods in health care have demonstrated that machine learning significantly affects health quality and safety (11,12).

This study compares the breast cancer classification performance of the gradient boosting machines (GBM), extreme gradient boosting (XGBoost), and light gradient boosting (LightGBM) models, which are boosting algorithms on the open-access breast cancer dataset, and evaluates the associate with breast cancer are determined.

Materials and Methods

Compliance with Ethical Standards

Ethical approval was not applicable and not obtained for this study because the open access dataset was used in this study. This study was conducted in accordance with the Declaration of Helsinki.

Study Design

The data were collected from the Department of General Surgery at the University of Wisconsin-Madison and presented to users as open access. The open-access dataset "Breast Cancer Wisconsin (Diagnostic) Data Set" was collected from the UCI Machine Learning Repository to study the light gradient boosting method's operation and to evaluate the model (13).

Variables in the Study

The following variables were used for this study: diagnosis (malignant, benign), radius mean (mean of distances from the center to points on the perimeter), texture mean (the standard deviation of grayscale values), perimeter mean (mean size of the core tumor), area mean, smoothness mean (mean of local variation in radius lengths), compactness mean (mean of perimeter 2/area - 1.0), concavity mean (mean of the severity of concave portions of the contour), concave points mean (mean for the number of concave portions of the contour), symmetry mean, fractal dimension mean (mean for "coastline approximation" - 1).

Boosting Algorithm

It was developed by Schapire in 1989. Recent work by Freud and Schapire and Friedman has further developed this algorithm. The boosting algorithm is a sequential method based on slow learning that tries to learn from errors. These algorithms combine several low-precision models to create high-precision models. As a general principle, it tries to obtain a strong model by combining the models obtained in each iteration within the framework of specific rules (14). First, random samples are generated from the training data during the boosting algorithm process. A classifier was trained for this sample, and the entire training data was tested. An error was calculated for each sample estimate. If the sample is misclassified, the weight is increased for that sample, and another sample is

created. These processes are repeated until a high degree of accuracy is obtained from the system (15). Within the scope of boosting algorithms, Light Gradient Boosting, one of the tree-based methods, will be used in this study.

Gradient Boosting Algorithm

GBM are learning algorithms that fit new models sequentially to obtain a more accurate estimate of the response variable. This strategy's basic idea is to generate new base learners with the highest correlation to the ensemble's negative gradient of the loss function. Although the loss functions can be chosen arbitrarily, for clarity's sake, if the error function is the conventional squared-error loss, the learning strategy will result in consecutive error fitting. In general, the researcher can choose the loss function, given the breadth of already determined loss functions and the possibility of constructing one's own task-specific loss (16,17).

Due to this great degree of adaptability, GBM may be tailored to any data-driven job. It introduces a great deal of flexibility into the model design, making the selection of the optimal loss function a question of trial and error. However, Boosting algorithms are reasonably simple to implement, allowing for experimentation with various model designs. Additionally, GBM has demonstrated tremendous effectiveness in various machine-learning and data-mining difficulties (18).

XGBoost Algorithm

XGBoost, short for extreme gradient boosting, is a machine learning method based on gradient boosting and decision tree algorithms. Friedman developed the original version of the XGBoost algorithm in 2002 (15). XGBoost is a viral algorithm, and it is used for health, energy, finance, etc. It has found applications in the fields. Compared to other algorithms, it is in a very advantageous position in terms of speed and performance. XGBoost has high accuracy for both classification and regression models. It is also 10 times faster than other algorithms. XGBoost includes a set of tweaks that improve performance and reduce overfitting or overlearning, thus achieving better performance. In addition, it ensures that the accuracy of the model is maximized by cross-validating itself without considering any parameters (19).

LightGBM Algorithm

The LightGBM algorithm is a different gradient boosting model that uses decision trees. Regression was used for classification and ranking analysis. Two strategies can be used when training each decision tree and separating data, focusing on the level of the tree (level-wise) and focusing on the leaves of the tree (leaf-wise). In the level-wise condition, the tree grows while maintaining the balance of the tree, while the leaf-wise strategy continues to split the leaf that reduces the loss the most. LightGBM's leaf-wise growing tree structure selects the losses in a particular branch and splits them based on their contribution to the overall loss. In most cases, trees with lower error rates learn faster than other depth-focused growing tree-based models (20). While the leaf-wise growth strategy can create any tree by level-wise training, the reverse is not true. Because of these features, over-learning can be prevented since the LightGBM model grows mainly horizontally and the tree depth does not increase much. This gives better results, especially for large datasets (21). Another advantage of the LightGBM model is that it does not require processes such as one-hot encoding to numerically analyze data with categorical variables. It shortens the training time of the model and reduces resource usage by converting the variables with continuous values into categorical values. In the studies conducted on different data sets, it has been concluded that the data learning process of the LightGBM model is 20 times faster than that of other models (22).

Repeated Stratified K-fold Cross-validation

This approach repeats the stratified K-fold cross validator n-times, with each repetition including distinct randomization. Stratified K-fold is similar to stratified K-fold in that the entire data set is partitioned into k subgroups. It approximately maintains the same percentage of samples from each target class during each cycle (23).

Statistical Analysis and Modeling

Quantitative variables are summarized using the median (minimum-maximum) method, while qualitative variables are expressed in terms of numbers and percentages. The Kolmogorov-Smirnov test was used to determine whether the distribution was normal. The Mann-Whitney U test was performed to determine whether there is a statistically significant difference between the categories of the dependent variable in terms of the input variables. Statistical significance was defined as $p<0.05$ values. All analyses were conducted using the IBM SPSS Statistics 26.0 for Windows package application and the Python 3.9.7 programming language (24). According to the studies, these models are superior over other machine learning methods in terms of performance, and these models are included in the study. In the study, during the modeling phase, it was divided into training (80%) and test (20%) data sets. Analysis was carried out using the repeated stratified K-fold cross-validation method.

Results

The data set in this study included 569 patients, 357 (62.7%) benign and 212 (37.3%) malignant breast

lesions. The correlation of the variables with each other is given in Figure 1.

Descriptive statistics for the variables included in the study are given in Table 1. When Table 1 is examined; there was a statistically significant difference between the dependent variable classes (benign/malignant) in terms of texture mean (p<0.001), radius mean (p<0.001), area mean (p<0.001), perimeter mean (p<0.001), smoothness mean (p <0.001), concavity mean (p<0.001), compactness mean (p<0.001), concave points mean (p<0.001) and symmetry mean (p<0.001). However, there was no statistically significant difference between the dependent variable classes (benign/malignant) in terms of fractal dimension mean variables (p=0.537).

The performance metrics [accuracy, recall, area under the curve (AUC), and precision (positive predictive value)] computed from the models developed to classify breast cancer are listed in Table 2. For the GBM model; accuracy, recall, AUC and precision (positive predictive value) values obtained from the model were 93.9%, 93.5%, 0.984, and 93.8% respectively. For the XGBosst model; accuracy, recall, AUC and precision (positive predictive value) values obtained from the model were 94.6%, 94%, 0.985, 94.6% respectively. For the LightGBM model; accuracy, recall, AUC and precision (positive predictive value) values obtained from the model were 95.3%, 94.8%, 0.987, 95.5% respectively. The best performance metrics were obtained from the LightGBM model. The number of times a feature is used in a model determines its importance in LightGBM. The data set is partitioned into several folds based on the feature importance score. We calculate the importance of each feature in each fold and average the importance of each feature across all folds. The feature importance score will be the average of the results. The reasoning behind this is that randomization is used in each run of LightGBM fitting. As a result, the ensemble mean can provide significant evidence for the significance of traits. For the LightGBM model with the best performance metrics, the importance values of breast cancer-related factors are given in Figure 2. The five most important factors are the mean of concave points, texture, concavity, radius, and perimeter, respectively.

Discussion

Breast cancer has the greatest fatality rate among women and is the second most common cancer form worldwide. Breast cancer is one of the most serious health issues due to its poor prognosis, high mortality rate, and new cases. A large number of deaths in women are recorded each year, indicating that there is still an urgent need for more effective and timely diagnosis for appropriate therapy in breast cancer. Despite advancements in cancer diagnosis and treatment, this disease is still a major problem in health (25).

The effectiveness of machine learning approaches in classification and definition has given computer technology the power to make judgments. These benefits of machine learning approaches have resulted in enhanced decision

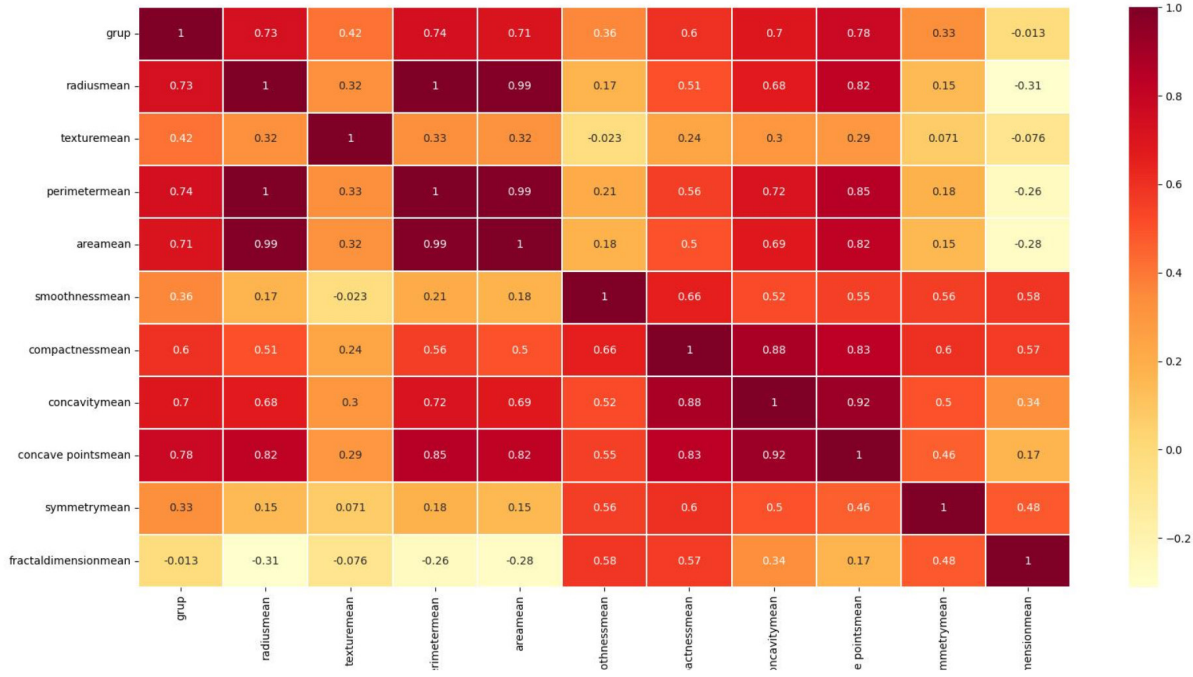

Figure 1. Correlations of the variables under question

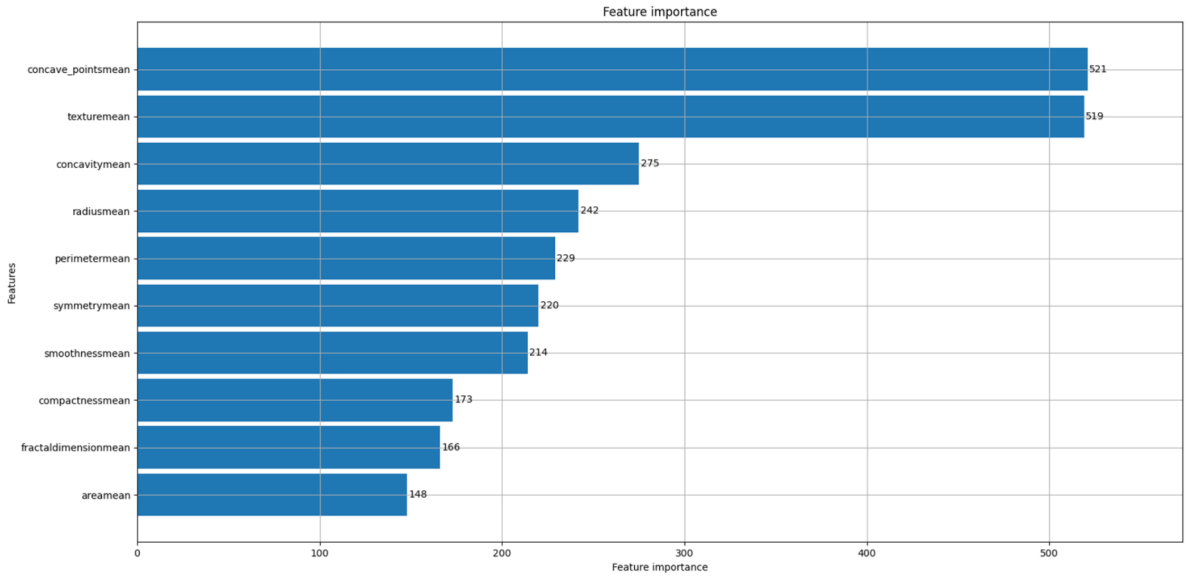

Figure 2. Importance values of variables according to LightGBM model

Table 1. Descriptive statistics for independent variables			
Variables	**Diagnosis**		**p-value**
	Benign (n=357)	**Malignant (n=212)**	
	Median (IQR)	**Median (IQR)**	
Texture mean	17.39 (4.665)	21.46 (4.4725)	<0.001
Radius mean	12.2 (2.305)	17.325 (4.525)	<0.001
Perimeter mean	78.18 (15.34)	114.2 (31.3)	<0.001
Smoothness mean	0.091 (0.018)	0.102 (0.017)	<0.001
Area mean	458.4 (175.35)	932 (500.55)	<0.001
Concavity mean	0.037 (0.0399)	0.151 (0.0939)	<0.001
Compactness mean	0.075 (0.0423)	0.132 (0.0642)	<0.001
Symmetry mean	0.171(0.0312)	0.19 (0.0364)	<0.001
Concave points mean	0.023 (0.0176)	0.086 (0.0394)	<0.001
Fractal dimension mean	0.062 (0.0073)	0.062 (0.01072)	0.537
*Mann-Whitney U test			

Table 2. The values of performance metrics			
Performance metrics / **Model**	**GBM value**	**XGBoost value**	**LightGBM value**
Accuracy (%)	93.9	94.6	95.3
Recall (%)	93.5	94	94.8
Precision (Positive predictive value) (%)	93.8	94.6	95.5
AUC	0.984	0.985	0.987
AUC: Area under the curve, GBM: Gradient boosting machines, XGBoost: Extreme gradient boosting, LightGBM: Light gradient boosting			

support systems that can assist specialists in diagnosis and treatment processes in the field of health. It is possible to achieve high success in the diagnosis of diseases using decision-support systems. Machine learning approaches, which are frequently used in cancer diagnosis processes, play an essential role in inference (26).

In this study, the breast cancer classification performances of the GBM, XGBoost, and LightGBM models, which are boosting algorithms on the open-access breast cancer dataset, are compared and the factors associated with breast cancer are determined.

Asri et al. (27) applied Support Vector Machines, decision tree (C4.5), Naive Bayes, and k-Nearest Neighbor machine learning algorithms to the Wisconsin breast cancer dataset in the UCI Machine Learning Repository in the WEKA environment. In their study, accuracy, sensitivity, sensitivity and specificity parameters were used while evaluating the classification models.

Abdel-Zaher and Eldeib (28) developed a clinical support system for detecting breast cancer. In the model used in this study, the weights were obtained from the deep belief network and the learning function of Liebenberg Marquardt, and the back propagation neural network was used. Promising accuracy was achieved compared to the previously published studies.

When the studies with the same data set are examined, the Wisconsin Original Data Set, which contains 569 records and 31 features/variables (30 predictors, 1 target), was used to improve the accuracy of breast cancer diagnosis using several machine learning algorithms. The accuracy of the suggested support vector machine model was determined to be 0.9766, and the study's findings indicated that the proposed model has a reasonable performance rate and will help increase breast cancer accuracy, a critical issue in modern times. In this study, the accuracy value for breast cancer classification was 0.9491 when only 11 features or variables (10 predictors, 1 dependent) were used on the same dataset (29). Breast cancer classification was successfully accomplished in this investigation by relying on fewer variables/features, and identical performance metrics were attained in the stated study.

Bayrak et al. (30) applied Support Vector Machines and Artificial Neural Network machine learning methods in the WEKA environment in their study on the Wisconsin (original) breast cancer dataset. The Support Vector Machines (SMO algorithm) performed best when the results of the algorithms were compared according to performance metrics such as accuracy, precision, sensitivity, and ROC area.

In the years 2020 and beyond, numerous studies have been conducted to study the classification of breast cancer using machine learning algorithms using the same data set. Rawal et al. (31) present a comparative analysis of the Wisconsin Diagnostic Data Set using several machine learning methods such as Support Vector Machine, Nave Bayes, Decision Tree, K-Nearest Neighbor, k-means clustering, and Artificial Neural Networks to detect early breast cancer.

Guldogan et al. (32) created a deep learning model for the classification of breast cancer with a 10-fold cross-validation method. Breast cancer-related factors were predicted from the deep learning model with accuracy, specificity, sensitivity, F1-score, positive and negative predictive values, and AUC. In this study, breast cancer classification was successfully performed, and similar performance success was achieved. When the effects of the variables on breast cancer were evaluated, the concave point mean and perimeter mean, two of the five most important variables, were similarly obtained during the process.

Harinishree et al. (33) have recently proposed several computer-aided frameworks to minimize multiple unnecessary breast biopsies. The mentioned article explores accessible directories of information for preparing machine learning models and presents a wide-ranging correlation between the various models to predict breast cancer.

Assegie et al. (34) analyzed the decision tree and adaptive boosting models' prediction performance. The adaptive boosting model is 92.53 percent accurate, whereas the decision tree is 88.80 percent accurate. Overall, the adaboost algorithm outperformed the decision tree approach.

Magesh and Swarnalatha (35) used decision tree, support vector machine, and SVM algorithms to predict breast cancer. The authors choose the best algorithm according to the accuracy and error rate. In the related study, data visualization and descriptive statistics were presented, and precision, recall, and F1-score measures were nearly 95% in SVM. After adjusting the SVM hiper-parameters, the accuracy increased to 97%.

Sakib et al. (36) made a comparison between machine learning and deep learning methods for breast cancer detection and diagnosis. Classification was carried out using five supervised machine learning techniques (i.e., SVM, decision tree, logistic regression, random forest, K-nearest neighbor) and a deep learning technique. The Breast Cancer Wisconsin (diagnosis) dataset was used as a training set to evaluate and compare the effectiveness and efficiency of each algorithm, including classification accuracy, recall, specificity, precision, false-negative rate, false-positive rate, F1-score, and Matthews correlation coefficient.

According to the findings obtained, GBM, XGBoost, and LightGBM, one of the boosting models showed that the classification performance on the open-access "Breast Cancer Wisconsin Dataset" gave successful predictions in classifying breast cancer according to the metric values. Among the three models, the LightGBM model gave the most successful results. In addition, the variable importance score values of cancer-related factors were estimated from the model created, unlike similar studies examining the same data set. The data set used in the study was open access and the other clinical and demographic data of the patients could not be reached. For this reason, there is no information about the subtypes of breast cancer in the study, and the findings cannot be interpreted for the subtypes. In future studies, the classification performances of many machine learning models and ensemble learning approaches can be examined to gain insights into the prediction of diseases.

Study Limitations

The main limitation of this study is that the data set was collected from a single center and shared. For this reason, the results obtained cannot be generalized according to multicenter studies and provide inferences for a certain region. The superiority of this study compared to other studies is that the importance of the variables obtained as a result of the modeling is given. Thus, risk factors that may be important related to breast cancer have been revealed.

Conclusion

Any advancements in the early detection and prediction of cancer and the implementation of alternative treatment procedures are essential for treatment. We compared the performance of three algorithms for breast cancer prediction. Applying the LightGBM approach in the medical field can help doctors make a quick and precise diagnosis. So we can help patients and doctors save time, and we can reduce medical testing and time limits.

Ethics

Ethics Committee Approval: Ethical approval was not applicable and not obtained for this study because the open access dataset was used in this study. This study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: The open access dataset study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: S.A., I.B.C., C.C., Design: S.A., I.B.C., Data Collection, or Processing: S.A., I.B.C., C.C., Analysis, or Interpretation: I.B.C., C.C., Literature Research: S.A., I.B.C., Writing: S.A., I.B.C., C.C.

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Original Article

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Parkinson's Disease and the COVID-19 Pandemic: Do Quarantine Affect the Motor and Non-Motor Symptoms of Patients with and without Deep Brain Stimulation?

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Abstract

Aim: Patients with chronic diseases were forced into lockdown due to the coronavirus disease-2019 pandemic. Extended quarantine could lead to physical inactivity and psychiatric problems. We investigated the effects of quarantine and social isolation during the pandemic on the motor and non-motor symptoms (NMS) of Parkinson's disease (PD) patients with and without deep brain stimulation (DBS).

Methods: This study included 168 patients with PD who were in quarantine for 2 months (between April 1, 2020 and May 31, 2020). Eighty-three patients had undergone bilateral subthalamic DBS surgery. A questionnaire with three parts was administered via phone: 1) motor symptoms, 2) NMS, and 3) the reasons for impairment.

Results: Of the patients, 54.7% reported impairment in at least one motor symptom and 58.9% reported impairment in at least one NMS. Increased tremors, difficulty with turning in bed, and insomnia were significantly more pronounced in patients without DBS. Patients with DBS complained less of being bored due to staying at home and had less deterioration due to lack of exercise and slower disease progression.

Conclusion: Half of the symptoms of patients with PD worsened during quarantine, but patients with DBS tolerated the lockdown better. Telemedicine and online physiotherapy programs should be recommended to prevent rapid disease progression.

Keywords: COVID-19, deep brain stimulation, Parkinson's disease, quarantine

Introduction

Coronavirus disease-2019 (COVID-19) can be fatal, particularly in the elderly and in patients with chronic diseases (1). The best way to avoid contracting the virus is to be to quarantine these individuals at home or in nursing homes. While quarantine prevents the spread of the disease, it also increases the likelihood of the emergence of physical and psychological problems. Physical inactivity due to staying home causes disability (2). Psychological problems such as depression, anxiety, and the feeling of loneliness are also frequent (3).

Parkinson's disease (PD) is a progressive, chronic disease characterized by motor and non-motor symptoms (NMS) (4,5). Regular neurologist follow-up has a significant positive effect on the disease symptoms and reduces the mortality rate (6,7). Dose titration of PD drugs under physician control and medication adherence is essential for controlling the motor symptoms, while

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physiotherapy and exercise are important for treating both motor symptoms and NMS (8-10). However, the need to stay at home, physical inactivity, the lack of visits by family members, and stress may lead to symptom deterioration (11). Prasad et al. (12) showed that 3 weeks of quarantine led to 10% impairment in motor symptoms and NMS in a group of 100 patients with PD. Falla et al. (13) found that the UPDRS-NMS scores worsened after 3 months of quarantine but not the motor scores.

Deep brain stimulation (DBS) is an effective treatment for controlling the symptoms of PD (14). Patients who have undergone DBS surgery are likely to experience both drug and battery problems during the pandemic, such as battery depletion, infection, and programming (15).

COVID-19 will continue to have an enormous effect worldwide, so being aware of how to remain in quarantine and face prolonged social isolation is necessary when making treatment plans for patients with PD. In this study, we investigated the effects of quarantine during the pandemic on PD symptoms in patients who had undergone DBS surgery and those who had not.

Materials and Methods

Compliance with Ethical Standards and Study Design

The study enrolled 168 patients (92 males and 76 females) with PD who were in quarantine and social isolation due to COVID-19 between April 1, 2020 and May 31, 2020 in two movement disorder centers. Patient records and phone numbers were obtained from the hospital database. Of these, 83 patients had undergone bilateral subthalamic nucleus (STN) DBS surgery (46 males and 37 females). The DBS batteries of the four patients were rechargeable. Two patients had a patient programmer. Patients who had been diagnosed with PD at least 1 year ago and who had undergone the DBS surgery at least 6 months previously were included. Patients who were at Hoehn and Yahr stage 5, had dementia, or had been diagnosed with COVID-19 were excluded.

The protocol for the research project has been approved by the Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (date: 03-07-2020 and approval number: 10840098-604.01.01-E.15486). The questionnaires designed to evaluate the motor symptoms and NMS of PD were administered to 91 patients (54.2% of the participants) and 77 caregivers (45.8% of the participants) who agreed to participate in the study. Questions were asked via phone calls by three neurologists (N.H.Y., B.B., and A.S.A.).

Patient Assessment

The information about the status of the 77 patients was obtained from the caregiver because these patients with PD did not want to talk on the phone for such a long time. Forty-three patients with PD with DBS and 48 patients with PD without DBS answered the questionnaire by themselves, while 40 with DBS and 37 without DBS let the caregiver answer.

The questionnaire consisted of three parts [tremors, slowness of movements, gait impairment, falls, imbalance, freezing of gait (FOG), difficulty with turning in bed, receiving help from the caregiver for standing up, and dyskinesia]. The second part evaluated the NMS [nervousness, anxiety, insomnia, daytime sleepiness, visual hallucinations, forgetfulness, pain, REM sleep behavior disorder (RBD), and constipation]. The response "better" was scored as 2 points, "already absent" was scored 0 points, "the same" was scored 1 point, and "worse" was scored 2 points. Total motor symptoms and NMS scores were calculated.

The third part included 10 questions investigating the causes of patient deterioration during this process. The 10 items were as follows:

1. I am under stress because of COVID-19.
2. I am bored because I am always at home.
3. My relatives/friends cannot visit me.
4. I cannot take my medications regularly/I sometimes take more drugs.
5. I finished my prescription and could not refill it.
6. I reduced my medication dose as I was afraid it would run out.
7. I cannot walk/exercise/do physiotherapy.
8. I can not visit my doctor for follow-up.
9. I think that my disease progressed during this period.
10. I cannot take care of myself/My caregiver cannot take care of me.

A "no" answer was scored at 0 points, and "yes" at 1 point. The total impairment score was calculated.

The patients with DBS were asked about the charge status of their battery, infection, problems with extension wires, and the need for programming.

Statistical Analysis

The data was evaluated using IBM SPSS ver. 24. Frequencies, percentages, means, standard deviations, and ranges were used to analyze the descriptive data. Chi-square and advanced chi-square tests were used to assess categorical variables. The Mann-Whitney U test was used to compare the mean values between groups when the data did not meet the parametric assumptions. A p-value of <0.05 was set as statistically significant.

Table 1. Distribution of age, educational status and the disease duration in PD patients with and without DBS			
	PD without DBS (n=85)	PD with DBS (n=83)	
	Mean ± SD	Mean ± SD	Z;p
Age (years)	67.49±8.61	65.76±7.19	3,131; 0.207
Duration of education (years)	7.52±4.82	8.02±5.15	3,775; 0.420
Duration of PD (years)	7.32±3.96	16.45±6.62	**6,367; <0.001**

Chi-square test (statistical analysis) DBS: Deep brain stimulation, n: number, SD: Standard deviation, PD: Parkinson's disease

Results

Table 1 summarizes the distributions of age, education status, and disease duration in the two groups. The disease duration was longer in the DBS group.

Table 2 shows the distribution of the motor scores in the patients with and without DBS.

Figure 1 shows the percentage of the patients whose motor symptoms worsened.

Ninety-two patients (46 without DBS, 46 with DBS) (54.7%) reported deterioration in at least one motor sign. When the two groups were compared, patients without DBS showed significant deterioration in the tremor (26 DBS- vs. 9 DBS+ patients; χ^2=9,239, p=0.002) and turning in bed (30 DBS- vs. 17 DBS+ patients; p=0.039).

The distributions of the NMS scores in the two groups are presented in Table 3.

Figure 2 shows the percentage of the patients whose NMS worsened.

In total, 99 patients (58.9%) (44 DBS- and 55 DBS+) reported impairment in at least one NMS sign. When the groups were compared, insomnia got significantly worse to a greater extent in the patients without DBS (24 without DBS vs. 11 with DBS; p=0.023).

Ten questions pertained to the subjective reasons for the symptom deterioration. Of the 168 patients, 48 (28.6%) stated that they were under stress because of COVID-19, 68 (40.5%) were bored staying at home, 44 (26.2%) felt badly because their relatives or friends could not come to visit them, 5 (3%) could not take their medications regularly, 8 (4.8%) had finished their medications, 2 (1.2%) had reduced the dose of the drugs as they feared their prescriptions would run out, 54 (32.1%) could not go walking, perform exercise, or receive physiotherapy. Fifty-seven (33.9%) could not visit their doctors for follow-up. Seventy-three (43.5%) believed that their illness had progressed during this process, and 24 (14.3%) stated that they could not take care of themselves or that their caregivers could not take care of them. Ninety-nine patients (79.0%) (58 without DBS and 41 with DBS patients) answered "yes" to at least one question.

When the two groups were compared, being bored due to staying at home, deterioration due to not being able to go for a walk, perform exercise, or receive physiotherapy,

Table 2. Distribution of scores of PD patients with and without DBS according to motor symptoms			
	PD without DBS (n=85)	PD with DBS (n=83)	
	Mean ± SD	Mean ± SD	Z;p
Tremor	0.90±0.92	0.33±0.72	**2,160;<0.001**
Slowness of movements	1.27±0.94	1.17±0.73	3,076; 0.118
Gait impairment	1.15±0.95	1.32±0.64	3,718; 0.507
Falls	0.36±0.85	0.51±0.80	**4,066; 0.046**
Imbalance	0.81±0.94	1.01±0.80	4,024; 0.096
FOG	0.62±0.83	0.87±0.86	**4,099; 0.047**
Difficulty with turning in bed	0.95±0.95	0.82±0.75	3,155; 0.210
Receiving help from the caregiver for standing up	0.68±0.94	0.43±0.78	**2,896; 0.020**
Dyskinesia	0.37±0.72	0.71±0.86	**4,351; 0.003**
Total motor score	7.12±5.36	7.19±3.96	3,550; 0.945

Chi-square test (statistical analysis) DBS: Deep brain stimulation, n: number, SD: Standard deviation, FOG: Freezing of gait, PD: Parkinson's disease

Table 3. Distribution of scores of PD patients with and without DBS according to the NMS scores			
	PD without DBS (n=85)	PD with DBS (n=83)	
	Mean ± SD	Mean ± SD	Z;p
Nervousness	0.78±1.06	0.57±0.95	3,094; 0.126
Anxiety	0.64±0.95	0.50±0,96	3,252; 0.294
Insomnia	0.59±1.12	0,63±0.70	3,527; 0.997
Daytime sleepiness	0.63±0.89	0.90±0.83	**4,170; 0.030**
Visual hallucination	0.34±0.78	0.27±0.62	3,441; 0.596
Forgetfulness	0.69±0.86	0.82±0.74	3,861; 0.257
Pain	0.73±0.97	0.77±0.87	3,582; 0,855
RBD	0.48±0.75	0.64±0.91	**4,227; 0.016**
Constipation	0.68±0.89	0.91±0.79	4,047; 0.078
Total NMS score	5.57±4.95	6.03±3.80	3,956; 0.173

Chi-square test (statistical analysis) NMS: Non-motor symptoms, DBS: Deep brain stimulation, n: number, SD: Standard deviation, RBD: REM sleep behaviour disorder, PD: Parkinson's disease

and believing that their disease had progressed during this period were significantly higher in the group without DBS (p=0.000, p=0.008, and p=0.020, respectively). The mean total impairment score was 2.65±2.46 in the patients without DBS versus 1.90±2.31 in the patients with DBS. The difference was significant (p=0.028).

Of the 83 patients with DBS, 33 (39.8%) required programming. Additionally, the batteries had depleted in six patients (7.2%). The patients with DBS did not report any problems with the DBS extension wire or infection.

Discussion

After a certain period of lockdown, patients with PD developed impaired motor symptoms, or NMS, or new symptoms. Schirinzi et al. (16) evaluated 162 patients with PD from Italy during 2 weeks of quarantine and found impaired motor signs in 50%, anxiety in 25%, hallucinations, and agitation in 18%, and other NMS in 16% of patients with PD. Baschi et al. (17) reported that motor, cognitive, and behavioral symptoms were impaired and new behavioral symptoms appeared during lockdown, leading to caregiver burden in 26% of patients. Luis-Martínez et al. (18) declared that there was an increased risk of falls in patients with PD after 2 months of quarantine. In our study, both motor and NMS symptoms deteriorated after 2 months of quarantine. At least 40% of the patients showed impairment of gait and motion. Nervousness, anxiety and pain were the most affected NMS in both groups.

DBS leads to significant improvement in motor signs (tremor, bradykinesia, and rigidity), while FOG and frequent falls develop in approximately 50% of patients during subsequent years (19,20). In our study, patients with PD with and without DBS were asked about how their motor signs of PD changed during quarantine. Falls and FOG were more common in patients with DBS, consistent with the literature. Tremors were less common in patients with DBS, and the proportion of those receiving help from a caregiver was lower. The long-term use of levodopa leads to dyskinesia, and patients with DBS frequently have a more advanced disease stage and motor fluctuations (21-23). DBS has positive effects on dyskinesia (19,23). The rate of dyskinesia was higher in the patients with DBS, which may be related to the higher rate of on–off fluctuations and longer disease duration in the patients with DBS. The slowness of movement and gait impairment (40% impairment) were the symptoms that worsened most frequently in both patient groups within 60 days of quarantine. The severity of tremor and difficulty in turning in bed were higher in the group without DBS than in the group with DBS.

Anxiety and depression, which are frequent in PD, reduce the quality of life, independent of the motor signs of PD (24). They also have adverse effects on motor signs and complications (25). While DBS improves some NMS, the severity of other NMS remains the same or deteriorates (26). Although bilateral STN DBS leads to increased sleep quality, it also leads to greater daytime sleepiness (27). Patients with RBD have a longer disease duration and a more advanced disease (28). In our cohort, the rates of daytime sleepiness and RBD were higher in patients with DBS. Overall, nervousness and anxiety were the NMS impaired most frequently (~30%). When the two groups were compared, insomnia was more common in the group without DBS.

Exercise and physiotherapy can positively affect the limitations of PD, reduce the severity of motor symptoms and improve daily activities (29). In a previous study, after a one month quarantine, the physiotherapy of 88.6% of the patients with PD was interrupted, and this led to a

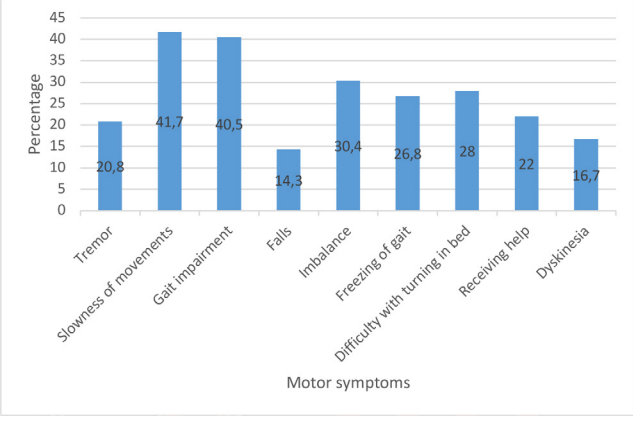

Figure 1. The percentage of motor symptoms: 20.8% tremor; 41.7% slowness of movements; 40.5% gait impairment; 14.3% falls; 30.4% imbalance; 26.8% freezing of gait; 28.0% difficulty with turning in bed; 22.0% receiving help; 16.7% dyskinesia

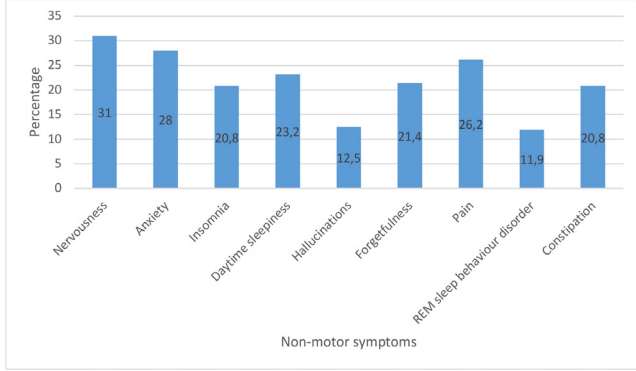

Figure 2. The percentage of non-motor symptoms: 31.0% nervousness; 28.0% anxiety; 20.8% insomnia; 23.2% daytime sleepiness; 12.5% hallucinations; 21.4% forgetfulness; 26.2% pain; 11.9% REM sleep behaviour disorder; 20.8% constipation
REM: Rapid eye movement

worsening of the motor symptoms (30). van der Heide et al. (31) reported that half of their patients became less inactive during quarantine, and the presence of anxiety, depression, and cognitive dysfunction before quarantine led to increased psychological distress during the pandemic. Zipprich et al. (32) found that while 58% of the patients had anxiety and worries, remaining immobile by staying at home and not being able to receive physiotherapy led to impaired PD signs in 31%. We also inquired about the reasons for subjective impairment in motor symptoms and NMS. While almost half of the patients suggested that the disease had progressed, one-third complained of not being able to go to their doctor, and one-third complained of not being able to go walking, exercising, or receiving physiotherapy.

In a previous study, the authors found that living alone during quarantine caused more deterioration of both motor and NMS (33). According to our results, most of the patients did not complain about being not visited (only 3%). In Turkey, there is traditionally a situation of helping parents and not leaving them alone.

In community-based studies, COVID-19-related stress is more common in the younger population and among females (34). The rate of stress reaches 80% in healthy individuals (35). In our study, this rate was 28%, half of that reported in a previous study of patients with PD (16). The stress due to COVID-19 was low in our patients, which might be because they already had a chronic disease (i.e. PD), were older, and were predominantly male.

Only 1-5% of the patients experienced difficulties with medications (1-5%), possibly because the government arranged a way for chronic disease patients to obtain their medications during the COVID-19 pandemic.

The numbers of patients who were bored because they stayed at home and who showed deterioration in their clinical condition because they could not go for walks, exercise, or undergo physiotherapy suggest that the disease had progressed more in the group without DBS. The disease duration and proportion of patients experiencing disability due to PD were higher in the patients with DBS. Learning how to cope with this disease, the significant improvement in motor signs after DBS surgery, and hoping for a future battery programming after the quarantine might have helped the patients feel safer. Approximately 40% of the patients with DBS thought that they needed battery reprogramming. The batteries had depleted in six patients, although this number will likely increase if the duration of quarantine is prolonged.

Study Limitations

There are several limitations of this study: First MDS-unified PD rating scale and NMS questionnaire are structured and frequently used scales for motor and NMS symptoms of PD. We did not apply these questionnaires because we wanted to ask the patients the change of symptoms, especially after quarantine, so we prepared a new questionnaire for lockdown. Second, we evaluated the patients by phone. It would be better to see the patients via a video call. Third, the gait impairment and FOG are motor problems that are difficult to evaluate by phone call. Finally, the current drug therapy was not administered to the patients. The equivalent dose of levodopa was not calculated. So we could not estimate the effect of drug therapy on these results.

Despite these limitations, the study has strengths: 1- This is the first study that questioned a high number of patients with PD with DBS under quarantine. 2- Both motor and NMS got worse according to our results. We also investigated the reasons for this clinical outcome with a specifically structured questionnaire.

Conclusion

While approximately half of the patients with PD had impaired motor symptoms and NMS, only 43% believed that their disease had progressed. Fewer patients with DBS indicated that their clinical condition had deteriorated, although they had longer disease durations. Considering these findings, providing psychological support using technology, making patients feel that they are not alone, and communicating with patients' and their relatives via video meetings could prevent deterioration of PD symptoms during the quarantine. It is necessary to allow the patients to walk outside during the hours when the rest of the population is inside and to schedule online exercise programs. Although patients with DBS seem to experience fewer problems than the group without DBS, adopting patient programmers and rechargeable batteries may be helpful.

Ethics

Ethics Committee Approval: The protocol for the research project has been approved by the Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (date: 03-07-2020 and approval number: 10840098-604.01.01-E.15486).

Informed Consent: We got consent from the patients and caregivers for this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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Original Article

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Comparison of Code Blue Practices Between the First Year of COVID-19 and the Previous Year

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Abstract

Aim: After the coronavirus disease-2019 (COVID-19) infection was declared a pandemic, there were some changes made to the code blue and resuscitation practices. We compared code blue practices between the first year of COVID-19 and the previous year.

Methods: We accepted the pre-pandemic (group 1) period from March 11th, 2019 to March 11th, 2020, and the post-pandemic (group 2) period from March 11th, 2020 to March 11th, 2021. The study was designed as a cross-sectional study. We investigated the incidence of code blue, the unit where the call was made, the team's time of arrival, the return of spontaneous circulation (ROSC), the duration of cardiopulmonary resuscitation, and the general outcomes. We analyzed the 6 month follow-ups of the patients.

Results: There was an increase in the incidence of code blue in group 2 (0.4-0.9%). The two groups showed a significant difference in the time of arrival, ROSC, and 1 month and 6 month survival. The ROSC rate and 1 month survival were lower in COVID-19 patients ($p<0.001$). Six month survival was lower in COVID-19 patients ($p=0.031$). We identified 63 faulty calls, and 38 of these patients died within 6 months.

Conclusion: The faulty code blue calls may be a predictor of poor prognosis, and early warning systems should be developed for patients with poor conditions.

Keywords: Code blue, cardiopulmonary resuscitation, COVID-19, survival rate

Introduction

The aim of code blue is to provide a rapid and organized response to medical emergencies by dedicated teams (1). When this call is made, healthcare professionals apply cardiopulmonary resuscitation (CPR) to individuals whose basic life functions (respiration and circulation) have stopped. Some cases that do not require CPR may be incorrectly identified as code blue. According to research, faulty code blue calls may be a predictor of poor prognosis (2,3). The implementation of code blue involves preparing a professional team, equipment, a technological call system, the time of arrival, effective intervention, a post-intervention period, and taking records (4).

After the coronavirus disease-2019 (COVID-19) infection was declared a pandemic in March 2020 (5), there were some changes made to the code blue and resuscitation practices. The World Health Organization (WHO) accepted CPR as an aerosol-generating procedure (due to the high aerosol spread during chest compressions and airway manipulations) and ranked rescuer safety as a priority in the updated guidelines (5-8).

Since rescuers needed to wear personal protective equipment (PPE) before resuscitation during the COVID-19 pandemic, significant delays were expected in performing CPR, estimating much lower survival rates (9,10). Research has shown lower survival rates after cardiac arrest in COVID-19 patients compared to other patients (11). However, previous studies have not mentioned faulty code blue calls in detail. This could stem from the fact that

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the severity of the pandemic may have differed among countries.

In this study, we compared the incidence and outcomes of code blue practices between the first year of the COVID-19 pandemic and the previous year, including faulty code blue calls.

Materials and Methods

Compliance with Ethical Standards

This research was conducted in a 1500-bed tertiary education and research hospital, designated for the COVID-19 pandemic. We adhered to the principles of the Declaration of Helsinki and obtained approval from the University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (2011-KAEK-25 2021/03-25) and the COVID-19 Scientific Research Platform (2021-03-17T14-23-31).

Study Design

This study was designed as a cross-sectional study. We analyzed the data based on Code Blue Notification Forms filled in from March 11th, 2019 to March 11th, 2021, and by accessing patient data from the hospital records. We designated the pre-pandemic (group 1) period as from March 11th, 2019 to March 11th, 2020, and the post-pandemic (group 2) period as from March 11th, 2020 to March 11th, 2021. The exclusion criteria were patients younger than 18 years and out-of-hospital code blue calls. We obtained the incidence of code blue calls, the date and time of events, patients' age, sex, and current diseases, the unit where the call was made, the units that participated in code blue, the team's time of arrival, the duration of CPR, the accuracy of the call, and the outcomes of the practice. We also examined 1 month and 6 month survival. Faulty calls were defined as those that did not require basic life support or advanced life support based on the Utstein Style (3). Faulty code blue calls were not excluded from investigating their outcomes. Patients who were not hospitalized and who applied for outpatient diagnosis and treatment were defined as outpatients. The team's time of arrival was accepted as the time between making the call and the team taking over the patient. The code blue dates and times were divided into two groups: working hours (8 am to 4 pm) and non-working hours (4 pm to 8 am on weekdays and all day on weekends). Holidays and public holidays were considered non-working hours.

Pandemic Measures

During the pandemic, some measures were taken and changes were made at our institution. To meet the increasing demand, inpatient services were reorganized; most were converted to COVID-19 units. The hospital personnel were assigned to these units on a rotational basis. COVID-19-positive patients and suspected patients were admitted to isolation wards. The criteria for suspected patients often consisted of clinical findings (acute respiratory disease) and epidemiological risk factors. Also, in our institution, patients with respiratory symptoms or fever were tested for COVID-19, then admitted to the isolation ward until their tests were negative. The staff who worked in these services used PPE for COVID-19. Besides, the use of surgical masks was mandatory in all other clinical areas.

Our Code Blue Practice

Pre-pandemic: Code blue can be given to all patients, patient relatives, or hospital staff who develop cardiopulmonary arrest in inpatient services, polyclinics, laboratories, imaging centers, and all waiting areas on the hospital campus. Code blue calls are not made from emergency rooms, operating rooms, or intensive care units, since the teams in these units must already have the skills and equipment for immediate resuscitation when necessary. The calls are made via a telephone line reserved for the code blue system. In our hospital, any healthcare personnel (doctor, nurse, or auxiliary personnel like healthcare worker or patient carrier) can give the code blue when necessary. Emergency bags and all the equipment needed for resuscitation are available on all floors of the hospital. Also, when the code blue is given, an anesthesia technician and a nurse arrive with their own emergency bag. The code blue team consists of anesthesia and intensive care physicians or internal medicine physicians, anesthesia technicians, and nurses. All healthcare personnel in the hospital are given theoretical and practical CPR training once a year by anesthesiology and reanimation specialists.

Post-pandemic: In our country, the first COVID-positive case was detected on March 11th, 2020. The WHO declared the pandemic on the same day and different code blue lists were created for pandemic services and other clinics. To shorten the time of arrival, the doctors working at the pandemic units were assigned as the code blue personnel. Therefore, all branch doctors were included in the code blue teams, and CPR training was carried out online during the pandemic.

Statistical Analysis

The statistical data was analyzed using SPSS Statistics for Windows version 20.0, 2011 (Armonk, NY: IBM Corp.). The normality of data distribution was tested with the Kolmogorov-Smirnov test, and non-normally distributed continuous variables were tested using the Mann-Whitney U test. The categorical data was analyzed using Pearson's chi-squared test or Fisher's exact test

(where appropriate). The chi-squared Goodness-of-fit test was used to analyze the monthly distribution of code blue cases. With a value of <5% for the probability of the null hypothesis, the alternative hypothesis was accepted.

Results

In our hospital, 54,400 patients were hospitalized in group 1 and 28,500 patients in group 2, with 236 and 267 code blue calls, respectively (Figure 1). In group 2, hospitalizations decreased by 47.6%, while the incidence of code blue increased from 0.4% to 0.9%. In this group, 66.3% of the patients for whom code blue was given were hospitalized in the COVID-19 ward. The months of November and December marked a significant increase in the number of code blue calls for group 2, both in comparison to the other months and the whole pre-pandemic period (p<0.05) (Figure 2).

There were significant differences between the two groups in terms of the team's time of arrival, return of spontaneous circulation (ROSC), and 1 month and 6 month survival after code blue (Table 1). There was no significant difference in terms of other parameters. ROSC and 1-month survival were significantly higher in group 1 (p<0.001). Six month survival was again significantly higher in group 1 (p=0.006). The mean time of arrival was longer in group 2 (p<0.001). The most common comorbidities were malignancy and neurological diseases in group 1 (p<0.001, p=0.017, respectively) and pneumonia and hypertension in group 2 (p<0.001, p=0.025, respectively) (Table 1).

Among code blue cases, we found no difference between the patients hospitalized in the COVID-19 wards and those in other services in terms of age, sex, or time of code blue (Table 2). However, the time of arrival was significantly longer in the COVID-19 services (p<0.001). ROSC and 1 month survival rates were lower in COVID-19 patients than in other patients (p<0.001). Again, 6 month survival was lower in COVID-19 patients (p=0.031).

In this study, the 3 units that most frequently participated in code blue were internal medicine, anesthesia and reanimation, and general practitioners (Figure 3). The 3 units with the highest CPR success were anesthesia and reanimation (55.2%), neurology (50.0%), and general surgery (46.4%). The lowest rates were in neurosurgery (9.1%), ear-nose-throat (0.0%), and orthopedics and traumatology (26.3%) (Table 3).

There were 63 faulty code blue calls, and 38 of these patients were detected to have died within 6 months. There were 42 faulty code blue calls in group 1 and 21 in group 2 (Table 4). The mean age of the patients was lower in group 1 (p<0.001). Also, 50% of the patients in this group were outpatients (p=0.002). In group 2, 52% of the patients who were given a faulty code blue call were COVID-19 patients, 57.1% of which were given during non-working hours (p=0.012). We found that 76.2% of the patients in group 1 and 28.6% of those in group 2 died within 6 months after the faulty code blue calls.

Table 1. Characteristics and outcomes of code blue cases in the pre-and post-pandemic period

	Group 1 (n=190)	Group 2 (n=241)	p-value
Age, Years; med (min.-max.)	74 (18-96)	75 (24-96)	0.157
Gender, Male; n (%)	108 (56.8%)	134 (55.6%)	0.845
Calling time, out of working hours; n (%)	137 (72.1%)	159 (66.0%)	0.176
Time to arrival; minutes; med (min.-max.)	1 (1-3)	2 (1-5)	<0.001*
CPR time; minutes	30 (3-100)	35 (0-70)	0.137
ROSC; n (%)	101 (53.2%)	68 (28.2%)	<0.001*
Survival at the 1st month (%)	44 (23.2%)	18 (7.5%)	<0.001*
Survival at the 6th month (%)	18 (9.5%)	7 (2.9%)	0.006*
Comorbidities			
Pneumonia	25 (13.8)	146 (62.1)	<0.001*
Malignancies	58 (32.0)	33 (14.0)	<0.001*
COPD	18 (9.9)	26 (11.1)	0.710
Diabetes mellitus	52 (28.7)	77 (59.7)	0.370
Hypertension	59 (31.1)	104 (43.2)	0.025*
Renal disease	21 (11.6)	42 (17.9)	0.077
Heart disease	51 (26.8)	83 (34.4)	0.137
Neurologic disease	39 (21.5)	30 (12.8)	0.017*
Other	32 (17.7)	9 (3.8)	<0.001*

*p<0.05. Mann-Whitney U test, chi-square test.
CPR: Cardiopulmonary resuscitation, ROSC: Return of spontaneous circulation, COPD: Chronic obstructive pulmonary disease, min.: Minimum, max.: Maximum, med: Median

Table 2. Characteristics and outcomes of code blue cases in COVID-19 patients			
	COVID-19 services n=160	Other services n=271	p-value
Age, Years; med (min.-max.)	76 (24-96)	74 (18-96)	0.950
Gender, Male; n (%)	86 (53.8)	156 (57.6)	0.482
Time to arrival; minutes; med (min.-max.)	2 (1-5)	1 (1-5)	<0.001*
ROSC; n (%)	36 (22.5)	133 (49.1)	<0.001*
Survival at the 1st month; n (%)	8 (5.0)	54 (19.9)	<0.001*
Survival at the 6th month; n (%)	4 (2.5)	21 (7.7)	0.031*

*p<0.05. Mann-Whitney U test, chi-square test
CPR: Cardiopulmonary resuscitation, COVID-19: Coronavirus disease-2019, ROSC: Return of spontaneous circulation, min.-max.: Minimum-maximum, med: Median

Table 3. Survival percentages of all patients after the code blue according to attending physicians' medical specialties				
	n	Successful CPR	Survival at the 1st month	Survival at the 6th month
Internal Medicine*	106	41 (38.7)	17 (16.0)	**8 (7.5)**
Anesthesiology and Reanimation	76	42 (55.2)	17 (22.4)	**7 (9.2)**
Family Medicine*	53	21 (39.6)	4 (7.5)	**2 (3.8)**
Orthopedics and Traumatology	38	10 (26.3)	1 (2.6)	**0 (0.0)**
General Surgery	28	13 (46.4)	7 (25.0)	**1 (3.6)**
Ear-Nose-Throat	23	3 (13.0)	0 (0.0)	**0 (0.0)**
Urology	23	10 (43.5)	3 (13.0)	**2 (8.7)**
Other*	23	8 (34.8)	4 (17.4)	**2 (8.7)**
Neurology	22	11(50.0)	5 (22.7)	**2 (9.1)**
Cardio-Thoracic*	18	5 (27.8)	3 (16.7)	**1 (5.6)**
Neurosurgery	11	1 (9.1)	0 (0.0)	**0 (0.0)**
Obstetrics and Gynecology	10	4 (40.0)	1 (10.0)	**0 (0.0)**
Total	431	169 (39.2)	62 (14.4)	**25 (5.8)**

Data are presented as n (%).
*indicates the compressed groups of medical specialties. Internal Medicine and Infectious Diseases and Clinical Microbiology were grouped as "Internal Medicine"; Family Medicine and General Practitioner were grouped as "Family Medicine"; Physical Therapy and Rehabilitation, Ophthalmology, Pathology, Medical Ecology and Hydroclimatology, and Psychiatry were grouped as "Other"; Cardiology, Chest Diseases, Cardiovascular Surgery, and Thoracic Surgery were grouped as "Cardio-Thoracic"

Table 4. Demographics of faulty code blue patients			
	Group 1 (n=42)	Group 2 (n=21)	p-value
Age, Years; med (min.-max.)	39.5 (21-90)	70 (22-93)	0.001*
Gender, Male; n (%)	25 (59.5)	10 (47.6)	0.427
COVID-19 (+); n (%)	N/A	11(52)	N/A
Outpatient; n (%)	21 (50.0)	2 (9.5)	0.002*
Calling time, out of working hours; n (%)	10 (23.8)	12 (57.1)	0.012*
Survival at the 6th month; n (%)	32 (76.2)	6 (28.6)	<0.001*

Mann-Whitney-U test, chi-square test.
COVID-19: Coronavirus disease-2019, N/A: not applicable, med: median, min.-max.: minimum-maximum

Discussion

In comparing code blue data from the first year of the COVID-19 pandemic and the previous year, we found that the incidence of code blue increased, whereas ROSC, 1 month survival, and 6 month survival decreased significantly in group 2. The number of code blue incidents in group 2 increased, particularly during November and December. It is known that the number of daily deaths peaked in these two months during the pandemic in Turkey. We believe that this reflected the increasing number of code blue incidents during November and December. During the pandemic, the number of patients having COVID-19 increased, so elective patient admissions were postponed in hospitals. During this period, there was an increased number of code blue incidents, despite a 47.6% decrease in hospitalizations. The literature reports the incidence of code blue as around 1-5/1000 hospitalizations (12,13). Here, our incidence of code blue was 3.4/1000 hospitalizations in group 1, in accordance with the literature; however, this number was more than twice that for group 2, with 8.5 calls per 1000 hospitalizations.

Research shows that the average time to start CPR ranges from 80 to 341 seconds (14-16). Starting CPR within 1.5-2 minutes has been reported to be more successful than after 5 minutes (14). Studies during the

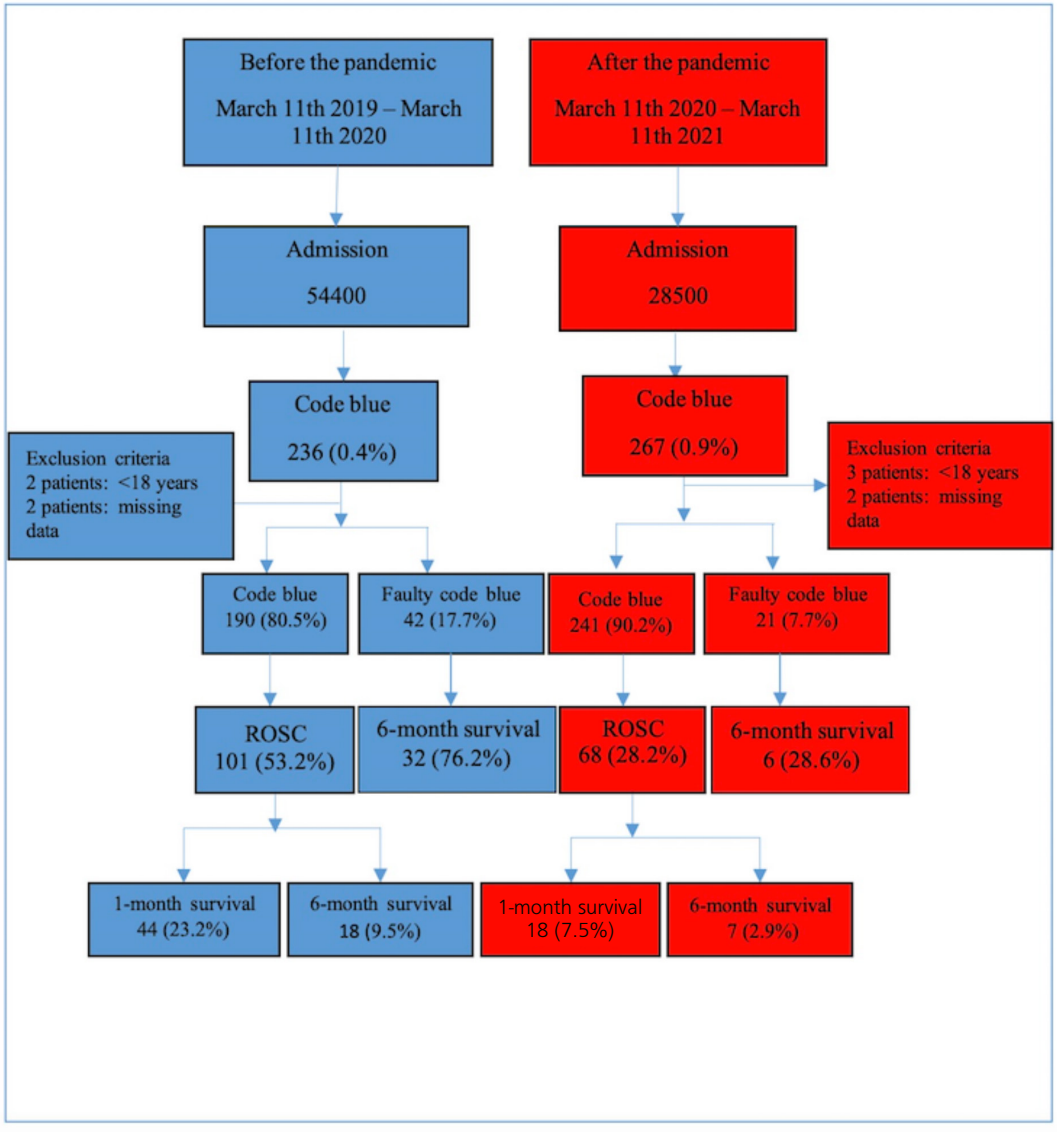

Figure 1. Workflow chart
ROSC: Return of spontaneous circulation

pandemic have suggested that wearing PPE delays CPR by up to 10 minutes (10). In this research, we observed that the mean time of arrival was longer in group 2 at 2.25±1.07 minutes. However, this time is still under 5 minutes. We associate this with the inclusion of doctors who are ready for PPE in code blue teams. In our study, we found no difference between code blue times. This indicates that the continuity of the system should be ensured both during working and non-working hours.

Studies before the pandemic report ROSC rates of 45.7-68%, while studies during the pandemic show lower ROSC rates (17-20). According to research, this result comes from the different etiology of cardiac arrest between the two periods. Before the pandemic, the most common cause was heart disease and during the pandemic it was respiratory system disease (21,22). Here, we found an ROSC rate of 53.2% in group 1, in parallel with the literature, and this rate was lower at 28.2% in group 2. The most common comorbidities were malignancy and neurological diseases in group 1 and pneumonia and hypertension in group 2. In 2010, the American Heart Association and the International Liaison Committee on Resuscitation determined the priority for CPR as chest compressions, airway, and breathing (23). Given that COVID-19 patients make up the majority of patients in group 2 and they often suffer from respiratory failure and may benefit from early ventilation, we believe that this priority should be

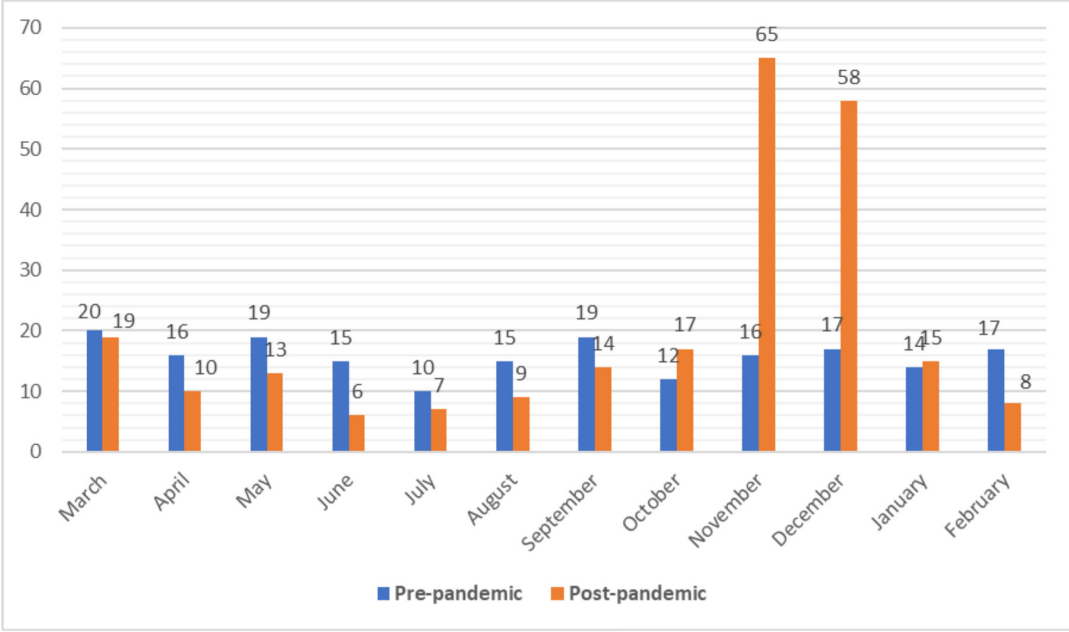

Figure 2. Bar chart of the distribution of code blue cases according to months
Footnote: The chi-square Goodness-of-fit test shows the distribution of post-pandemic code blue cases were statistically significantly different ($p<0.001$), and there was no significance in the distribution of the pre-pandemic code blue cases ($p=0.885$) according to months

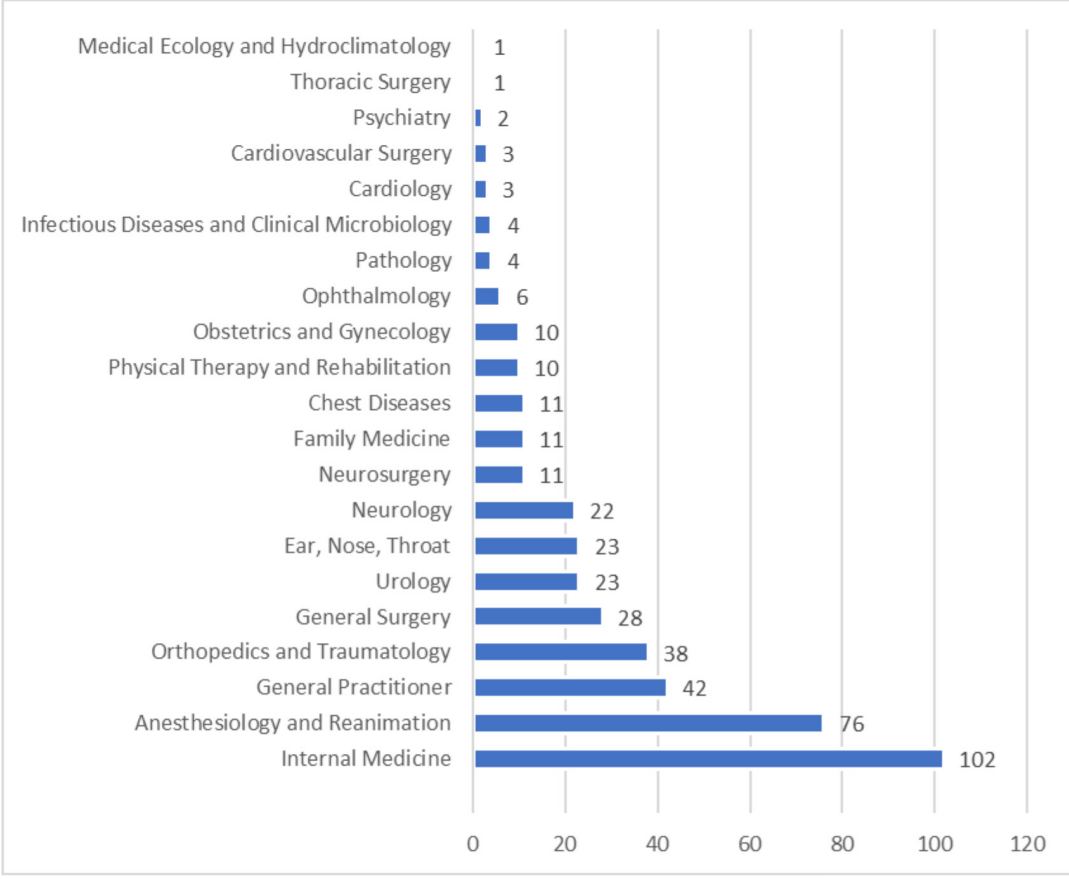

Figure 3. The distribution graphic of the physicians' medical specialties attended to code blue (n)

investigated to determine whether it is a disadvantage for COVID-19 patients.

Outcomes after IHCA vary between hospitals (24). According to the literature, studies before the pandemic reported in-hospital survival rates of 0-42% and 6-month survival rates of around 9.7% (25-27). Here, in group 2, 1-month survival decreased from 23.2 to 7.5% and 6-month survival decreased from 9.5 to 2.9%. We associate this with the fact that COVID-19 patients constituted 66.3% of all patients during the pandemic and had a poor prognosis. Still, further research is needed to increase overall survival, which is still low in all patients with cardiopulmonary arrest.

Compared with code blue patients in the COVID-19 wards with other patients, we found no difference in terms of age or sex. The time of arrival was longer with COVID-19 patients. During the pandemic, the time of arrival was expected to rise to 10 minutes (10), although we found a mean time of fewer than 5 minutes. We believe that the changes made in our code blue lists after the pandemic have influenced this finding. According to research, mortality and 1-month survival rates after code blue in COVID-19 patients were 75.0% and 2.9%, respectively (11,28). We found an ROSC rate of 22.5% and a 1-month survival rate of 5.0% in COVID-19 wards; both the 1-month and 6-month survival rates were significantly lower than those other patients. We think further research is needed on the long-term care and treatment of COVID-19 patients after a positive response to CPR.

During the pandemic, the doctors working in the code blue system were mostly from internal medicine, anesthesiology and reanimation, and family medicine clinics. After CPR and 1-month follow-up, survival rates were higher in the units of anesthesia and reanimation. We believe that there has been an increasing awareness of the importance of CPR among all doctors, regardless of the unit, during the pandemic.

In our study, we noted 63 faulty code blue calls in two years. We found the rates of these faulty calls to be 17.7% in group 1 and 7.7% in group 2. Although it is believed that faulty calls cause loss of workforce in the team, 3 of 59 patients (5%) who were given a faulty code blue call died within 6 months (3). In fact, the 1-year survival rate after a faulty call has remained the same as after CPR with VF/VT rhythm and positive response (3). We observed that 76.2% of the patients in group 1 and 28.6% of the patients in group 2 died within 6 months after a faulty call. A faulty code blue call is defined as a patient in poor condition when the call is made but one who does not develop cardiopulmonary arrest. Looking at our findings, we think patients with faulty calls may be at risk and should be investigated in detail. There have been studies on early warning systems and early intervention teams for patients with a deteriorating general condition (29,30). We believe that such practices should become widespread, as they can positively affect the number of in-hospital arrests and faulty code blue calls. In our group 1, the rate of faulty calls was higher during non-working hours. In group 2, COVID-19 patients in particular had to be followed up in isolated wards. These patients may have felt uneasy in these wards, which may have increased the rate of faulty code blue calls during non-working hours.

Study Limitations

The main limitations of this study were its single-center, retrospective design and its inability to present initial arrest rhythms, drugs used in patients, and neurological status of surviving patients due to insufficient data.

Conclusion

We compared the first year of the COVID-19 pandemic with the previous year and found increased rates of IHCA and decreased rates of ROSC, 1-month survival, and 6-month survival. We believe that faulty code blue calls may be a predictor of poor prognosis and early warning systems should be developed for patients with poor conditions. Long-term follow-up and more detailed research are needed to increase survival rates after cardiac arrest in both COVID-19 and other patients. The strength of the study is the detailed analysis of faulty blue codes.

Ethics

Ethics Committee Approval: We adhered to the principles of the Declaration of Helsinki and obtained approval from the University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (2011-KAEK-25 2021/03-25).

Informed Consent: Patient files were reviewed with the approval of the ethics committee.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: N.K., D.K., M.G., Design: N.K., D.K., M.G., H.G., Data Collection and/or Processing: N.K., S.E., S.E.A., Analysis and/or Interpretation: N.K., D.K., S.E., H.G., Literature Research: N.K., S.E.A., S.E., Writing: N.K., H.G., D.K., B.O.

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Original Article

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The Mental Health and Marital Adjustment of Mothers of Children with Attention Deficit Hyperactivity Disorder

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Abstract

Aim: The mental health of parents is affected by the behavior of their children due to parent-child relationships. This study aimed to examine the marital adjustment, emotional problems, and attention deficit hyperactivity disorder (ADHD) symptoms in the mothers of children with ADHD, and the relationships of these parameters with each other and with the offspring's behavioral problems.

Methods: This study was conducted with 152 mothers, 90 of whom had children with ADHD, between October 2020 and April 2021. The Conners' parent rating scale-revised long version (CPRS-RL) was used to rate the children's symptoms. Mothers were evaluated using a sociodemographic information form, the Beck anxiety inventory (BAI), the Beck depression inventory (BDI), the adult ADHD self-report scale (ASRS), and the marriage adjustment scale (MAS). Statistical comparisons were made between the data obtained from scales and hospital records.

Results: Significant associations were observed between oppositional and anxious-shy symptoms in children and the BAI and ASRS; between social problems and psychosomatic symptoms and the BAI, BDI, ASRS, and MAS; between restless-impulsive symptoms and BAI-BDI, ASRS, and MAS; between emotional lability and BAI, BDI, and ASRS; between inattention and BAI; and between hyperactivity-impulsivity and ASRS scores ($p<0.05$). The BAI, BDI, and ASRS scores were significantly higher, and MAS scores were significantly lower in the mothers of children with ADHD compared to the controls ($p<0.05$). A positive correlation was observed between ASRS scores and BAI ($r=0.497$ $p=0.001$) and BDI ($r=0.04$ $p=0.001$) scores. MAS scores were significantly negatively correlated with ASRS ($r=-0.383$ $p=0.001$), BAI ($r=-0.477$ $p=0.001$), and BDI ($r=-0.437$ $p=0.001$) scores.

Conclusion: This study demonstrated that in children with ADHD, problematic behaviors exacerbate anxiety, depression, and adult attention deficiency symptoms and reduce marital adjustment in mothers.

Keywords: Problem behavior, attention deficit disorder with hyperactivity, mothers, mental health, parent-child relations

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common childhood neurodevelopmental disorder. Inattention, impulsivity, and hyperactivity symptoms emerge before the age of 12 and lead to disturbances in daily life. It has been reported that approximately 5% of children worldwide are affected by ADHD (1). The etiology is complex and heterogeneous, with genetic and environmental factors being implicated (2,3). Children and adolescents with ADHD suffer impairment in academic, familial, and social contexts. Additionally, parents of these children must come face to-face with their offspring's various coercive problems, such as problems in interpersonal relationships, risk-taking behavior, conflicted parent-child interaction, substance use, academic failure, and employment difficulties (4,5).

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Parental stress is widespread among parents of children of all ages. However, it is higher among families with factors such as negative child behavior and neurocognitive disorders, including ADHD (6-8). It has been reported that parents of children with ADHD experience higher rates of ADHD, and maternal depression/anxiety and psychiatric symptom levels are adversely affected by the problem behaviors of their children (9-11). However, some authors have espoused the opposite perspective, reporting that psychiatric disorders in mothers, such as anxiety and depression, can also exacerbate ADHD symptoms or problematic behaviors in children (12-14). Problem behavior in children can also gradually adversely affect the quality of the parents' relationship (15). Additionally, mothers have experienced higher parental stress than fathers (16). Our review of the literature showed that these difficulties in children may result in a greater psychiatric burden in mothers and may also have an adverse impact on the marital relationship of the parents.

Our hypothesis was that the mothers of children diagnosed with ADHD would have higher ADHD, anxiety, and depression levels and lower marital adjustment than mothers of children with no chronic medical or psychiatric disease, and that these would be associated with behavioral problems of their children. The aims of this study were to examine the levels of marital adjustment, emotional problems, and ADHD symptoms in mothers of children aged 6-18 with ADHD; and to establish the relationships of these parameters with each other and the child's behavioral problem levels.

Materials and Methods

Compliance with Ethical Standards

Approval for the study was granted by the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethical Committee (no. 2020-21-14 dated 19.10.2020). Participants were informed that the data would only be used for scientific purposes. Written and verbal consent were obtained from all participants.

Study Population

This study was conducted between October 2020 and April 2021 at the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Child and Adolescent Psychiatric. The biological mothers of children aged 6-18 years, diagnosed with ADHD and followed up for at least six months, and the mothers of healthy children with no psychiatric diagnosis were included in the study. All children of the participating mothers were evaluated by a child and adolescent psychiatrist through a DSM-V-based examination. Individuals experiencing difficulty in reading and understanding the forms or who were unable to complete the evaluation process were excluded from the study. The presence of a comorbid psychiatric disorder in children with ADHD and the presence of another offspring with a psychiatric disorder in the family were the other exclusion criteria. Mothers scheduled for inclusion in the control group whose children had any psychiatric or organic diseases were excluded from the research. The study was initially planned with 250 participants, but following the application of the exclusion criteria, it was finally completed with 152 participants-mothers of children diagnosed with ADHD (n=90) and mothers of healthy children (n=62).

Psychometric Instruments

Conners' parent rating scale-revised long version (CPRS-RL) was used to rate symptoms in children diagnosed with ADHD. An information form developed by the authors was used to evaluate the sociodemographic data of the mothers and their medical and familial characteristics. The Beck anxiety inventory (BAI), Beck depression inventory (BDI), adult ADHD self-report scale (ASRS), and marriage adjustment scale (MAS) were applied to evaluate the mothers themselves.

The Conners' parent rating scale-revised long version

The CPRS-RL is used to assess both internalizing and externalizing problems in children aged 3-17 years and consists of 80 items and 14 subscales (17). Problem behavior is evaluated using seven subscales: hyperactivity-impulsivity, psychosomatic, cognitive problems, anxious-shy, perfectionism, social problems, and oppositional. The ADHD Index, intended to determine ADHD based on DSM-IV criteria, is another 12-item subscale differentiating patients from those with no such problem. The Conners global index is used as an assistant tool for problem behavior (Restless-Impulsive, Emotional Lability, Total Score). Additionally, the DSM-IV Symptom Subscale consists of 18 DSM-IV-based criteria aimed at determining and yielding inattention, hyperactivity-impulsivity, and total score. Each item consists of four response options: not at all true (never, rarely) - 0 points; somewhat true (sometimes) - 1 point; quite true (usually, often) - 2 points; and very true (very often) - 3 points. Higher scores from a subscale indicate a higher level of possession of the problem defined by that subscale (Conners). The reliability and validity of the Turkish-language version of the scale were confirmed by Kaner et al. (18).

The Beck Depression Inventory

The BDI is a four-point likert-type self-report developed by Beck et al. (19). It was developed to measure the risk

of depression and the level and severity of depressive symptoms in adults. It consists of 21 items, each of which evaluates a specific behavior. The validity and reliability of the Turkish version were confirmed by Hisli (20). Higher scores indicate higher depressive levels. The cut-off point for the scale was set at 17. In our study, the total scale score was used.

The Beck Anxiety Inventory

The BAI is a four point (0-3) likert type self-report developed to measure anxiety symptom levels (21). It is a self-assessment scale used to determine the frequency of anxiety symptoms experienced by individuals. It consists of 21 items. Our raw score ranged between 0 and 63. Higher scores indicate a higher anxiety state. This has been shown in a Turkish validity and reliability study (22). In this study, the total scale scores were evaluated.

The Adult ADHD Self-Report Scale

The ASRS is used to assess ADHD symptoms in adults. The scale was arranged according to the ADHD diagnostic criteria in DSM-IV (23). The 18 questions contained in the scale investigated the frequency of the appearance of each symptom within the previous six months. Nine items of this five-point Likert-type self-report scale (0= never, 1= rarely, 2= sometimes, 3= often, 4= very often) evaluated inattention, the other nine were concerned with hyperactivity/impulsivity symptoms. "Stepwise logistic regression" analysis showed that six of the 18 questions were more accurate in diagnosing ADHD. Therefore, only the questions in Section A were included in the analysis. The validity and reliability of the Turkish-language version of the scale were confirmed by Doğan et al. (24).

The Marriage Adjustment Scale

The MAS was developed by Locke and Wallace (25). It consists of 15 items, with possible scores ranging from 1 to 60, with higher scores indicating greater marital adjustment and lower scores lacking marital adjustment. In addition to general marital adjustment, the scale measures agreement or disagreement on subjects such as the family budget, the expression of emotions, friends, sexuality, and philosophy of life, as well as relationship type in terms of trust, conflict resolution, and spare time and outside activities. The validity and reliability of the Turkish-language version of the scale were confirmed by Tutarel Kışlak (26).

Statistical Analysis

In this study, mean, standard deviation, median, frequency, percentage, minimum, and maximum values were used in the research data. The normality of the distribution of quantitative data was checked using the Shapiro-Wilk test and chart examinations. Normally distributed quantitative variables were compared between two groups using the Student's t-test and non-normally distributed quantitative variables using the Mann-Whitney U test. Non-normally distributed quantitative variables were compared between more than two groups using the Kruskal-Wallis test and the Dunn-Bonferroni test. Qualitative data was compared using Pearson's chi-square tests, Fisher's exact tests, and the Fisher-Freeman-Halton test. A Spearman's correlation analysis was performed to determine correlations between quantitative variables. Statistical significance was defined as p-values less than 0.05.ANCSS 11 (Number Cruncher Statistical System, 2017 Statistical Software) software and MedCalc Statistical Software version 18 were used in our analysis. (MedCalc Software Bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

Results

The study was completed with 152 mothers. Of those, 90 had a child diagnosed with ADHD (the ADHD group), and 62 had a child with no psychiatric or chronic disease (control group). The mean age of the participating mothers was 37.2±5.4 years, ranging between 28 and 50 years. The two groups were similar in terms of age, education, employment status, monthly family income, number of children, and presence of physical medical diseases ($p>0.05$). No difference was observed between the ADHD and control groups in terms of their socio-demographic characteristics (Table 1).

The correlation between the scores of CPRS-RL and maternal self-reports revealed that there was a significant positive correlation between children's oppositional scores and mothers' BAI and ASRS scores ($p<0.05$). A significant positive correlation was also determined between hyperactivity-impulsivity scores in children and ASRS scores in mothers ($p<0.05$). Anxious-shy scores in children were significantly positively correlated with mothers' BAI and scores ($p<0.05$). A significant positive correlation was also observed between children's social problems scores and mothers' BAI, BDI, ASRS, and MAS scores ($p<0.05$) (Table 2).

Social problems in children impacted adversely on all the parameters we evaluated in mothers. A significant positive correlation was observed between children's psychosomatic scores and mothers' BAI and ASRS scores, and a negative correlation with mothers' MAS scores ($p<0.05$). A significant correlation was determined between children's restless-impulsive scores and mothers' BAI, BDI, ASR, and MAS scores ($p<0.05$). Children's emotional lability scores were significantly positively correlated with mothers' BAI, BDI, and ASRS scores ($p<0.05$). Total Conners' global index scores were

Table 1. Comparison of the socio-demographic characteristics of the ADHD and control groups				
		ADHD	**Control**	**P-value**
Age	Mean ± SD Min.-Max. (Median)	37.18±5.53 28-49 (37)	37.28±5.33 28-50 (37)	[a]0.775
		n (%)	**n (%)**	
Educational level	Primary school	56 (62.2)	38 (61.3)	[b]0.055
	Middle school	18 (20.0)	20 (32.3)	
	University	16 (17.8)	4 (6.4)	
Employment status	Not working	68 (75.6)	42 (67.7)	[c]0.077
	In regular employment	18 (20.0)	20 (32.3)	
	Frequently change jobs	4 (4.4)	0 (0.0)	
Monthly family income	<MW	16 (17.8)	12 (19.4)	[b]0.316
	1-2 MW	64 (71.1)	38 (61.3)	
	≥2 MW	10 (11.1)	12 (19.4)	
Number of children in the family	1	24 (26.7)	18 (29.0)	[c]0.818
	2	44 (48.9)	26 (41.9)	
	3	20 (22.2)	16 (25.8)	
	4	2 (2.2)	2 (3.2)	
Physical disease	Absent	80 (88.9)	58 (93.5)	[b]0.329
	Present	10 (11.1)	4 (6.5)	
Previous psychiatric admissions	Absent	60 (66.7)	58 (93.5)	**[b]0.001**
	Present	30 (33.3)	4 (6.5)	

[a]Student's t-test, [b]Pearson chi-square test, [c]Fisher-Freeman-Halton exact test
Bold values denote statistical significance at the p<0.05 level
MW: Minimum wage, ADHD: Attention deficit hyperactivity disorder, SD: Standard deviation, Min.: Minimum, Max.: Maximum

significantly correlated with mothers' BAI, BDI, ASRS, and MAS (p<0.05). Inattention scores from the DSM-IV symptom subscale were significantly correlated with mothers' BAI and ASRS scores, hyperactivity-impulsivity scores with ASRS, and total scores with BAI and ASRS (p<0.05). No correlation was found between children's Conners' global ındex scores, age, comorbid behavioral disorder, or number of children in the family and mothers' BAI, BDI, ASRS, or MAS scale scores (p≥0.05) (Table 2).

BAI, BDI, and ASRS were significantly higher (p=0.005, p=0.001, p=0.043, respectively) and MAS scores (p=0.001) were significantly lower in the ADHD group than in the control group (Figure 1).

Correlation analysis between mothers' self-report scales in the group of mothers with ADHD showed that ASRS scores were positively correlated with BAI and BDI scores (p<0.05). Anxiety and depression levels increased in line with the mothers' ADHD scores. Anxiety and depression levels in mothers were also significantly positive correlated with one another (p<0.05). MAS scores were negatively correlated with ASRS, BAI, and BDI scores (p<0.05). Marital adjustment decreased as mothers' anxiety, depression, and ADHD symptoms increased (Table 3).

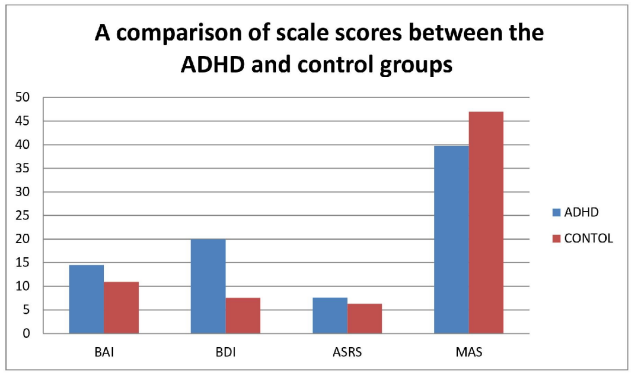

Figure 1. Comparison of scale scores between the ADHD and control groups
BAI: Beck anxiety inventory, BDI: Beck depression inventory, ASRS: Adult ADHD self-report scale, MAS: Marriage adjustment scale, ADHD: Attention deficit hyperactivity disorder

Discussion

This study examined the mothers of children with ADHD to determine their marital adjustment, emotional problems, and ADHD symptom levels and the relationships of these parameters with each other and with their offspring's behavioral problems. The study findings confirmed our original hypothesis; mothers of

Table 2. Distribution of CPRS-RL scores in the ADHD group, and correlation with maternal scale scores

Children's CPRS-RL scale score distribution			Correlation with mothers' scale scores			
		Mean ± SD Min.-Max. (Median)	BAI r p	BDI r p	ASRS r p	MAS r p
CPRS-RL	**Oppositional**	23.04±10.20 0-43 (24)	0.239 **0.023**	0.131 0.220	0.217 **0.040**	-0.162 0.127
	Cognitive problems	11.71±6.20 0-23 (11)	0.204 0.053	0.049 0.648	0.118 0.270	-0.135 0.203
	Hyperactivity-impulsivity	11.98±5.64 0-26 (12)	0.163 0.125	0.140 0.190	0.292 **0.005**	-0.176 0.096
	Anxious-shy	13.24±5.02 2-23 (14)	0.241 **0.022**	0.185 0.081	0.222 **0.036**	-0.154 0.147
	Perfectionism	3.64±2.28 0-8 (3)	0.159 0.135	0.106 0.319	0.103 0.335	-0.027 0.799
	Social problems	9.58±4.42 1-18 (9)	0.282 **0.007**	0.253 **0.016**	0.254 **0.016**	-0.229 **0.030**
	Psychosomatic	18.67±7.21 0-32 (20)	0.273 **0.009**	0.168 0.114	0.299 **0.004**	-0.250 **0.017**
Conners' ADHD index		3.04±2.96 0-11 (2)	0.246 **0.020**	0.263 **0.012**	0.166 0.118	-0.195 0.065
Conners' global index	**Restless-impulsive**	3.96±3.26 0-13 (3)	0.287 **0.006**	0.329 **0.002**	0.255 **0.015**	-0.243 **0.021**
	Emotional lability	5.62±3.54 0-18 (5)	0.251 **0.017**	0.246 **0.019**	0.303 **0.004**	-0.166 0.118
	Total score	6.07±3.69 0-17 (6)	0.347 **0.001**	0.333 **0.001**	0.231 **0.029**	-0.228 **0.031**
DSM-IV symptom subscale	**Inattention**	11.00±6.14 0-24 (11)	0.266 **0.011**	0.186 0.079	0.245 **0.020**	-0.131 0.217
	Hyperactivity- impulsivity	14.91±7.77 0-32 (14)	0.161 0.130	0.142 0.183	0.257 **0.015**	-0.190 0.072
	Total score	12.20±5.99 0-28 (12)	0.285 **0.007**	0.198 0.061	0.232 **0.028**	-0.102 0.337
AGE		125.04±26.40 84-204 (120)	-0.017 0.876	-0.042 0.696	0.051 0.633	-0.188 0.076
Number of children		1 24 (26.67) 2 44 (48.89) 3≤ 22 (24.44)	[e]0.487	[e]0.051	[e]0.650	[e]0.329

[e]Kruskal-Wallis test, [d]Mann-Whitney U test, r= Spearman's Correlation Coefficient, bold values denote statistical significance at the p<0.05 level
CPRS-RL: Conners' parent rating scale long form-revised, ADHD: Attention deficit hyperactivity disorder, DSM-IV: Diagnostic and statistical manual of mental disorders, fourth edition, BAI: Beck anxiety inventory, BDI: Beck depression inventory, ASRS: Adult ADHD self-report scale, MAS: Marriage adjustment scale, CGI: Clinical global impression SD: Standard deviation, Min.: Minimum, Max.: Maksimum

children diagnosed with ADHD were found to possess lower marital adjustment scores, and greater anxiety, depression, and ADHD symptoms. Marital adjustment was also correlated with levels of problem behaviors in children, in addition to mothers' anxiety, depression, and ADHD symptoms.

Previous studies have observed that behavioral/emotional problems in children with ADHD adversely impact mothers' parental stress levels (27,28). This situation is reciprocal, and parental stress can negatively affect ADHD symptoms in the child (29,30). Behavioral disturbances in children with ADHD have been shown to be associated with maternal depression, and these behavioral problems also adversely affect parenting (31,32). Most studies have shown higher depressive findings in mothers of children with ADHD compared to mothers of children without ADHD (11,33,34). Additionally, children of depressive mothers exhibit more behavioral problems than those of non-depressive mothers (35). Mothers of children with ADHD exhibit significantly higher anxiety scores than the mothers of typical-developed children (11). It was also found that there was a significant positive relationship between the ADHD symptoms of the children and the severity of the mother's anxiety symptoms (36). High anxiety in parents of children with ADHD adversely affects child and parent interaction (less parental warmth,

less positive participation, negative discipline, and social problems) (34,37). Similarly, this study demonstrated that mothers of children with ADHD exhibited greater depressive and anxious symptoms than mothers of children without ADHD, and their anxiety and depression exacerbated their offspring's behavioral problems. Maternal depression and anxiety have previously been reported not to be associated with the level of hyperactivity symptoms in children diagnosed with ADHD (38). However, findings similar to those of this research are more common in studies with a higher impact power in the literature. There is a clear relationship between ADHD-related problem behaviors in children and maternal depression and anxiety. We think that, by their nature, these relationships can result in adverse outcomes for both mother and child. Additionally, similar to Kashdan et al. (37), correlation analysis revealed that the effects of these anxiety and depression scores in mothers produced an adverse effect on one another. We believe that this is associated with the increased psychological burden on mothers.

Higher inattention/cognitive problems/hyperactivity/irritability/impulsivity and emotional indecision and lower self-esteem have been shown in the parents of children with ADHD compared with parents of children without ADHD (39). It has been reported that maternal ADHD may be associated with ADHD in children in later years due to its mediating effects (40). Additionally, ADHD is considered an inherited disorder in which genes play a role in its pathogenesis (41). The mothers of children with ADHD exhibit higher clinical levels of ADHD symptoms than those of children without ADHD (27,34). Additionally, increased maternal ADHD symptoms have been linked to a greater severity of ADHD symptoms, emotional problems, and peer problems in children (42). Similarly, in this study, the mothers of children with ADHD reported higher ADHD findings, and maternal ADHD symptom levels were positively correlated with child ADHD. This finding of this study is consistent with previous studies examining familial clustering of ADHD.

Table 3. Evaluation of the relationship between scale scores

		BAI	BDI	ASRS	MAS
BAI	**r** **p**	–	0.709 **0.001**	0.497 **0.001**	-0.477 **0.001**
BDI	**r** **p**	0.709 **0.001**	–	0.400 **0.001**	-0.437 **0.001**
ASRS	**r** **p**	0.497 **0.001**	0.400 **0.001**	–	-0.383 **0.001**
MAS	**r** **p**	0.477 **0.001**	-0.437 **0.001**	-0.383 **0.001**	–

r= Spearman's Correlation Coefficient, bold values denote statistical significance at the p<0.05 level
BAI: Beck anxiety inventory, BDI: Beck depression inventory, ASRS: Adult ADHD self-report scale, MAS: Marriage adjustment scale, ADHD: Attention deficit hyperactivity disorder

The parenting and communication established by a parent with ADHD symptoms with a child diagnosed with ADHD have been reported to be frequently perceived negatively by the other partner (43). ADHD symptoms in mothers may compromise not only mother-child interactions, but also marital adjustment by impairing the partner relationship. In this study, increased ARDS scores in mothers were negatively correlated with MAS scores. Consistent with previous studies (44,45), this result shows that maternal ADHD adversely impacts on marital adjustment. Additionally, this study showed that in children with ADHD, higher levels of behavioral problems adversely affected marital adjustment in their parents. Wymbs (46). previously reported that disruptive behavior in children deteriorated adjustment among parents. It seems that ADHD symptoms in both the mother and her offspring appear to have adversely affected marital adjustment.

Study Limitations

One limitation of this study was its cross-sectional nature. The investigation of the relationships examined in longitudinal studies with larger sample groups will yield stronger results. Additionally, although this study focused solely on the effects of ADHD, other comorbid psychiatric disorders are observed in many children diagnosed with ADHD in clinical practice. We believe that further studies that also include the parents of children with ADHD and other comorbid disorders will contribute to the significance of this field. The strength of our study is that we could evaluate many factors together in a large clinical group. Although some of these parameters have been studied one by one before, the fact that we have examined the relationship between them increases the value of the study.

Conclusion

This study revealed that the mothers of children diagnosed with ADHD have greater anxiety, depression, and adult attention deficit symptoms and lower marital adjustment than the mothers of children without ADHD. Problem behavior in children with ADHD was associated with increased anxiety, depression, and adult attention deficit symptoms in mothers, and with decreased marital adjustment. Considering potential psychiatric symptoms in mothers when intervening in children with ADHD will be beneficial to avoid negative outcomes for both the child and mother.

Ethics

Ethics Committee Approval: Approval for the study was granted by the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital

Clinical Research Ethical Committee (no. 2020-21-14, dated: 19.10.2020).

Informed Consent: Written and verbal consent were obtained from all participants.

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Authorship Contributions

Concept: S.Y, F.A.K., T.K., Design: S.Y, F.A.K., T.K., Data Collection, or Processing: S.Y, F.A.K., T.K., Analysis, or Interpretation: S.Y, F.A.K., T.K., Literature Research: S.Y, F.A.K., T.K., Writing: S.Y, F.A.K., T.K.

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Original Article

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Aberrant Activation-Induced Cytidine Deaminase Gene Expression Links BCR/ABL1-Negative Classical Myeloproliferative Neoplasms

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Abstract

Aim: Activation-induced cytidine deaminase (AID) has been associated with tumor initiation and development because of its ability to generate DNA damage and somatic mutations that cause genomic instability. This study aimed to investigate the relationship between AID expression levels and the risk of developing BCR/ABL1-negative myeloproliferative neoplasms (MPNs) by comparing the AID expression levels of the patients and controls.

Methods: This case-control study was conducted on 117 cases (64 essential thrombocythemia, 23 primary myelofibrosis, and 30 polycythemia vera) with MPNs and 69 healthy controls. The *JAK2* V617F somatic mutation analysis was performed using a real-time polymerase chain reaction (RT-PCR). The relative expression levels of *AID* in the patient and the control groups were analyzed using quantitative RT-PCR and the $2^{-\Delta\Delta CT}$ method.

Results: *AID* expression levels were significantly higher in the patient group compared to the control group ($p<0.001$). *AID* expression levels were higher in patients with the *JAK2* V617F mutation compared to patients without the mutation, but the difference was not statistically significant.

Conclusion: The results of our study suggest that although overexpression of *AID* does not seem to support the *JAK2* driver gene, it may contribute to the development of MPNs through other mechanisms.

Keywords: Cytidine deaminase, mutations, genomic instability

Introduction

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders in which erythroid, granulocytic, and megakaryocytic cells are overproduced. The major diseases within BCR/ABL1-negative classical MPNs are polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). In MPN, there is a deterioration in the JAK2 kinase signaling pathway. Mutations in the genes encoding *JAK2, CALR,* and *MPL* are driver mutations in MPN (1). Additional genetic alterations in genes involved in epigenetic mechanisms, such as *TET2, IDH1/2, ASXL1, EZH2, SF3B1, SRSF2,* and *U2AF1*, are also common in MPNs (2,3). The single point mutation *JAK2* V617F is present in approximately

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95% of PV patients and 50-60% of ET and PMF patients (4). Additionally, some MPN patients may have a "mutator" phenotype (5,6). Neoplastic clones may arise in neoplastic cells gradually because of the accumulation of mutations that occur mainly in DNA repair pathways (7).

Activation induced cytidine deaminase (AID), a member of the AID/apolipoprotein B editing complex (APOBEC) catalytic protein family, is highly expressed in germinal center B lymphocytes (8). By deaminating the cytosine residues in the immunoglobulin (Ig) variable region, the AID enzyme normally generates somatic hypermutation (SHM) and class-switch recombination (CSR) processes in *Ig* genes (7). SHMs create point mutations and insertions/deletions in the DNA sequence with a very high frequency of 10^{-2} to 10^{-3} base pairs per generation (9). The conversion of cytosine to uracil by AID is attempted and repaired through base excision repair or mismatch repair mechanisms. These processes are prone to errors as they can create mutations that cause dU: dG mismatches. Moreover, AID can alter gene expression by DNA demethylation, which can induce tumor initiation or progression because of genomic instability, so its tight control is important (10). AID-induced demethylation has also been shown to play a role in the expression of tumor progression factors (8). Several research groups have reported the aberrant expression of Igs in non-lymphoid cancer cells, suggesting a complex mechanism emphasizing Ig expression in cancer cells (10,11). Furthermore, there is evidence that AID is expressed not only in lymphoid cells but also in non-lymphoid cells, suggesting that AID also mutates genes other than Igs (8). Therefore, many studies have focused on *AID* for its potential role in the generation of both point mutations and chromosomal rearrangements in different types of cancer. It has been reported that many genes, such as *c-MYC*, *CARD11*, *EZH2,* and *MMP14* are affected by AID activity in various types of cancers (12).

Various researchers are trying to elucidate the role of *AID* in different types of cancer, but there is no study that has been carried out on MPN patients. In this study, we hypothesized that somatic mutations in the *JAK2* driver gene could be induced by both the SHM and the methylation-demethylation activity of AID. Thus, we investigated whether *AID* expression was involved in the etiopathogenesis of BCR-ABL1-negative classical MPNs by comparing patients and controls in terms of *AID* gene expression levels and by investigating the relationship between *AID gene* expression levels and the presence of the *JAK2* V617F mutation.

Materials and Methods

Ethical Approval and Study Design

Approval was obtained from the Istanbul University, Istanbul Faculty of Medicine Ethics Committee (approval number: 2010/1025-325 date: 04.01.2011) for our project, which we carried out in accordance with the Declaration of Helsinki. This study comprised 117 patients with BCR/ABL1-negative classic MPNs who were followed up in the Hematology out-patient Clinic of Istanbul University, Istanbul Faculty of Medicine between January 2009 and January 2011. The patients' diagnoses were reviewed according to the recommendations of the World Health Organization, revealed in 2008 (13). Clinical and laboratory data collected during diagnosis and at study entry were collected from patients' medical files and electronic medical records. The control group consisted of 69 healthy volunteers who were hospital staff and had no history of MPN in themselves or their relatives (as age-appropriate with patients). Peripheral blood samples were drawn in 2 mL of sterile tubes containing EDTA. A complete blood count was also performed during sampling.

DNA Extraction and *JAK2* V617F Mutation Analysis

Automated DNA extraction was carried out with the MagNA Pure Compact Instrument (Roche Diagnostic, Germany). The *JAK2* V617F mutation assay with RT-PCR was performed by the JAK2 MutaScreen Kit using the manufacturer's recommended protocol (Ipsogen, Luminy Biotech, France).

RNA Extraction and cDNA Synthesis

Total RNA was isolated from whole blood with a High Pure RNA Isolation Kit (Roche Diagnostics, Germany) following the manufacturer's instructions. The quantity and purity of RNAs were measured using the NanoDrop 2000c spectrophotometer (Thermo Scientific, Wilmington, DE). Then, cDNA was synthesized from 1 µg of total RNA using the Transcriptor First Strand cDNA Synthesis Kit (Roche Diagnostics, Germany).

Quantitative Real-time PCR

Quantitative Real-time PCR (qRT-PCR) was performed with 50 ng total RNA in 20 µL total volume using the Real-Time Ready Universal ProbeLibrary Assay (Roche Diagnostics, Germany). The RT reactions were carried out on a LightCycler® 480II system. Each sample was studied in duplicate. Hypoxanthine phosphoribosyltransferase 1 (*HPRT1*) was used for the normalization of relative qRT-PCR studies. Relative expression levels were calculated according to the $2^{-\Delta\Delta CT}$ method.

The primers used for the amplification of AID were as follows: forward: 5′-TGGACACCACTATGGACAGC-3′ and reverse: 5′-GCGGACATTTTTGAATTGGT-3′)

(ENST00000229335). The primers used for amplification of the reference gene *HPRT1* were as follows: forward: 5′-GACCAGTCAACAGGGGACAT-3′ and reverse: 5′-GTGTCAATTATATCTTCCACAATCAAG-3′).

Statistical Analysis

The statistical software program SPSS (ver. 21.0) was used for the analysis. The Kolmogorov-Smirnov test was used to check whether the distribution was normal. The Student's t-test and the Mann-Whitney U test were used for the analysis of the data with and without normal distribution, respectively. Chi-square tests were used to analyze categorical data. Continuous variables were defined as mean ± standard deviation. Statistical significance was set as a p-value less than 0.05.

Results

The clinical characteristics and laboratory analysis of the patients in the MPN patient group are presented in Table 1. The patient group consisted of 117 cases with MPN (30 PV, 64 ET, and 23 PMF). Two of the patients with PMF had transformed from acute myeloid leukemia. The mean age was 53.95±13.86. The mean ages between the two groups and between females and males were similar. The female to male ratios of the groups were not different. Leukocyte counts at diagnosis and during sampling were similar between ET, PV, and PMF patients. The platelet count at the time of diagnosis and during sampling was found to be significantly higher in ET patients than in PMF patients. (p=0.001, p=0.005, respectively). The LDH count detected at the time of diagnosis in PMF patients was significantly higher than in ET and PV patients (p=0.001, p=0.047, respectively). LDH count during sampling was also significantly higher in PMF patients than in ET and PV patients (p<0.001, p=0.02, respectively). The disease duration and lymphocyte count at diagnosis/during sampling were similar between the three subgroups. The *JAK2* mutation was present in 38 of 64 ET (59.38%), 15 of 23 PMF (65.22%), and 28 of 30 PV (93.33%) patients. The frequency of *JAK2* V617F was found to be significantly higher in PV patients than in patients with ET and PMF (p=0.004).

AID expression levels in the study groups are shown in Table 2 and Figure 1a. *AID* expression levels were significantly higher in the patient group than

Table 1. Clinical features and laboratory findings of the patient group

	ET	PMF	PV	All patients
Number of patients	64	23	30	117
Female/Male	30/34	14/9	14/16	58/59
Mean age (mean ± SD)	51.33±13.99	60.3±14.32	54.67±11.82	53.95±13.86
Leukocyte at diagnosis ($X10^9$/L) (mean ± SD)	10±4.11	13.39±10.93	12.65±4.51	11.27±6.23
Leukocyte during sampling ($X10^9$/L) (mean ± SD)	7.82±3.28	8.74±5.16	10.83±4.98	8.79±4.33
Lymphocyte at diagnosis ($X10^9$/L) (mean ± SD)	2.32±1.01	2.37±1.68	2.23±8.03	2.31±1.11
Lymphocyte during sampling ($X10^9$/L) (mean ± SD)	2.08±0.92	2.16±2.3	2.03±0.8	2.08±1.26
Platelet count at diagnosis ($X10^9$/L) (mean ± SD)	982.33±405.63	472.35±400.09	415.93±202.32	747.71±452.72
Platelet count during sampling ($X10^9$/L) (mean ± SD)	617.55±396.84	353.35±272.66	366.53±232.41	500.51±359.42
LDH at diagnosis (U/L) (mean ± SD)	430.41±182.04	727.47±335.94	547.12±197.11	513.53±246.37
LDH during sampling (U/L) (mean ± SD)	442.78±208.24	953.52±387.77	667.78±422.77	607.49±372.71
JAK2 V617F (+) n (%)	38 (59.38%)	15 (65.22%)	28 (93.3%)	81 (69.23%)
Bone marrow reticulin fibrosis degree n (%)				
0	14 (21.88%)	0	2 (6.67%)	16 (13.68%)
1	32 (50%)	0	22 (73.33%)	54 (46.15%)
2	17 (26.56%)	3 (13.04%)	4 (13.33%)	24 (20.51%)
3	1 (1.56%)	17 (73.92%)	2 (6.67%)	20 (17.1%)
4	0	3 (13.04%)	0	3 (2.56%)
Splenomegaly (+) n (%)	23 (35.9%)	22 (95.7%)	19 (63.3%)	64 (54.7%)
Thrombosis risk n (%)	13 (20.31%)	6 (26.09%)	13 (43.33%)	32 (27.35%)
Use of hydroxyurea n (%)	43 (67.18%)	15 (65.22%)	22 (73.33%)	80 (68.38%)
Hydroxyurea usage time; years (mean ± SD)	3.68±4.72	2.8±3.43	4.2±5.14	3.64±4.60
Disease duration, years (mean ± SD)	4.89±5.1	7±5.78	5.2±5.54	5.38±5.36

Data are presented as mean ± SD and n (%).
ET: Essential thrombocythemia, PMF: Primary myelofibrosis, PV: Polycythemia vera, LDH: Lactate dehydrogenase, n: Number of samples, SD: Standard deviation

Table 2. AID expression levels in the study groups		
Study groups	***AID* expression levels**	**p-value**
All patients (n=117)	0.033±0.084	0.001[a]
Controls (n=69)	0.020±0.018	
ET (n=64)	0.035±0.698	NS
PMF (n=23)	0.046±0.151	
PV (n=30)	0.020±0.018	
JAK2 V617F positivity		
JAK2 V617F (+) (n=81)	0.036±0.096	0.467
JAK2 V617F (-) (n=36)	0.024±0.044	

Data are presented as mean ± SD: Standard deviation
n: Number of samples, ET: Essential thrombocythemia, PMF: Primary myelofibrosis, PV: Polycythemia vera, NS: Not significant
[a]: Students' t-test, p<0.001 (*AID* expression levels were significantly higher in the patient group than in the control group)

in the control group. (p<0.001). But *AID* expression levels were similar within the three subgroups of MPN (Figure 1b). Although *AID* expression was higher in patients harboring *the JAK2* V617F mutation than in patients without this mutation, there was no statistically significant difference. *AID* expression levels in terms of the *JAK2* V617F mutation situation are shown in Table 2. *AID* expression levels were found to be higher in hydroxyurea users than in non-users, but the difference was not significant. There was no statistical difference between the *AID* levels of the patients with regard to age, gender, splenomegaly, risk of thrombosis, and degree of reticulin degree.

Discussion

Recently, it has been understood that the AID/APOBEC DNA deaminase family generates mutations/mutation showers by recognizing certain motifs in the DNA chain (14). Since AID, a member of this family, causes point mutations or chromosomal rearrangements, was identified as the first mutator enzyme (15).

In this study, our aim was to explore the gene expression levels of *AID*, which causes SHM and CSR in both Ig and non-Ig genes that may contribute to the etiology of MPN, in the Turkish population. Although there are publications investigating the relationship of the *AID* gene with various cancers, there is no study investigating its role in the development of MPNs.

Several studies have discovered a link between increased AID expression and various types of cancer, including hematologic cancers (8,16-25). First, aberrant *AID* expression was reported in transgenic mice with lymphoma and diffuse large B cell lymphoma (26,27). A study on breast cancer cells demonstrated the importance of AID on the epithelial to mesenchymal transition, which is essential in normal morphogenesis and tumor metastasis (8). Then, AID was shown to play a crucial role in regulating myeloid and erythroid lineage differentiation but not in self-renewal or myeloid transformation of hematopoietic stem/progenitor cells (28). AID takes part in the hypermutation of tumor suppressor genes as well as DNA repair genes in CML (21) and *AID* expression levels were found to be higher in BCR-ABL1 (+) acute lymphoblastic leukemia (ALL) cells (secondary to CML or *de novo*) compared with BCR-ABL1 (-) ALL cells (18). AID expression levels have also been found to be elevated in cases of myelodysplastic syndrome, chronic lymphocytic leukemia (CLL), and T-cell leukemia/lymphoma (19,16,25). A study on multiple myeloma patients emphasized the function of AID in early mutagenesis, implying that it causes mutations in driver genes that are the targets of AID (22). A recent study in mice reported a close

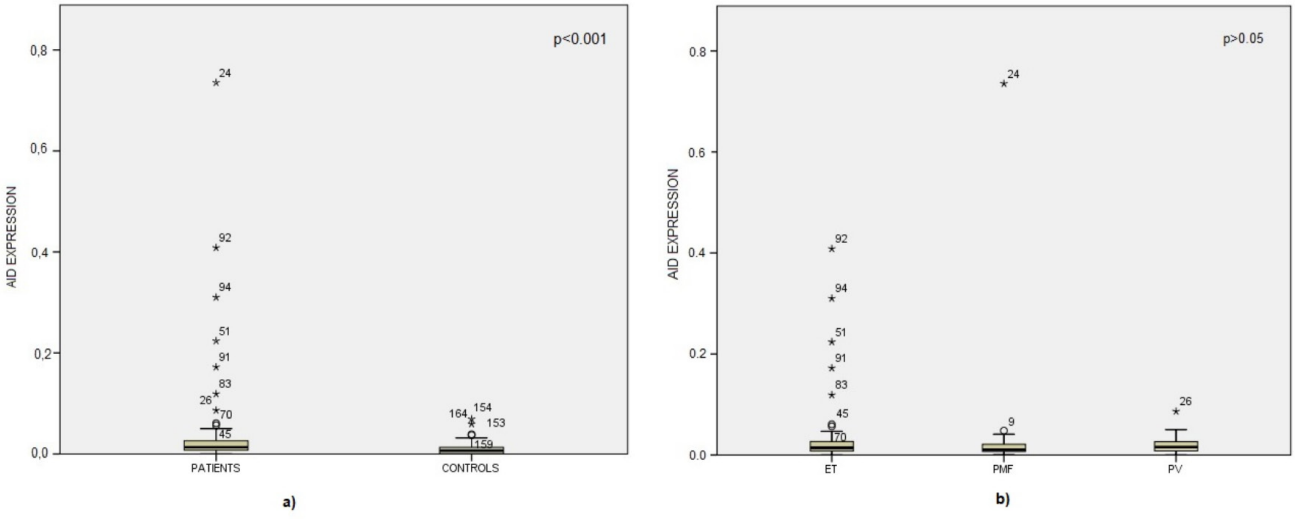

Figure 1. a) *AID* expression levels in patient and control groups b) *AID* expression levels in patients with ET, PMF and PV
ET: Essential thrombocythemia, PMF: Primary myelofibrosis, PV: Polycythemia vera

association between CLL driver mutations and increased AID activity, suggesting that AID encourages aggression in CLL (23). *AID* was also suggested to be an oncogene that triggers tumorigenesis and a treatment that suppresses AID can also suppress cell proliferation, migration and invasion (14,24,28,29). Moreover, tumor cells escaped from therapy through various genetic and epigenetic mechanisms due to genetic instability (30).

Our results were compatible with the previous studies conducted in patients with multiple types of cancer, as we found elevated *AID* expression levels in our patient group. Because of the mutagenic role of AID, we examined the possible relationship between *AID* expression and *JAK2* V617F, a common driver mutation in MPNs. Although *AID* expression was higher in patients with *JAK2* V617F than in those without *JAK2* V617F, the difference did not reach statistical significance, suggesting the contribution of other mechanisms in the generation of this mutation. Interestingly, *AID* expression levels were higher in patients who were not using hydroxyurea compared with those who were using it, but the difference was not statistically significant, suggesting that hydroxyurea treatment increases *AID* expression in MPNs. However, hydroxyurea treatment may also lead to mutations through chemotoxicity and DNA damage (31). Owing to its ability to generate mutations, AID appears to play a crucial role in the development of MPNs as well as in various other types of cancer.

Study Limitations

There were some limitations in our study. The first limitation was the relatively small number of study groups enrolled in the study. The second limitation was the lack of data regarding patients' status of *CALR* and *MPL* gene mutations, which are also driver mutations in MPNs. Therefore, these driver mutations could not be compared with *AID* expression. Despite all these limitations, we believe that our study will make important contributions to the literature.

Conclusion

Our data demonstrate the overexpression of *AID* in patients with MPN compared with controls, suggesting an important role in the etiogenesis of MPNs. To our knowledge, this is the first study investigating the role of *AID* in the development of MPNs. Prospective, randomized genetic and functional studies with larger groups are needed to elucidate the function and significance of overexpression of the *AID* gene in MPN patients.

Ethics

Ethics Committee Approval: Approval was obtained from the Istanbul University, Istanbul Faculty of Medicine Ethics Committee (approval number: 2010/1025-325 date: 04.01.2011) for our project.

Informed Consent: Written informed consent was taken from all patients and healthy controls.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.D., A.S.Y., Design: H.D., A.S.Y., Data Collection and/or Processing: H.D., M.N., A.S.Y., Analysis and/or Interpretation: A.D.A., A.B.A.T., V.S.H., M.Y.G., Literature Research: H.D., A.S.Y., Writing: A.D.A., H.D., A.S.Y.

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

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Original Article

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A Prospective Analysis of the Relationship Between Sexual Dysfunction and Allergic Rhinitis in Men

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Abstract

Aim: Allergic rhinitis (AR) affects patients' quality of life in many areas. The aim was to investigate the effect of AR on the quality of sexual life (QoSL).

Methods: The study was conducted prospectively between June 2021 and January 2022. All subjects were questioned for AR symptoms, and skin prick tests (SPTs) were performed. Thirty-six AR patients were in the study group. The control group consisted of thirty-six healthy subjects. QoSL was evaluated using the International Index of Erectile Function questionnaire-5 (IIEF-5). IIEF-5 questions were grouped into the first 4 (Q1-Q4) and the final question (Q5). The patient group was asked whether AR affects their sexuality. The effect of symptoms on sexuality was evaluated. After AR treatment, the IIEF-5 was repeated. The obtained data was analyzed statistically.

Results: Pre-treatment IIEF-5 and IIEF-5 (Q1-Q4) scores were significantly lower than those in the control group ($p<0.05$). The number of patients who stated that AR affects their sexuality was 19 (52%). In the examination of symptoms, rhinorrhea, which is the most common symptom affecting sexuality, was significantly higher compared with other symptoms ($p=0.0003$). Post-treatment IIEF-5 and IIEF-5 (Q1-Q4) scores were significantly higher than the pre-treatment scores ($p<0.05$). No significant difference was found between the groups in terms of other parameters.

Conclusion: Allergic rhinitis may affect QoSL. Patients with sexual dysfunction should be questioned for AR and they should be provided with the necessary treatment.

Keywords: Rhinitis, allergic/etiology, erectile dysfunction, quality of life, sexual dysfunction

Introduction

Allergic rhinitis (AR) is a chronic allergic disease that affects up to 18.1% of the worldwide population (1). The symptoms of classic AR are nasal congestion, rhinorrhea, sneezing, and itching (1,2). AR affects patients' quality of life (QoL) in many areas, such as academic, athletic, and job performance (3,4).

Erectile dysfunction (ED) is a prevalent medical condition described by the National Institutes of Health (NIH) as "the inability to attain and maintain an erection of sufficient quality to permit satisfactory sexual intercourse" and affects approximately 100 million men worldwide (5,6). Penile erection (PE) is a multiplex process that is affected by many conditions, such as psychogenic, neurogenic, vascular, and hormonal factors (7). The International Index of Erectile Function Questionnaire (IIEF) is a 15-item self-reported inventory developed by Rosen et al. (8) to provide a brief measure of erectile function and capacity that has become the primary and standard method in ED studies. The IIEF-5 is a variant of this form that is used in patients who present with the complaint of sexual dysfunction (SD). The test consists of five questions. The first four questions are for ED, and the last question is for sexual satisfaction (9).

The incidence of ED that negatively affects QoL increases with the accompanying chronic diseases such as chronic lung diseases, diabetes, dyslipidemia, hypothyroidism, cardiovascular disease, genitourinary diseases, obesity,

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sleep apnea, and psychiatric disorders (10). AR is also a chronic upper airway disease that mostly affects the nose. Kirmaz et al. (11) showed that AR causes SD as first in literature. Since the first study, there are limited studies in the literature examining the relationship between AR and SD. This study examined the frequency of SD in men with AR and its response to medical treatment.

Materials and Methods

Compliance with Ethical Standards

This study was conducted prospectively on AR patients and volunteers who applied to Inegol State Hospital between June 2021 and January 2022 with the approval of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (decision number: 604.01.02-74239). Informed consent was obtained from the individuals.

Populations, Inclusion and Exclusion Criteria

All participants in the study applied to the Clinic of Otorhinolaryngology, Inegol State Hospital. Sexually active male patients with AR symptoms and positive skin prick tests (SPTs) for non-seasonal allergens (negative in SPT for grass, cereal, weed, and tree pollen extracts) were included in this study as a study group.

The exclusion criteria, conditions that may be risk factors for SD, were as follows: previous or active sexual or psychiatric disorders, such as depression; the presence of chronic disease, especially asthma; diseases associated with atherosclerosis; the regular use of any medication, including anti-allergic drugs, in the past 6 months; body mass index (BMI)≥30 kg/m^2; alcohol dependence; smoking; Lack of mental capacity and refusal to enter the study or to complete the questionnaire (12).

The control group consisted of thirty-six sexually active healthy male subjects with no AR symptoms and negative SPT (Figure 1).

Sample Size and Sampling Technique

A stratified sampling method was used in this study. People who applied to our clinics were separated into subgroups according to whether they had AR or not. Those with diseases and habits that may affect the investigated parameters were excluded from the AR subgroup. The minimum sample size was estimated on the basis of the study by Kirmaz et al. (11). The minimum sample size with a 95% confidence interval and 5% tolerable error assumptions was 16 for each group. However, statistical analyses in the prior study were performed using non-parametric tests (11). In our study design, we planned to use parametric tests to obtain more statistically significant results. At least 30 patients were planned to be included in each group since the minimum sample size for parametric tests was thirty (13). In accordance with this information, considering that we will exclude samples that may disrupt the normal distribution and that some subjects might be excluded from follow-up, we included 36 patients in the study group and 36 healthy individuals in the control group. In addition, a post-hoc test analysis was planned at the end of the study to calculate the sampling power of valid equations.

Procedures and Data Collection

All AR patients were questioned for allergic symptoms and sexual activity. Endoscopic nasal examinations were performed, BMIs were calculated, and SPTs were planned. The SPTs were performed according to the European Academy of Allergology and Clinical Immunology guidelines to support the diagnosis of allergy and to determine the allergens in the etiology of AR (14). The SPT was performed using_mites [Dermatophagoides (D) pteronyssinus, D. farinae], weeds (Plantago lanceolata, Artemisia vulgaris, Taraxacum vulgare, Urtica dioica), fungi (Cladosporium, Aspergillus, Penicillium, Alternaria), animal fluff (Dog and Cat), grasses (Dactylis glomerata, Phleum pratense, Hulcus lanatus, Poa pratensis, Lolium perenne, Fectuca pratensis), tree pollens (Fraxinus excelsior, Quercus robur, Ulmus scabra, Alnus glutinosa, Olea europaea), grains (Secale cerela, Hordeum vulgare, Triticum sativum, Avena sativa) and food allergens (Banana, cocoa, egg, fish, nuts), latex and cockroach extracts (Prick test kit, Stallergenes Greer, France). Positive control was performed with histamine hydrochloride (10 mg/mL). The reactions were reported for 20 minutes by the investigator who performed the test. SPT was evaluated according to the diameter of induration and diameters of 3 mm and larger were accepted as positive.

The quality of sexual life was evaluated using the IIEF questionnaire-5 (IIEF-5). This survey has been commonly used to assess male sexual function. It consisted of five questions. Each question was rated from 1 to 5. The

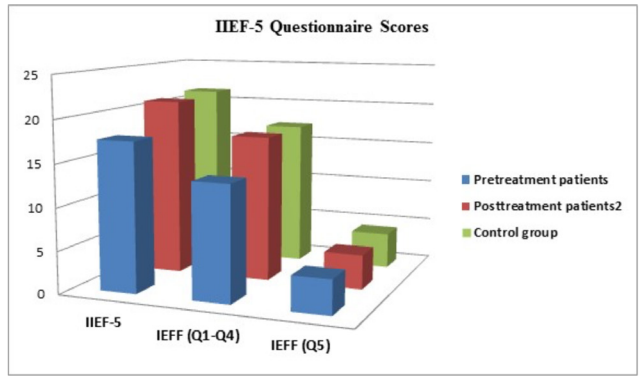

Figure 1. The IIEF-5 questionnaire scores
IIEF: International Index of Erectile Function questionnaire-5

individual scores in each domain were rated to identify the grade of clinical dysfunction; score numbers were determined as follows: 5= no dysfunction, 4= mild dysfunction, 3= mild-to-moderate, 2= moderate, and 1= severe. Lower scores identify higher grades of dysfunction, while higher rates mean lower dysfunction (9). The IIEF-5 was administered to patients in about 15 minutes by the same person. The age and BMI distributions of the groups were compared. The IIEF-5 questions were grouped into themselves, with the first 4 questions (Q1-Q4) and the last question (Q5) separate.

The patient group was asked whether AR affects their sexuality. Those who answered yes to the question were asked which symptoms (nasal congestion, rhinorrhea, sneezing, and itching) affect their sexuality. The frequency was calculated according to the response and symptoms. The effect of symptoms on sexuality was compared statistically.

To avoid systemic effects, the patients included in the study were given local steroid and antihistamine treatment in accordance with the literature (15). The AR patients were treated with azelastine hydrochloride (Nazetin, Berko, Turkey) and beclomethasone dipropionate (Rinoclenil®, Chiesi Farmaceutici, Italy), with one puff in each nostril twice a day for two months. After two months of treatment, the IIEF-5 questionnaire was administered to the patients again.

The values of AR patients before treatment were compared with the control group. Afterward, treatment, AR patients' IIEF-5 scores were compared with both the pre-treatment values and the values of the control group.

Statistical Analysis

The calculations of the minimum sample size and sample power were performed by the G*Power software (16). SPSS 21 was used for statistical analysis. The Kolmogorov-Smirnov and Levene's tests were used to assess the normal distribution and homogeneity of data. For analysis, the paired-samples t-test, Independent samples t-test, and chi-square test were used. The statistical significance level was determined as $p<0.05$.

Results

All individuals included in the patient and control groups completed the study. The mean ages of the groups were 31.06±8.49 for the AR patients and 32.89±8.94 for the control group. The mean BMI was 23.42±1.67 in the AR group and 23.10±1.37 in the control group. There was no significant difference between the groups according to age and BMI (Independent samples t-test, $p=0.380$; $p=0.346$, respectively).

The pre-treatment IIEF-5 and IIEF-5 (Q1-Q4) scores were found to be significantly lower than those of the control group ($p<0.05$). Although the pre-treatment IIEF-5 (Q5) score was lower than that of the control group, no significant difference was found to be according to IIEF-5 (Q5) score ($p=0.249$) (Table 1) (Figure 1).

The frequency of "YES" answers to the question, "Does your rhinitis affect your sexuality?" is 19 (52.8%). The distribution of symptoms that affect the sexuality of these patients was determined. Rhinorrhoea, which is the most common symptom affecting sexuality, was significantly higher compared with other symptoms ($p=0.0003$) (Table 2).

The post-treatment IIEF-5 and IIEF-5 (Q1-Q4) scores were significantly higher than the pre-treatment scores ($p<0.05$). Although the post-treatment IIEF-5 (Q5) score was higher than the pre-treatment score, there was no significant difference according to IIEF-5 (Q5) score ($p=0.822$) (Table 1) (Figure 1).

The post-hoc test, which was used to determine the sampling power of this study, was performed using a 5% error probability. The sample power (1-β err prob) was 0.9998.

Discussion

AR is an inflammatory disease with an IgE-mediated immune response that negatively affects social life (17,18). The decrease or loss in sexual function is a status that affects the QoL and may be associated with AR. ED or SD was described as persistent (at least 6 months) inability to attain and maintain an erection sufficient to permit satisfactory sexual activity (5). ED can be affected by many

Table 1. Evaluation of IIEF-5 questionnaire scores

Questionnaire	Mean ± Standard deviation			p-value		
	Control Group	Pretreatment AR patients	Posttreatment AR patients	Pretreatment vs Control	Posttreatment vs Control	Pretreatment vs Posttreatment
IIEF-5	21.39±3.05	17.55±4.18	20.97±2.85	**0.00003***	0.552	**0.00003****
IIEF (Q1-Q4)	17.22±2.75	13.5±3.7	17.17±2.27	**0.00001***	0.926	**0.00001****
IIEF (Q5)	4.22±0.64	4.03±0.77	4.05±0.53	0.249	0.232	0.822

*Independent sample t-test $p<0.05$
**Paired sample t-test $p<0.05$
IIEF: International Index of Erectile Function questionnaire-5

mental and physical diseases and is also associated with otorhinolaryngological diseases. In this study, we showed that SD is more common in AR patients, who do not have conditions known to cause SD, than in healthy individuals, and this case disappears with appropriate AR treatment.

In previous studies, ED was identified in patients with hearing loss, apnea, equilibrium disorders, and halitosis (19-21). Bakır et al. (19) showed that the risk of ED was higher in patients with hearing loss. However, Ozler and Ozler (20). examined patients with hearing loss and reported that there was no negative effect on erectile function and intercourse satisfaction, parts of IIEF-15, whereas the other parts of the questionnaire showed the negative effects. With SDs related to the otolaryngological diseases that there is conflicting information in the literature improve depending on the treatment of the primary disease (11,21).

In previous studies, an increased frequency of SD in AR patients has been reported (21-25). The IIEF form was used in previous studies investigating the presence of SD in patients with AR (11). ED is defined by the NIH as an inability of at least 6 months. Therefore, the IIEF-5 form, which examined the 6-months, instead of the IIFF form, which examined the one-month, would be more appropriate for evaluating the association between AR and ED. In this study, we evaluated the risk of ED in AR patients with IIEF-5 as the first in the literature. Patients with positive SPT for seasonal allergens (grass, cereal, weed and, tree pollen extracts) were investigated in previous studies (11). However, the positive SPT for seasonal allergens was an exclusion criterion in this study to maintain allergic effects for at least 6 months as in the ED definition.

The IIEF-5 consists of five questions; the first four questions are for ED and the last question is for sexual satisfaction (9). In the literature review, although there are studies comparing the IIEF scores in AR patients with the control group, there is no study comparing the test questions by grouping them according to the functions they perform (11). For the first time in literature, although we used the questionnaires as a whole in the comparison of the groups, we also used the questions by grouping them according to ED (Q1-Q4) and sexual satisfaction (Q5).

In this study, we detected the IIEF-5 (Q1-Q4), which is the test section for ED, and total IIEF-5 scores in the AR patients without treatment were statistically significantly lower than the control group ($p<0.05$). No statistical significance was found for IIEF-5 (Q5) scores, which is the test part for sexual satisfaction. In this study, we gave local treatment to AR patients to avoid possible systemic effects. We found that the total post-treatment IIEF-5 and IIEF-5 (Q1-Q4) scores were significantly higher than before the treatment, and no significant difference was found between the post-treatment scores and the control group's scores. This comparison by dividing the questions, which is the first in the literature, suggests that SD detected in the AR patients is related to ED rather than satisfaction and that this disease disappears with proper treatment. In addition, this study suggested that there was no reduction in sexual satisfaction in the case of attaining an erection in AR patients.

Table 2. Symptoms and sexuality

Symptom		Entity			p-value
		Yes	No	Total	
Congestion	Count	11	8	19	
	% within symptom	57.9%	42.1%	100%	
	% within entity	29.7%	20.5%	25%	
Rhinorrhea	Count	16	3	19	
	% within symptom	84.2%	15.8%	100%	
	% within entity	43.2%	7.7%	25%	
Sneeze	Count	4	15	19	
	% within symptom	21.1%	78.9%	100%	**0.0003***
	% within entity	10.8%	38.5%	25%	
Itching	Count	6	13	19	
	% within symptom	31.6%	68.4%	100%	
	% within entity	16.2%	33.3%	25%	
Total	Count	37	39	76	
	% within symptom	48.7%	51.3%	100%	
	% within entity	100%	100%	100%	

*Pearson chi-square: 18,275, df: 3, $p<0.05$

ED in AR patients can be explained by multiple conditions and mechanisms seen in AR. One of these situations is the impact of AR on the sense of "sexiness" discussed by Benninger and Benninger (25). To examine this issue, we asked our patients, "Does your rhinitis affect your sexuality?". Nineteen of 36 patients (52%) answered this question as "yes". These people were asked what symptoms they were affected by. Rhinorrhoea, which is the most common symptom affecting sexuality, was statistically significantly higher compared with other symptoms ($p<0.05$).

Study Limitations

In this study, we made comparisons according to the parameters that were not used before. However, the lack of a mechanical outcome limits this study. We wanted to include more participants in this study, which is unique in the literature with its many features, to establish a more robust clinical relationship. However, some factors limited the number of participants in this study. Firstly, we had difficulty in finding patients who do not use drugs, including antiallergic drugs, because reaching the drugs is so easy in our time. Secondly, since smoking is very common today, we had difficulty in finding non-smoking patients. For the last and most important reason, sexuality is still seen as a taboo. For this reason, the patients did not show the desire to participate in the study. Although these, the sample power of this study was calculated by the post-hoc test and was found to be statistically adequate (0.9998). Another limitation is that we questioned the effect of symptoms on sexuality with a yes or no question, and we did not question the relationship between sexuality and AR symptoms after treatment. If we had obtained numerical pre-treatment and post-treatment data using a scale such as a visual analogue scale instead, our results would have been statistically stronger.

Conclusion

Allergic rhinitis is a risk factor for SD. SD should be questioned in patients with AR, and AR should also be investigated in patients with SD. The repetition of the obtained data with the larger subject numbers and studies on the pathophysiology of SD seen in patients with AR are needed.

Ethics

Ethics Committee Approval: Approval was obtained from the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (decision number: 604.01.02-74239).

Informed Consent: Informed consent was obtained from the individuals.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.C., E.O., Design: D.C., S.U., E.O., Data Collection and/or Processing: D.C., E.O., Analysis and/or Interpretation: D.C., S.U., Literature Research: D.C., S.U., E.U., Writing: D.C., S.U., E.U.

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

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Original Article

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The Effect of Platelet-Rich Fibrin on Postoperative Morbidity after Rhinoplasty: A Comparative Analysis with Respect to Edema, Ecchymosis and Pain

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Abstract

Aim: Platelet-rich fibrin (PRF) effectively improves the surgical effect in augmentation rhinoplasty; while there are a limited number of studies regarding its impact on postoperative morbidity in primary open rhinoplasty with conventional osteotomy (COS). This study was designed to investigate the utility of PRF in reducing the short-term postoperative morbidity in primary open rhinoplasty with conventional osteotomy.

Methods: A total of 61 adult patients who underwent primary open rhinoplasty with conventional osteotomy, either alone (COS group; n=31) or combined with the application of PRF over the osteotomy line (COS-PRF group; n=30) were included in this prospective study conducted between March 1, 2020 and March 1, 2021. Data on postoperative morbidity, including edema and periorbital ecchymosis (on postoperative day 2 and day 7), pain [via visual analogue scale (VAS) and verbal rating scale (VRS)] and the analgesic use (on postoperative days 1, 2, 3 and 7) were recorded.

Results: COS and COS-PRF groups were similar in terms of the likelihood of eyelid edema and periorbital ecchymosis on any postoperative day. The study groups were also similar in terms of average VAS (median 2.5 vs. 2.4, p=0.680) and VRS (median 1.5 vs. 1.4, p=0.521) scores and the number of analgesics used (median 1.5 vs. 1.3, p=0.196) during the 7-day postoperative period and daily VAS, VRS and analgesic usage records.

Conclusion: Our findings indicate no significant impact of using local PRF application over osteotomy line in reducing postoperative eyelid edema, periorbital ecchymosis, or pain within the first postoperative week of open rhinoplasty.

Keywords: Platelet-rich fibrin, rhinoplasty, osteotomy, morbidity

Introduction

Rhinoplasty is one of the most commonly performed and most challenging procedures in facial plastic surgery due to complex interplay among the different tissues and anatomical regions of the nose (1-3).

Postoperative pain, edema and ecchymosis, albeit minor and temporary in general, are the main postoperative morbidities following rhinoplasty, and their duration and severity change depending on the degree of soft-tissue injury and types of osteotomies and surgical techniques (1,2). Given the strategic position of the nose on the face and its aesthetic and functional importance, reducing the amount and duration of ecchymosis, edema and pain after rhinoplasty is considered important due to the likelihood of a significant practical, emotional, and financial (lost work days) effect on patients even they are minor consequences (1,3).

In this regard, various techniques, instruments, and intra- and postoperative methods and biomaterials (i.e., intraoperative steroid injection, intraoperative cold, saline-soaked gauze compression, postoperative taping, piezoelectric surgery, creation of subperiosteal tunnels) have been employed by surgeons in terms of their efficacy in reducing these uncomfortable morbidities, and thus

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to enable optimal healing, scar tissue formation and the intended morphologic result (2-5).

Platelet-rich fibrin (PRF), a second-generation platelet concentration that activates wound healing through increased fibroblast and growth factor, has been mainly used in orthopedic and dental procedures (6,7). As an autologous biomaterial rich in leukocytes and platelets, PRF is considered to generate a smaller inflammatory response and rejection than other types of biomaterials (1,8).

PRF has also become increasingly popular in facial plastic and reconstructive surgery, due to its proposed efficacy in decreasing edema and ecchymosis, improved hemostasis, and expedited postoperative recovery (9,10).

Although, the role of PRF alone or in mixed with cartilage tissue or high-density fat effectively improves the surgical effect in augmentation rhinoplasty (11-14), there are a limited number of studies regarding the impact of PRF on postoperative morbidity in primary open rhinoplasty with conventional osteotomy.

This study investigated the utility of PRF in reducing the short-term postoperative morbidity (edema, ecchymosis and pain) in primary open rhinoplasty with conventional osteotomy

Materials and Methods

Study Design and Ethical Considerations

A total of 61 consecutive adult patients who underwent primary open rhinoplasty with conventional osteotomy were included in this prospective study conducted between March 1, 2020 and March 1, 2021. Patients were randomly assigned to two groups including conventional osteotomy alone [COS group; n=31, mean ± standard deviation (SD) age: 24.8±8.0 years, 83.9% were females] and conventional osteotomy plus application of PRF over the osteotomy line (COS-PRF group; n=30, mean ± SD age: 23.9±5.4 years, 83.3% were females). The presence of a previous history of rhinoplasty, ongoing anticoagulant treatment, hypertension, chronic disease, bleeding diathesis, inflammatory skin disease and skin allergy were the exclusion criteria of the study. Written informed consent was obtained from each patient following a detailed explanation of the objectives and protocol. The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and ethical approval for this study was obtained from the University of Health Sciences Turkey, Istanbul Training and Research Hospital Clinical Research Ethics Committee (approval no: 2011-KAEK-50/2687, date: 22.01.2021).

Assessments

Data on patient demographics (age, gender), nasal skin thickness (thin: <1 cm, normal: 1-2 cm and thick: >2 cm), operative time minute (min) and postoperative morbidity, including edema (right and left, on postoperative day 2 and day 7), periorbital ecchymosis (right and left, on postoperative day 2 and day 7), pain (on postoperative days 1, 2, 3 and 7) via visual analogue scale (VAS) and verbal rating scale (VRS), and the analgesic use (number of daily tablets on postoperative days 1, 2, 3 and 7) were recorded in COS and COS-PRF groups.

PRF Protocol

In the COS-PRF group, as per the PRF protocol that requires single centrifugation without the addition of an anticoagulant; 10 mL of venous blood was taken approximately 15 min before the completion of operation and added to sterile glass tubes and immediately centrifuged at 3000 rpm for 10 min. The fibrin clot formed in the middle layer, in which most of the platelets and leucocytes are concentrated, was used as PRF, while the topmost layer that consists of cellular plasma was removed. PRF was applied to the osteotomy line during open rhinoplasty in the COS-PRF group.

Rhinoplasty Procedure

The same senior surgeon performed all the operations through an open approach. Following a mid-columellar v incision, the nasal skeleton was exposed in the subperichondrial and subperiosteal surgical anatomical plane. The complete subperiosteal degloving of the entire nasal bone up to the nasal maxillary sulcus, medial canthus, and nasion was performed with cauterization of visible vessels to minimize the soft-tissue injury. Afterwards, septal mucoperichondrium was elevated bilaterally and cartilage grafts were harvested from cartilaginous septum to be used in nasal reshaping and reconstruction. The nasal dorsal hump was removed via Rubin Osteotome, while median-oblique and lateral osteotomy, using a conventional 2 mm guarded straight osteotome, was performed following nasal tip plasty. Cold ice-soaked gauze compression was applied to control small vessel bleeding following the osteotomies and to prevent edema and ecchymosis. In the COS-PRF group, PRF material was applied to the osteotomy line bilaterally just before the skin closure. In all patients, nasal tamponing was performed for 24 h and an external nasal splint was applied for 7 days (Figure 1 and 2).

Postoperative Edema and Ecchymosis

Postoperative eyelid edema and periorbital ecchymosis were assessed on postoperative days 2 and 7 by the two independent surgeons not participated in surgery and blinded to the study protocol.

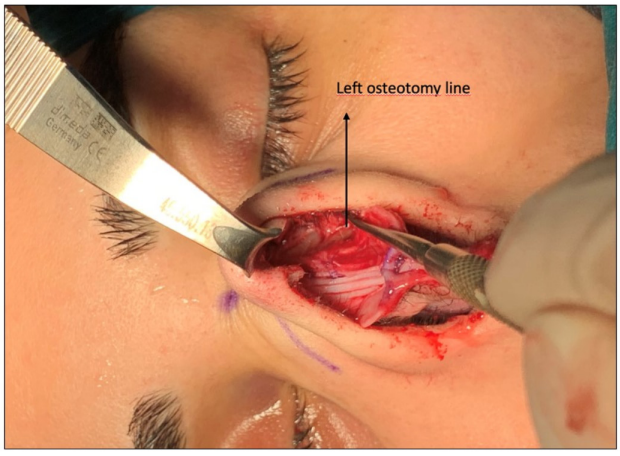

Figure 1. Rhinoplasty procedure: exposed nasal bone (Informed consent was obtained)

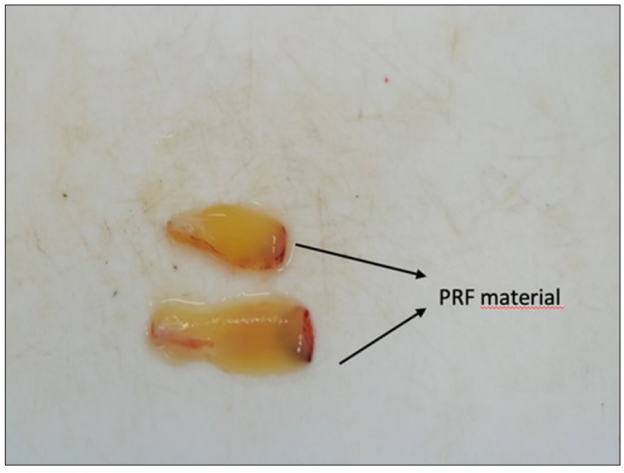

Figure 2. Prepared PRF material
PRF: Platelet-rich fibrin

The eyelid edema and periorbital ecchymosis were scored from 0 to 4, according to a graduated scoring system (15). Accordingly, eyelid edema was scored using a 4-point scale (0: no edema, 1: minimal edema, 2: edema extending onto iris without closing the eyelids, 3: edema covering the iris and extending to the pupil but not to eyelids and 4: massive edema with the eyelid swollen shut) (Figure 3).

Periorbital ecchymosis was scored using a 4-point scale (0: no ecchymosis, 1: ecchymosis involving 1/4 of the medial part of the eyelid, 2: ecchymosis involving 1/2 of the medial part of the eyelid extending to pupil, 3: ecchymosis passing the midline of the eyelid involving the maximum 3/4 of eyelid, 4: exceeds 3/4 of the eyelid and covers the eyelid completely) (Figure 3).

Visual Analogue Scale

The pain VAS is a self-administered unidimensional psychometric response scale used to measure pain intensity, which has been widely used in diverse adult populations. It is a continuous 10 cm scale anchored by 2 verbal descriptors for pain intensity, including "no pain" (score of 0) and "worst imaginable pain" (score of 10). Participants were asked to make a mark on the line that represented their pain intensity, and the pain intensity level was scored by measuring the distance from the "no pain" end to the patient's mark. VAS provides a range of scores from 0-10 with higher scores indicating greater pain intensity (16).

VRS is a continuous scale anchored by verbal descriptors for pain intensity, including no pain, mild pain, disturbing pain, severe pain, extreme pain and worst imaginable pain. The scores 0, 2, 4, 6, 8, and 10 were assigned to each verbal descriptor, with "none" scored as 0 to "worst pain" scored 10, with higher numbers associated with more intense adjectives. Participants are asked to pick the

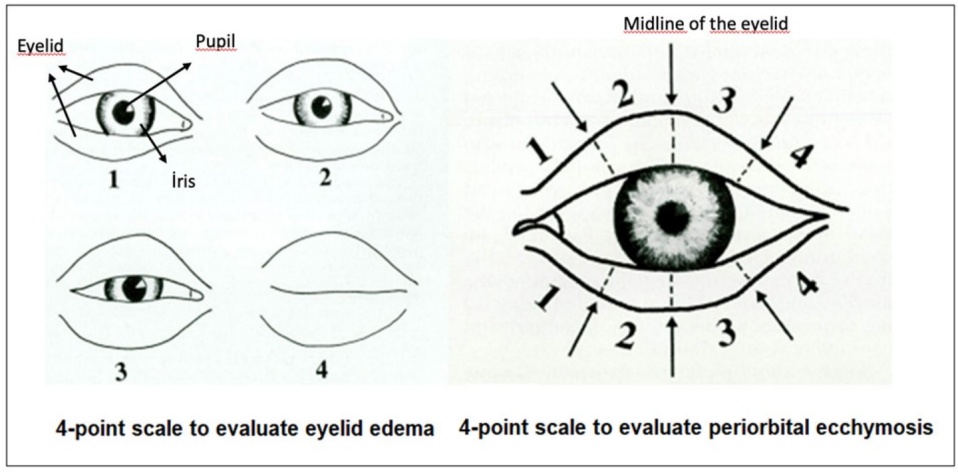

Figure 3. Scoring system used for assessment of postoperative eyelid edema and periorbital ecchymosis

word that best described their pain intensity, and their VDS intensity score is the number associated with the word they chose (16).

Statistical Analysis

Statistical analysis was performed using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). Shapiro-Wilks test was used to investigate the normal distribution. Descriptive statistics were reported for categorical data. Chi-square test (Yates continuity correction or Fisher's exact test where available) was used for the analysis of categorical variables. Mann-Whitney U test was used to compare two independent non-normally distributed variables. Data were expressed as "mean ± SD, median (minimum-maximum) and percentage (%) where appropriate. P<0.05 was considered statistically significant.

Results

Baseline Characteristics

No significant difference was noted between the COS and COS-PRF groups in terms of patient age (mean ± SD 24.8±8.0 vs. 23.9±5.4 years), gender (females: 83.9 vs. 83.3%), nasal skin thickness (normal: 581 vs. 63.3%) or operative time (mean ± SD 218.5±35.4 vs. 210±23.8 min) (Table 1).

Postoperative Eyelid Edema and Periorbital Ecchymosis

On postoperative day 2, grade 3 eyelid edema was more prevalent in both the COS (58.1% on the right side and 61.3% on the left side) and COS-PRF (53.3% on the right side and 40.0% on the left side) groups. On postoperative day 7, grade 1 edema was more prevalent in both the COS (74.2% on both sides) and COS-PRF (60.0% on the right side and 66.7% on the left side) groups (Table 2, Figure 4).

On postoperative day 2, grade 2 to 3 periorbital ecchymosis was more prevalent in both the COS (70.0% on the right side and 64.6% on the left side) and COS-PRF (46.6% on the right side and 60.0% on the left side) groups. On postoperative day 7, periorbital ecchymosis was not evident or was at grade 1 in most patients in both the COS (100.0% on the right side and 93.5% on the life side) and COS-PRF (93.4% on the right side and 90.0% on the left side) groups (Table 2, Figure 4).

No significant difference was noted between the COS and COS-PRF groups in terms of the likelihood of eyelid edema and periorbital ecchymosis on any postoperative day (Table 2).

Postoperative Pain and Analgesic Use

No significant difference was noted between the COS and COS-PRF groups in terms of average VAS scores during the 7-day postoperative period (median 2.5 vs. 2.4, p=0.680) as well as daily VAS records on day 1 (median 3.0 for each), day 2 (median 4.0 for each), day 3 (median 3.0 and 2.0 respectively) and day 7 (median 0 for each) (Table 3, Figure 5).

No significant difference was noted between the COS and COS-PRF groups in terms of average VRS scores during the 7-day postoperative period (median 1.5 vs. 1.4, p=0.521) as well as daily VRS records on day 1 (median 1.0 vs. 2.0, respectively), day 2 (median 2.0 for each), day 3 (median 2.0 and 1.0 respectively) and day 7 (median 0 for each) (Table 3, Figure 5).

No significant difference was noted between the COS and COS-PRF groups in terms of the average number of analgesics used during the 7-day postoperative period (median 1.5 vs. 1.3, p=0.196) as well as the daily number of medications on day 1 (median 1.0 for each), day 2 (median 3.0 vs. 2.0, respectively), day 3 (median 2.0 and 1.0 respectively) and day 7 (median 0 for each) (Table 3, Figure 5).

Table 1. Baseline characteristics in the COS vs. COS-PRF groups

		COS (n=31)	COS-PRF (n=30)	p-value
Age (year)	Mean ± SD	24.8±8.0	23.9±5.4	0.965[1]
	Median (min.-max.)	22 (17-52)	22 (19-39)	
Gender, n (%)				
Female		26 (83.9)	25 (83.3)	>0.05[2]
Male		5 (16.1)	5 (16.7)	
Operative time (min.)	Mean ± SD	218.5±35.4	210±23.8	0.279[3]
	Median (min.-max.)	225 (155-285)	210 (175-255)	
Skin thickness, n (%)	Thin: <1 cm	7 (22.6)	5 (16.7)	0.842[2]
	Normal: 1-2 cm	18 (58.1)	19 (63.3)	
	Thick: >2 cm	6 (19.4)	6 (20)	

COS: Conventional osteotomy alone, COS-PRF: Conventional osteotomy plus platelet-rich fibrin, min.: Minute, SD: Standard deviation, min.-max.: Minimum-maximum
[1]Mann-Whitney U test, [2]χ^2 test, [3]Student's t-test

Discussion

Our findings revealed no significant difference between the COS and COS-PRF groups in terms of postoperative morbidity including eyelid edema, periorbital ecchymosis and pain after primary open rhinoplasty with conventional osteotomy. Overall, a higher-grade eyelid edema and periorbital ecchymosis as well as higher VAS and VRS pain scores and the analgesic use were evident on postoperative days 2 and 3, while all three parameters revealed improved scores with ease of postoperative morbidity on postoperative day 7 in both groups.

The higher edema and ecchymosis scores on postoperative day 2 vs. day 7 in the current study support the data from a past study revealed the higher postoperative edema and ecchymosis scores on day 2 vs. day 7 after conventional osteotomy (17-19). Also, given the previously reported VAS cut-off values of >3.1 (20,21) and >4.0 (22) to discriminate between mild and moderate pain, our findings indicate that our rhinoplasty patients, regardless of the use of PRF, had moderate pain only on postoperative day 2 (median VAS score: 4.0 for both groups). Likewise, in past studies using the same cut-off values, rhinoplasty patients were reported to have moderate pain only on the

Table 2. Postoperative eyelid edema and periorbital ecchymosis in the COS vs. COS-PRF groups

		COS (n=31)					COS-PRF (n=30)					p-value COS vs COS-PRF
Postoperative morbidity		0	1	2	3	4	0	1	2	3	4	
Eyelid edema, n (%)												
Day 2	Right	0	1 (3.2)	11 (35.5)	18 (58.1)	1 (3.2)	0	2 (6.7)	12 (40.0)	16 (53.3)	0	0.687
	Left	0	0	10 (32.3)	19 (61.3)	2 (6.5)	0	2 (6.7)	14 (46.7)	12 (40.0)	2 (6.7)	0.237
Day 7	Right	6 (19.4)	23 (74.2)	2 (6.5)	0	0	9 (30)	18 (60.0)	3 (10)	0	0	0.498
	Left	5 (16.1)	23 (74.2)	3 (9.7)	0	0	8 (26.7)	20 (66.7)	2 (6.7)	0	0	0.581
Periorbital ecchymosis, n (%)												
Day 2	Right	0	4 (13.3)	10 (33.3)	11 (36.7)	5 (16.7)	0	7 (23.3)	7 (23.3)	7 (23.3)	9 (30.0)	0.337
	Left	0	4 (12.9)	10 (32.3)	10 (32.3)	7 (22.6)	0	4 (13.3)	15 (50.0)	3 (10.0)	8 (26.7)	0.185
Day 7	Right	15 (48.4)	16 (51.6)	0	0	0	14 (46.7)	14 (46.7)	0	2 (6.7)	0	0.341
	Left	17 (54.8)	12 (38.7)	2 (6.5)	0	0	15 (50.0)	12 (40.0)	1 (3.3)	2 (6.7)	0	0.486

COS: Conventional osteotomy alone, COS-PRF: Conventional osteotomy plus platelet-rich fibrin
χ^2 test and Fisher's exact test

Table 3. Postoperative pain and analgesic use in the COS versus COS-PRF groups

	Postoperative scores									
	Day 1		Day 2		Day 3		Day 7		Average	
	Mean ± SD	Median (min.-max.)	Mean ± SD	Median (min.-max.)	Mean ± SD	Median (min.-max.)	Mean ± SD	Median (min.-max.)	Mean ± SD	Median (min.-max.)
VAS scores										
COS	3.3±2.2	3 (0-8)	3.9±2.3	4 (0-8)	3.3±2.2	3 (0-8)	0.9±1.2	0 (0-4)	2.9±1.7	2.5 (0-6.5)
COS-PRF	3.4±2.6	3 (0-9)	3.7±2.3	4 (0-9)	3±2.5	2 (0-9)	0.5±0.8	0 (0-2)	2.7±1.7	2.4 (0-6.8)
p-value	0.924[2]		0.734[1]		0.539[2]		0.316[2]		0.680[1]	
VRS scores										
COS	1.5±1	1 (0-4)	2.1±1.2	2 (0-4)	1.7±1	2 (0-4)	0.5±0.7	0 (0-2)	1.4±0.7	1.5 (0-3.3)
COS-PRF	1.6±1.1	2 (0-4)	1.8±1.1	2 (0-4)	1.5±1.1	1 (0-4)	0.3±0.5	0 (0-1)	1.3±0.7	1.4 (0-3)
p-value	0.490[2]		0.487[2]		0.256[2]		0.351[2]		0.521[1]	
Number of analgesics										
COS	1.1±1	1 (0-4)	2.8±1.1	3 (1-5)	2±1.2	2 (0-5)	0.4±0.8	0 (0-2)	1.6±0.8	1.5 (0.3-3.8)
COS-PRF	1.1±0.9	1 (0-4)	2.3±1.2	2 (0-5)	1.6±1.3	1 (0-5)	0.3±0.5	0 (0-2)	1.3±0.7	1.3 (0-3)
p-value	0.849[2]		0.169[2]		0.079[2]		0.837[2]		0.196[2]	

COS: Conventional osteotomy alone, COS-PRF: Conventional osteotomy plus platelet-rich fibrin, VAS: Visual analogue scale, VRS: Verbal rating scale, SD: Standard deviation, min.-max.: Minimum-maximum
[1]Student's t-test, [2]Mann-Whitney U test

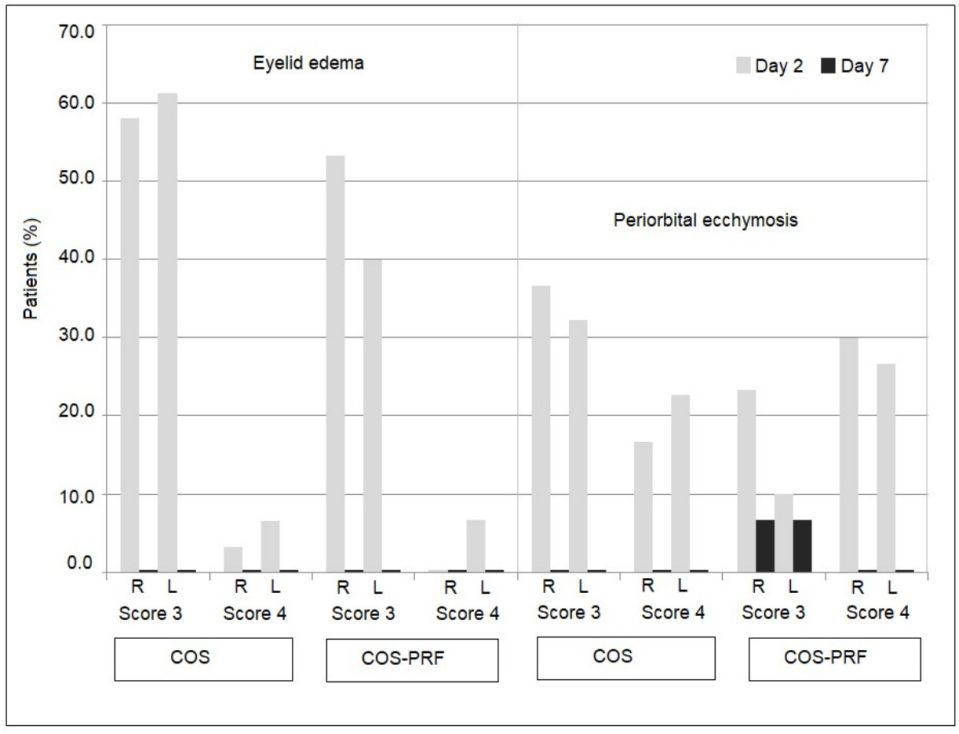

Figure 4. Postoperative (day 2 and day 7) scores 3 and 4 postoperative eyelid edema and periorbital ecchymosis on the left and right side in conventional osteotomy (COS) and conventional osteotomy plus platelet-rich fibrin (COS-PRF) groups

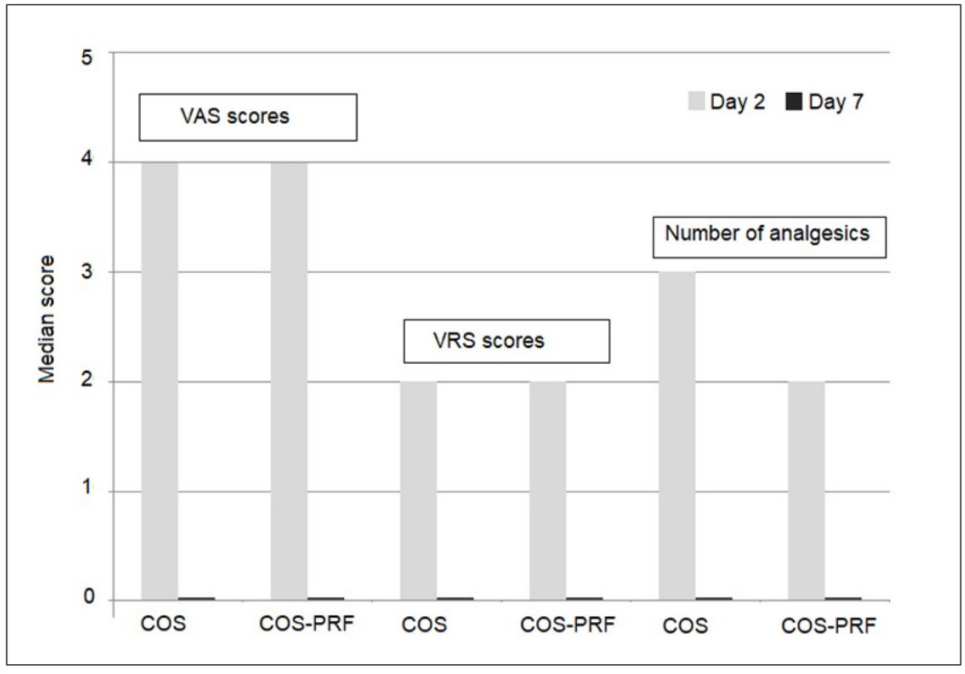

Figure 5. Postoperative (day 2 and day 7) pain and analgesic use in conventional osteotomy (COS) and conventional osteotomy plus platelet-rich fibrin (COS-PRF) groups
VAS: Visual analogue scale, VRS: Verbal rating scale

day of surgery (for a cut-off >4.0) or postoperative days 1 and 2 (for a cut-off >3.1) (23).

The association PRF with release of factors that improve and accelerate the tissue regeneration is considered to improve short-term postoperative outcome; whereas in the long term, PRF is considered to enable security and functional and aesthetic improvement after rhinoplasty (24-26). Hence, the practicality of PRF as well as its immuno-biologic properties is considered to make it an excellent alternative to other methods in rhinoplasty (1,12,27).

Notably, PRF is considered advantageous, particularly in structured rhinoplasty involving a small area of the body surface, given the likelihood of small and refined gains in the healing quality to offer lasting and satisfactory aesthetic and functional results (1).

Accordingly, PRF combined with autologous high-density fat-granule transplantation for augmentation rhinoplasty was reported to achieve a good and stable long-term effect with no adverse reactions and a good orthopedic and cosmetic effect (14).

In a past study on follow-up for 12 months a series of cases in which the PRF membrane was used as an alternative to the camouflage and filling-in techniques used in primary or secondary rhinoplasties, the authors reported that PRF membrane was an excellent surgical alternative to the camouflage and filling in rhinoplasty (1). The use of a cartilage graft wrapped in PRF matrix in open septorhinoplasty was also reported to be associated with successful results in dorsal grafting and tip area (28). Additionally, the application of PRF to the mucosal surface after the completion of septoplasty was reported to have a positive effect on olfactory function and pain, particularly in the early postoperative period (7).

Moreover, in a past study with 38 patients who underwent open approach primary rhinoplasty, the application of a PRF membrane over the bony dorsum and cartilage framework of the supratip area was reported to have a positive effect on postoperative edema, especially in the early postoperative period (13).

In contrast to the above-mentioned studies, our findings revealed no advantage of using local PRF application over osteotomy line in improving short-term postoperative morbidity among patients undergoing open rhinoplasty with conventional osteotomy. Nonetheless, given that 20% of our patients had thick nasal skin, note that in the long-term these patients may have benefit from the PRF application, since the use of PRF is suggested in patients with thicker skin and thus bigger tendency to form dead space to be filled with scar tissue, which consequently leads to persistent edema and poor cosmetic outcome (4,13).

Indeed, previous studies in the dentistry field also revealed no additional impact of using PRF or advanced PRF (A-PRF) on postoperative edema and pain after the mandibular third molar surgery (29-31), while A-PRF vs. PRF has also been reported to reduce postoperative pain, swelling and the analgesic need after the mandibular third molar surgery (32).

Study Limitations

The major strength of the current study seems to be the assessment of postoperative morbidity via a graduated scoring system for eyelid edema and periorbital ecchymosis and via both VAS and VRS for pain. However, potential lack of generalizability seems to be an important limitation due to the relatively small sample size.

Conclusion

Our findings on short-term postoperative morbidity among patients undergoing open rhinoplasty with conventional osteotomy indicate no significant impact of PRF application in reducing postoperative eyelid edema, periorbital ecchymosis, or pain within the first postoperative week. Larger scale studies addressing the efficacy of PRF along with other potential techniques, methods, or biomaterials for morbidity reduction may help reveal the optimal approach to reduce this uncomfortable postoperative morbidity in rhinoplasty patients and to enable long-term favorable outcomes regarding optimal healing and the intended morphologic result.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Health Sciences Turkey, Istanbul Training and Research Hospital Clinical Research Ethics Committee (approval no: 2011-KAEK-50/2687, date: 22.01.2021).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.Y., T.K., O.O., O.Y., Design: E.Y., T.K., O.O., O.Y., Data Collection and/or Processing: E.Y., T.K., M.T., A.C., O.Y., Analysis and/or Interpretation: E.Y., T.K., M.T., A.C., Literature Research: E.Y., T.K., O.O., M.T., A.C., O.Y., Writing: E.Y., O.O., M.T., A.C., O.Y.

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Original Article

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The Impact of Age on Percutaneous Thrombectomy Outcomes in the Management of Lower Extremity Deep Vein Thrombosis

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Abstract

Aim: Percutaneous thrombectomy (PT) results may differ in elderly patients compared to younger patients. We analyzed the effect of being elderly on PT results for lower extremity deep vein thrombosis (DVT).

Methods: We retrospectively reviewed patient charts who were treated with PT for lower extremity (common iliac, external iliac, femoral, and popliteal veins) DVT between October 2016 and March 2021, and patients with unilateral lower extremity DVT and older than 18 years old were enrolled in the cohort study. Patients' preoperative characteristics, operative parameters, and post-procedural outcomes were stored in the electronic data system. All participants were divided into 2 groups according to being elderly or not, as patients <65 years and patients ≥65 years. The two groups were compared in terms of preoperative patient data, operative parameters, and postoperative results.

Results: One hundred and five patients were enrolled in the study (62 patients were <65 years of age and 43 patients were ≥65 years of age). The mean hospitalization time was 3.1 days for non-elderly patients and 3.8 days for elderly patients (p=0.030). In addition, the duration of mean intensive care unit (ICU) stay was significantly longer in elderly patients (1.2 vs 1.7, p=0.024). Older patients had a lower success rate, but the difference was not statistically significant (93.5% vs 88.4%, p=0.482). Grade 1-2 Clavien-Dindo complications and the overall complication rate were significantly higher in elderly patients (6.4% vs 20.9%, p=0.027 and 12.9% vs 30.2%, p=0.029). The Pearson correlation test revealed that older age was associated with longer hospitalization time and ICU stay (p=0.001 and p=0.001).

Conclusion: Elderly patients are more frail depending on age and comorbidities, and the hospitalization time and ICU stay after PT are prolonged in these patients. In addition, elderly patients face significantly more complications following PT in comparison with non-elderly patients.

Keywords: Aged, venous thrombosis, lower extremity, hospitalization, thrombectomy

Introduction

Deep vein thrombosis (DVT) is described as an abnormal clot formation, particularly in the deep veins of the lower extremities. Untreated DVT is a serious health problem and results in edema, pain, ulceration, pulmonary embolism, and even death (1). The incidence of DVT is influenced by many factors, including the presence of motion-restricting disease, the presence of cancer, obesity, and aging. Silverstein et al. (2) investigated the incidence of DVT according to age and found that the incidence DVT was stable until the age of 65 and increased 3-fold after the age of 65. On the other hand, the World Health Organization considers individuals over the age of 65 to be elderly. Due to better living conditions, healthcare facilities, and nutritional possibilities, life expectancy has increased from the fifties to the eighties in the last century (3). Thus, the number of individuals who seek treatment for DVT has increased. Although aging is not a disease per

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se, aging-associated deterioration in body functions can be determined, and the selection of treatment options becomes more complicated in the elderly.

Percutaneous thrombectomy (PT) is an alternative minimally invasive surgical modality instead of long-lasting anticoagulation for lower extremity DVT Loffroy and colleagues performed PT for patients with lower extremity DVT, and the authors achieved an 86.7% venous patency rate during 22.3 months of follow-up (4). In another study by Dumantepe and Uyar (5), 68 patients diagnosed with lower extremity DVT were treated with PT. Dumantepe and Uyar (5) obtained a 95% success rate with complications in three cases.

Although previous studies investigated the effectiveness and reliability of PT for the management of lower extremity DVT, no studies to date have evaluated the effect of age on PT outcomes. In elderly patients, changes in vascular structure and existing comorbidities may affect PT results. In this study, our purpose was to analyze the effect of being elderly on PT results for lower extremity DVT.

Materials and Methods

Ethical Standards

The study was approved by the local ethics committee (Ethics Committee of Bezmialem Vakif University, approval number: 2020-112, date: 17.04.2020). Also, the study was planned in accordance with the Helsinki Declaration.

Study Design

In this study, we retrospectively reviewed patient charts who were treated with PT for lower extremity (common iliac, external iliac, femoral, and popliteal veins) DVT between October 2016 and March 2021. Before PT, all patients were informed about how the procedure would be performed, its success rate, and possible complications, and informed consent was obtained from all patients. The PT procedures were performed in the same manner. Patients with unilateral lower extremity DVT and those older than 18 years old were enrolled in the study. Diagnostic DVT was done with a detailed physical examination and venous duplex ultrasonography. Exclusion criteria were presence of bilateral lower extremity DVT, presence of active neurologic and/or psychiatric disorder(s), inability to access preoperative and operative patient data and being <18 years old.

Patients' preoperative characteristics, operative parameters, and post-procedural outcomes were saved in the electronic data system, prospectively. Recorded preoperative parameters were age (years), sex, body mass index (BMI), duration of symptoms (days), the presence of hypertension, diabetes mellitus, coexistent malignancy, and DVT history. Also, thrombus properties (length, location, and side), operation and fluoroscopy time (minutes), estimated blood loss (milliliters), and stenting rates were noted. Also, the hospitalization period and duration of intensive care unit (ICU) stay (minutes), requirements for re-operation, complications according to the Clavien-Dindo classification, and success of the procedure were noted. Procedures with the removal of thrombus during the procedure and cases with venous patency in the first month of follow-up were considered successful.

PT Technique

Under local anesthesia, 5000 IU of heparin sodium was used for anticoagulation and a vena cava filter was placed two centimeters below the renal veins from the contralateral femoral vein. Percutaneous access was obtained from the popliteal vein with an 18 F gauge needle, and an introducer sheath with an 8 F (INVAMED, Ankara, Turkey) size was inserted. Then, thrombus characteristics and venous patency were evaluated by venography, and a 0.035-size guidewire was placed beyond the thrombus. Mechanical thrombectomy was performed repeatedly until the thrombus was removed. At the end of the procedure, venography was performed to assess venous patency, and the success was re-assessed with venous duplex ultrasonography at the end of the first month.

Finally, all participants were divided into 2 groups according to being elderly or not, as patients <65 years and patients ≥65 years. The two groups were compared in terms of preoperative patient data, operative parameters, and postoperative results.

Statistical Analysis

For statistical evaluation, The Statistical Package for the Social Sciences version 25 (SPSS IBM Corp., Armonk, NY, USA) was used. The variable distribution was assessed by the Shapiro-Wilk test and Q-Q plots. The independent Student's t-test was used for the comparison of normally distributed values between groups. The Mann-Whitney U test was performed for the comparison of non-normally distributed variables. Quantitative data is summarized as mean ± standard deviation values. Categorical values were categorized and compared using the χ^2 test or Fisher's exact test. Correlations between age, and complications, duration of hospitalization, and duration of ICU were calculated using Pearson's correlation test. The data was analyzed with a 95% confidence level, and a p-value less than 0.05 was considered statistically significant.

Results

One hundred and five patients were enrolled in the study (62 patients were <65 years of age and 43 patients were ≥65 years of age). The sex ratio, mean BMI, smoking status, presence of diabetes mellitus, hypertension,

malignant status, and DVT history were not statistically significant among the groups (p=0.619, p=0.513, p=0.330, p=0.177, p=0.055, p=0.710, and p=0.557, respectively). The mean age was significantly higher in elderly patients (42.9 years and 72.6 years, p=0.001). Preoperative patient data is summarized in Table 1.

Comparison of elderly and non-elderly patients demonstrated that length, location and side of thrombus were similar between groups (p=0.755, p=0.953, and p=0.907, respectively). The mean operation time and the mean fluoroscopy time were longer in patients <65 years, but the differences were not statically significant (p=0.940 and p=0.291) (Table 2).

The mean hospitalization time was 3.1 days for non-elderly patients and 3.8 days for elderly patients (p=0.030). In addition, the duration of mean ICU stay was significantly longer in elderly patients (1.2 vs 1.7, p=0.024). Older patients had a lower success rate, but the difference was not statistically significant (93.5% vs 88.4%, p=0.482). Grade 1-2 Clavien-Dindo complications and the overall complication rate were significantly higher in elderly patients (6.4% vs 20.9%, p=0.027 and 12.9% vs 30.2%, p=0.029). However, Grade 3-5 Clavien-Dindo complications were comparable between the groups (p=0.588) (Table 3). The Pearson correlation test revealed that older age was associated with longer hospitalization time and ICU stay (p=0.001 and p=0.001) (Table 4).

Discussion

The aging of the world population has increased the number of elderly patients who will need treatment in many medical disciplines (6). Lower extremity DVT is common in elderly individuals. However, to our knowledge, no study has investigated the efficiency and reliability of PT in the elderly population. In this study, we showed the impact of being elderly on PT outcomes. We found that hospitalization time and the duration of ICU stay were significantly longer in elderly patients. Additionally, overall complications and Clavien-Dindo grade 1-2 complications were significantly more common in patients with ≥65 years old.

Table 1. Comparison of preoperative demographic data of patients according to their age

	Age <65 years (n=62)	Age ≥65 years (n=43)	p-value
Age (years), mean ± SD	42.9±9.3	72.6±6.7	**0.001**[a]
Gender, n (%) Male Female	 33 (53.2%) 29 (46.8%)	 25 (58.1%) 18 (41.9%)	 0.619
BMI (kg/m²), mean ± SD	28.6±4.1	28.1±3.9	0.513
Smoking status, n (%)	33 (53.2%)	27 (62.8%)	0.330
Diabetes mellitus, n (%)	7 (11.3%)	9 (20.9%)	0.177
Hypertension, n (%)	15 (24.2%)	18 (41.9%)	0.055
Coexistent malignancy, n (%)	34 (53.9%)	22 (51.2%)	0.710
DVT history, n (%)	31 (50.0%)	24 (55.8%)	0.557
Duration of symptoms (days), mean ± SD	6.8±4.2	6.5±3.7	0.701

[a]: Student's t-test
BMI: Body mass index, SD: Standard deviation, DVT: Deep vein thrombosis

Table 2. Comparison of the operational data of the patients according to their age

	Age <65 years (n=62)	Age ≥65 years (n=43)	p-value
Site of DVT, n (%) Iliofemoral Popliteal Femoral Femoral/popliteal	 15 (24.2%) 12 (19.3%) 9 (14.5%) 26 (41.9%)	 11 (25.6%) 9 (20.9%) 7 (16.3%) 16 (37.2%)	 0.953
Side involved, n (%) Right Left	 31 (50.0%) 31 (50.0%)	 22 (51.1%) 21 (48.9%)	 0.907
Lesion length (cm), mean ± SD	10.5±2.6	10.4±2.1	0.755
Operation time (min), mean ± SD	124.5±24.6	124.1±27.8	0.940
Flouroscopy time (min), mean ± SD	23.7±10.8	21.5±9.7	0.291
Amount of blood (mL), mean ± SD	253.7±38.4	258.9±40.9	0.508
Stenting rate, n (%)	3 (4.8%)	2 (4.6%)	0.965

DVT: Deep vein thrombosis, SD: Standard deviation

Table 3. Comparison of postoperative results and complications according to their age			
	Age <65 years (n=62)	**Age ≥65 years (n=43)**	**p-value**
Hospital stay (days), mean ± SD	3.1±1.5	3.8±1.7	**0.030**[a]
ICU stay (days), mean ± SD	1.2±1.1	1.7±1.2	**0.024**[a]
Success, n (%)	58 (93.5%)	38	0.482
Decrease of Hgb (g/dL), mean ± SD	1.1±0.9	1.3±1.1	0.300
Complications, n (%)	8 (12.9%)	13 (30.2%)	**0.029**[b]
Clavien-Dindo grade 1-2	4 (6.4%)	9 (20.9%)	**0.027**[b]
Bradycardia Hemoglobinuria Leg pain	1 (1.6%) 2 (3.2%) 1 (1.6%)	3 (7.0%) 3 (7.0%) 3 (7.0%)	
Clavien-Dindo grade 3-5	4 (6.4%)	4 (9.3%)	0.588
Acute renal failure Major hemorrhage Pulmonary embolism Sepsis	1 (1.6%) 2 (3.2%) 1 (1.6%) None	1 (2.3%) 1 (2.3%) 1 (2.3%) 1 (2.3%)	
Re-operation, n (%)	1 (1.6%)	1 (2.3%)	0.793

*Mean ± standard deviation, [a]: Student's t-test, [b]: Chi-squared test
ICU: Intensive care units, SD: standard deviation

Complications occurring in elderly patients may be more difficult to manage and could be fatal. Batchelor et al. (7) analyzed the outcomes of percutaneous coronary interventions in 7472 elderly individuals and stated that there were significantly higher complications, including vascular complications, renal failure, stroke, and death, in elderly patients. In another study, Polanczyk et al. (8) compared elderly and non-elderly patients in terms of complications following non-cardiac surgeries, and the authors found that perioperative complications increased 1.8-times and 2.1-times in patients between 70 and 79 years and ≥80 years in comparison with patients between 50 and 59 years. However, no study has investigated the complications in the elderly according to the complication severity classification. In this study, the overall complication rate was significantly higher in elderly patients. In addition, evaluating complications according to their severity revealed that serious complication rates (Clavien-Dindo grade 3-5) were similar in elderly and non-elderly patients, but slight complications (Clavien-Dindo grade 1-2) were significantly higher in elderly patients.

The effect of being elderly on hospitalization time and duration of ICU is a controversial topic and has not been evaluated following PT yet. Lin et al. (9) compared outcomes for elderly and non-elderly patients following surgery for left-sided valve infective endocarditis and discovered a longer duration of ICU stay in elderly patients (4.5 days vs 3.0 days, p=0.001), but similar hospitalization time between elderly and non-elderly patients (37.5 vs 37 days, p=0.405). In Polanczyk et al.'s (8) study, the mean hospitalization time was 7.4 days in patients aged 50-59 years and 9.2 days in patients aged 70-79 years. In this study, we found significantly longer hospitalization time and ICU stay following PT in elderly patients in comparison with non-elderly patients. We believe that movement restrictions of the skeletal system, relatively low lung capacity, and longer extubation time in the elderly may play a role in these results. A different study may be necessary to determine factors affecting hospitalization time and the duration of ICU stay in the elderly.

Table 4. Correlation analysis of hospital stay and ICU stay time with age			
Pearson correlation		**Hospital stay**	**ICU stay**
Age	Correlation coefficient[a] Sig. (2-tailed) N	0.384 **0.001**[b] 105	0.462 **0.001**[b] 105

[a]: Between 0.3-0.7 values shows a moderate correlation, [b]: Pearson correlation test
ICU: Intensive care units

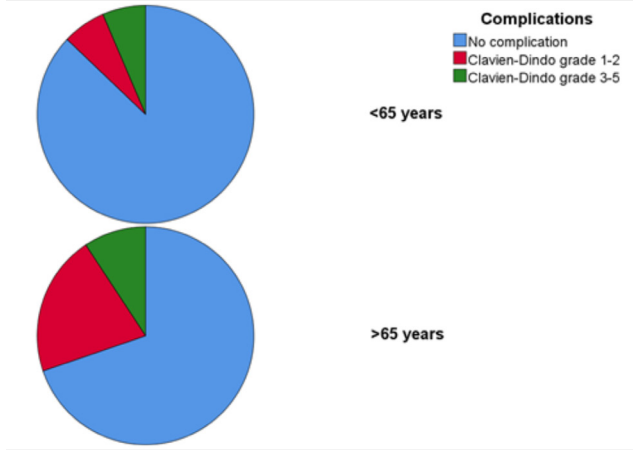

Figure 1. Distribution of complications according to groups

Although the definition of being elderly was not similar in different studies, many reports stated that being elderly was not an unfavorable factor for minimal invasive procedures (10,11). Tamburino and colleagues analyzed the charts of 663 patients who underwent transcatheter aortic valve implantation and reported 98% success rate following surgery, with a similar success rate to the non-elderly population (12). In another study, Klein et al. (13) investigated the impact of aging on percutaneous coronary interventions, and the authors achieved angiographic success in 93% of elderly patients. In this study, we did not find a significant difference in PT success between elderly and non-elderly patients. We suggest that performing the same technique regardless of age in all patients and not being a factor in changing the procedure technique have led to this situation.

Study Limitations

Small patient numbers and the retrospective nature of the study could be considered limitations of this study. Despite the retrospective evaluation of the data, all parameters were recorded in the electronic database prospectively. Secondly, being elderly was accepted as aged ≥65 years, but biological age could be different according to individuals and the effects of comorbidities. Additionally, this study included only a one-month follow-up outcome after the procedure, long-term follow-up results are lacking. We believe that long-term outcomes of PT among elderly patients could be the subject of another study. Finally, we did not compare the cost of physical therapy in elderly and non-elderly populations, which will be clarified in future research.

Conclusion

This study showed for the first time that hospitalization time and duration of ICU stay were significantly longer in elderly patients. In addition, elderly patients faced significantly more complications following PT in comparison with non-elderly patients. Our findings should be supported by prospective randomized studies with higher patient numbers.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (Ethics Committee of Bezmialem Vakif University, approval number: 2020-112, date: 17.04.2020).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: H.K.C., Design: H.K.C., Data Collection, or Processing: C.B., Analysis, or Interpretation: C.B., Literature Search: C.B., Writing: H.K.C.

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

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Original Article

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Determination of the Relation Between Passive Cigarette Smoking in Children and Respiratory Tract Infections by Evaluation of Urine Cotinine/Creatinine Levels

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Abstract

Aim: Passive smoking is an important public health issue due to the clinical problems it causes. In this study, we determined the effect of passive smoking on respiratory tract infections using a survey method, family history, and urine cotinine/creatinine ratio.

Methods: Seventy-two children who came to the Pediatric Outpatient Clinic at Istanbul Bagcilar Training and Research Hospital for a check-up with no current health problems between November 2020 and March 2021 were included in this prospective cross-sectional study. The study group included 36 children with at least one active smoker in the house, and the control group included 36 children with no active smokers in the house. With the survey, sociodemographic variables about the family and child as well as the frequency of lower or upper respiratory tract infection history were questioned. Cotinine and creatinine levels were measured using the urine samples of the patients included in the study.

Results: The frequency of respiratory tract infections in the last two years was increased in the group with an active smoker in the household. The frequency of bronchopneumonia in the case group was 44.4%, whereas it was 5.6% in the control group. The sinus infection was seen in 22.2% of those in the case group, while there were no sinus infections reported in the control group. Bronchopneumonia and sinus infections were statistically significant in the case group ($p<0.01$ and $p<0.01$ respectively). The median cotinine levels in the active smokers in the house group were 20.94 ng/mL (0-491) and 16.62 ng/mL (0-121) in the nonsmoker group. 55.6% of children with a history of cigarette smoke exposure and a urine cotinine level higher than 10 ng/mL were considered passive smokers (the normal range is 0-10 ng/mL).

Conclusion: Frequent respiratory tract infections and hospitalization may be prevented by informing families about the risks of exposure to cigarette smoke as well as raising awareness of the harms of cigarette smoke.

Keywords: Children, passive cigarette smoking exposure, respiratory tract infection, urine cotinine, urine cotinine/creatinine

Introduction

Exposure to cigarette smoke is critical since it is very common, but also preventable. According to the report on the Global Tobacco Outbreak by the World Health Organization (WHO) in 2017, tobacco use causes more than 7 million deaths per year. One in every ten deaths is caused by tobacco usage. Furthermore, 600,000 (170,000 children) of these deaths are the result of passive smoking. WHO also reports that 700 million children are exposed to cigarette smoke by 1.2 billion smokers, mainly in their home environment (1).

Passive smoking is defined as even though the person does not actively smoke, is exposed to cigarette smoke in closed environments and inhales all the harmful substances in the smoke (2). The prevalence of passive smoking in children is very high, especially in developing countries, and is reported as 29-69%. According to studies

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in our country, 14.8 million people use tobacco products, and of those, 94.8% smoke cigarettes. Passive smoking in children is reported as 53-92% (3,4).

Passive smoking has become a major health problem since people spend most of their time in closed environments (5). Passive smoking, which is as harmful as active cigarette smoking, causes important health issues in children. It increases and facilitates upper and lower respiratory tract diseases starting from early childhood. Passive cigarette smoking significantly increases hospitalization and health expenses in children due to respiratory system diseases (6).

The most reliable and important biological indicator of exposure to cigarette smoke and active smoking is cotinine. Cotinine is the major metabolite of nicotine. In cases where obtaining a 24-hour urine sample is impossible, urine cotinine levels and cotinine/creatinine ratios are the most appropriate gatherable data for the determination of exposure to the cigarette.

This study aims to compare the urine cotinine levels and cotinine/creatinine ratios with the results of the survey to determine passive smoking exposure more objectively in children aged 2-5 years, and to evaluate the relationship between passive smoking exposure and respiratory tract infections.

Methods

Ethical Standards

The study was approved by the Istanbul Bagcilar Training and Research Hospital Clinical Studies Ethical Board on September 11th, 2020, with the number 2020.09.2.07.124. Certain questions were asked by the families of those included, and families were informed that a urine sample would be collected from their children. A written consent form was obtained from all the families.

Study Design

Seventy two children who came to the pediatric outpatient clinic at University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital, for a check-up with no current health problems between November 2020 and March 2021 were included in this prospective cross-sectional study. Children were divided into two groups based on whether they were exposed to cigarette smoke or not. Thirty six children between the ages of 2-5 years old were reported as passive smokers, with at least one active smoker in the household, and 36 children in the same age range were included as non-passive smokers. This age range was selected because of the fact that children between the ages of 2 and 5 are more susceptible to cigarette smoking and are less likely to be exposed to external factors since they do not attend school.

The data was collected by the researcher herself, using a face-to-face interview technique. In the survey, the relation of the child and interviewee, child's age, number of siblings, occupation of mother and father, education of mother and father, type of the house they live in, the ventilation system of the house, the heating system of the house, whether mother or father are smokers, if they are smoker number of cigarettes smoked per day, whether other people in the house smoke, if there are; the number of cigarettes they smoke, the total number of cigarettes smoked in the house per day, whether cigarette was being smoked in the same room as the child, number of people the child shares the room with, if the child or any other member of the family has a history of any disease that require prescription drugs or routine controls, whether the child had any respiratory tract infection within the past two years, if the answer is yes, how many times and what kind were asked.

Collection of Urine Samples

Gathering samples with a urine bag interferes with the laboratory standardization of urinalysis. Therefore, the samples were collected using urine cups. To evaluate the cotinine levels, at least 5 cc of urine samples were collected in urine cups with no preservatives and placed in +4 °C refrigerators. They were centrifuged at 4000 cycles for 20 min, then the supernatant parts were separated. All the samples were frozen at -80 °C. Following the collection of all samples, the urine samples were defrosted at room temperature. The supernatant parts were again separated and the samples were placed in the devices. Urine cotinine levels were studied using a DPC labeled Immulite 2000 device (Siemens, USA) using the chemiluminescence immunoassay method. Urine creatinine levels were measured using the Beckman Olympus AU 5800 device.

Cotinine levels lower than 10 ng/mL were accepted to signify no contact or very little contact with cigarette smoke. Values between 10-500 ng/ml signified passive smoking. Urine cotinine levels higher than 500ng/ml were accepted as active smoking (7).

Statistical Analysis

For statistical analysis, the NCSS (Number Cruncher Statistical System) program was used. Complementary statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the data. The Shapiro-Wilk test and graphical analysis were used to determine the suitability of quantitative data for normal distribution. A Mann-Whitney U test was used to compare the two groups of data that did not have a normal distribution. The Pearson chi-square test, Fisher's-exact test, and Fisher-Freeman-Halton tests were also used to compare

the quantitative data. Statistical meaningfulness was accepted as p<0.05.

Results

The study was conducted with a pediatric population of 72 children, 47.2% (n=34) female and 52.8% (n=38) male patients. The children were aged between 2 and 5 years old, with an average of 4,014±0.99 years. 50% of the children (n=36) did not have an active smoker at home, while the other 50% (n=36) had at least one active smoker at home. In houses with smokers, the mother was the smoker in 5.6% (n=2), the father was the smoker in 69.4% (n=25), both parents were smokers in 11.1% (n=4) and 13.9% (n=5), another person in the house was the smoker (Table 1) (Figure 1). The number of cigarettes smoked per day ranged between 2 and 40, with an average of 11.89±8.86.

The average age of the study group was 4,014±0.97 and the average age of the control group was 4,014±1.02 with no statistically meaningful difference in age between both groups (p>0.05). There were 14 female and 22 male patients in the study group, and 20 female and 16 male patients in the control group. There was no statistically meaningful difference in the gender distribution of both groups (p>0.05) (Table 2).

Socio-demographic data of the control group and those exposed to passive cigarette smoking are shown in Table 2.

There was a statistically meaningful difference in the work status of mothers (p=0.014; p<0.05). The proportion of working mothers in the study group was significantly higher than that in the control group (Table 2).

The groups' backgrounds (personal and family history) were compared. The history of respiratory tract infections was found to be statistically meaningfully high in the study group compared to the control group (p=0.008; p<0.01) (Table 3).

Table 1. According to the survey results, smoking in the home

		n	(%)
House status	Smokers	36	(50)
	Non-smokers	36	(50)
Person who smokes (n=36)	Mother	2	(5.6)
	Father	25	(69.4)
	Mother+father	4	(11.1)
	Other	5	(13.9)
Daily cigarette smoking	Average ± standard deviation	11.89±8.86	
	Median (minimum-maximum)	10 (2-40)	

Table 3, shows the comparison of the number and types of respiratory tract infections over the past two years for both groups. The number of respiratory tract infections over the past 2 years was statistically meaningfully high in the study group (p=0.001) (Figure 2).

Comparing the types of infections in each group showed that there was no statistically meaningful difference in the occurrence of tonsillitis, pharyngitis, and bronchiolitis (p>0.05) whereas bronchopneumonia and sinusitis were statistically meaningfully higher in the study group (p<0.01, p<0.01 respectively) (Figure 3).

Urine cotinine levels of children in the study ranged between 0 and 491.16 with an average of 49.60±89.20. 44.4% (n=32) had no contact (0-10) whilst 55.6% (n=40) was passive smoker (Table 4).

Once the groups were compared on the basis of urine cotinine and urine cotinine/creatinine ratios, there was no statistically meaningful difference found (p>0.05, p>0.05 respectively) (Table 5).

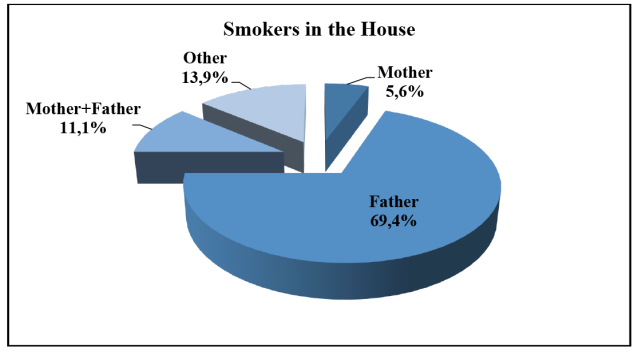

Figure 1. Distribution based on smokers in the house

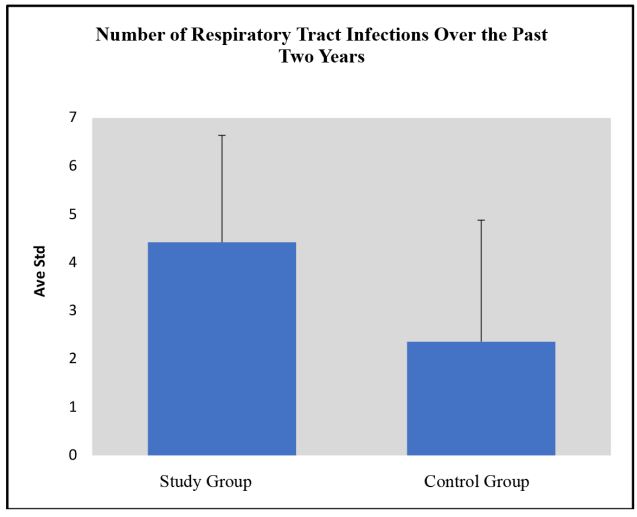

Figure 2. Distribution of the groups based on the number of respiratory tract infection in the past two years

Discussion

Passive cigarette smoking is one of the subjects that is highly discussed sociologically, legally, and medically. Children are exposed to passive smoking through different routes. The pediatric population is mostly passive smokers due to close relatives who smoke. It is caused by the mother being a passive or active cigarette smoker during prenatal time or the child being exposed to cigarette smoke postnatally by a smoking parent or another family member (8). Passive smoking may cause various health issues in children. Both intrauterine and postnatal passive cigarette exposure increase the frequency of respiratory

Table 2. Comparison of both groups based on epidemiological and socio-demographic data

		Study (n=36)	Control (n=36)	p-value
Age	**Average ± Standard deviation**	4.014±0.97	4.014±1.02	[a]**0.958**
Sex, n (%)	**Female** **Male**	14 (38.9) 22 (61.1)	20 (55.6) 16 (44.4)	[b]**0.157**
Number of siblings, n (%)	**None** **1** **2** **≥3**	8 (22.2) 14 (38.9) 9 (25) 5 (13.9)	4 (11.1) 17 (47.2) 8 (22.2) 7 (19.4)	[b]**0.569**
Number of people the child shares the room with, n (%)	**None**	1 (2.8)	1 (2.8)	[c]**0.328**
	1	2 (5.6)	4 (11.1)	
	2	8 (22.2)	15 (41.7)	
	3	17 (47.2)	12 (33.3)	
	4	4 (11.1)	3 (8.3)	
	5	4 (11.1)	1 (2.8)	
Number of people in the house. n (%)	**3 People**	7 (19.4)	4 (11.1)	[b]**0.200**
	4 People	9 (25)	16 (44.4)	
	5 People	20 (55.6)	16 (44.4)	
Smoking in the same room where the child stays, n (%)	**No**	28 (77.8)	36 (100)	[d]**0.003****
	Yes	8 (22.2)	0 (0)	
Mother's education, n (%)	**Illiterate**	8 (22.2)	4 (11.1)	[c]**0.328**
	Literate	1 (2.8)	2 (5.6)	
	Primary school	10 (27.8)	10 (27.8)	
	Middle school	11 (30.6)	7 (19.4)	
	High school	5 (13.9)	8 (22.2)	
	University	1 (2.8)	5 (13.9)	
Father's education, n (%)	**Illiterate**	5 (13.9)	2 (5.6)	[c]**0.398**
	Literate	1 (2.8)	0 (0)	
	Primary school	12 (33.3)	11 (30.6)	
	Middle school	10 (27.8)	9 (25)	
	High school	6 (16.7)	7 (19.4)	
	University	2 (5.6)	7 (19.4)	
Mother's occupation, n (%)	**Worker**	9 (25)	1 (2.8)	[c]**0.014***
	Unemployed	27 (75)	34 (94.4)	
	Government official	0 (0)	1 (2.8)	
Father's occupation, n (%)	**Shopkeeper**	1 (2.8)	1 (2.8)	[c]**0.053**
	Worker	35 (97.2)	29 (80.6)	
	Unemployed	0 (0)	4 (11.1)	
	Government official	0 (0)	2 (5.6)	
Heating system of the house, n (%)	**Coal stove**	1 (2.8)	0 (0)	[d]**1.000**
	Natural gas	35 (97.2)	36 (100)	

[a]Mann-Whitney U test, [b]Pearson chi-square test, [c]Fisher-Freeman-Halton test, [d]Fisher's exact test
**p<0,01

tract diseases and decrease the lung capacity of children (9-12).

This cross-sectional study evaluating the exposure of children to cigarette smoke found that in 5.6% of the cigarette smoking houses, the mother is the smoker, in 69.4% the father is the smoker; in 11.1% both parents are smokers; and in 13.9% another household member is the smoker. Research by Gursoy et al. (13) in 2008 showed that even though parents are aware of the harmful effects of passive cigarette smoking, their children are still exposed to cigarette smoke. Zafar Ullah et al. (14) showed that 55% of households have at least one active smoker,

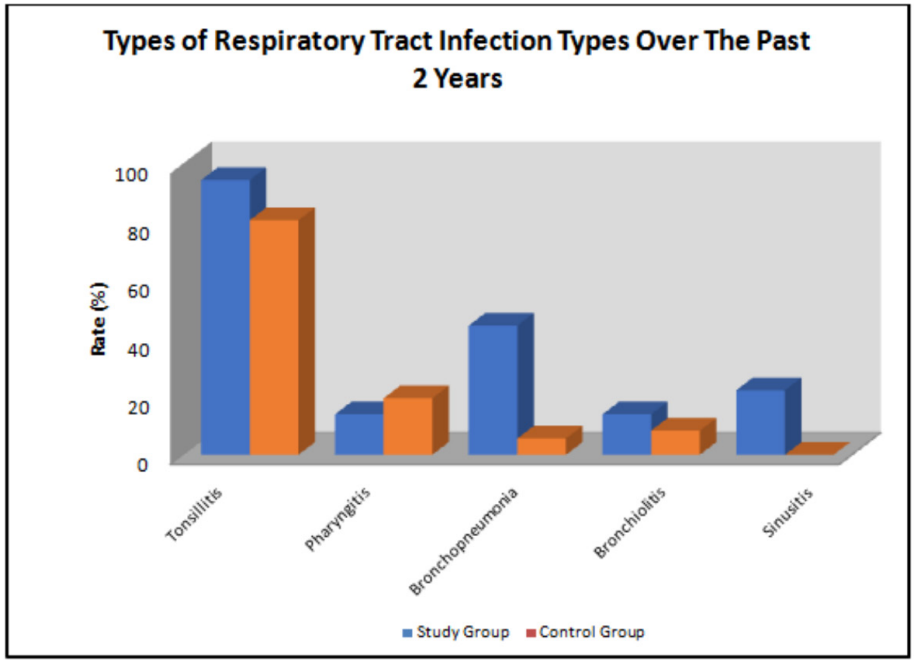

Figure 3. Distribution of types of respiratory tract infections over the past 2 years

Table 3. Comparison of the groups based on personal history and respiratory tract infections over the past two years

		Study group (n=36)	Control group (n=36)	p-value
Personal history of respiratory infection, n (%)	**No**	9 (25.0)	20 (55.6)	[b]**0.008****
	Yes	27 (75.0)	16 (44.4)	
Personal history of chronic disease, n (%)	**No**	32 (88.9)	31 (86.1)	[d]**1.000**
	Yes	4 (11.1)	5 (13.9)	
Family history of chronic disease, n (%)	**No**	35 (97.2)	35 (97.2)	[d]**1.000**
	Yes	1 (2.8)	1 (2.8)	
Number of respiratory tract infections in the past 2 years, n (%)	**None**	0 (0.0)	7 (19.4)	
	1 time	4 (11.1)	10 (27.8)	
	2 times	3 (8.3)	9 (25.0)	
	3 times	7 (19.4)	1 (2.8)	
	4 times	3 (8.3)	2 (5.6)	
	≥5 times	19 (52.8)	7 (19.4)	
	Average ± standard deviation	4.42±2.22	2.36±2.52	[a]**0.001****
Respiratory tract infections that were seen, n (%)	**Tonsillitis**	34 (94.4)	29 (80.6)	[c]**0.151**
	Pharyngitis	5 (13.9)	7 (19.4)	[b]**0.527**
	Bronchopneumonia	16 (44.4)	2 (5.6)	[b]**0.001****
	Bronchiolitis	5 (13.9)	3 (8.3)	[c]**0.710**
	Sinusitis	8 (22.2)	0	[d]**0.005****

[a]Mann-Whitney U test, [b]Pearson chi-square test, [c]Fisher-Freeman-Halton test, [d]Fisher's exact test
**p<0.01

and of those, 30% smoke when a child is present. Liao et al. (15) showed that two-thirds of parents smoke in a room where their child is at home. A study conducted in China showed that 48.3% of children are exposed to passive cigarette smoke and 76.5% of cigarette smokers smoke next to their children (16). In our study, the rate of smoking when a child was found to be 11.1%.

Recent studies show that while determining passive smoking in children, quantitative data such as cotinine levels must also be evaluated together with the information provided by the family. In our study, cigarette exposure based on urine cotinine levels was found to be 55.6%. Studies in Turkey show that passive cigarette smoking in children based on cotinine levels ranges approximately 53-92% (3,4).

Several studies show that the information provided by families on cigarette smoke exposure does not correlate with measured cotinine levels; therefore, the information by parents alone is not enough to determine the presence of exposure (17,18). Karadag et al. (19) point out that the answers to the survey conducted on parents of children who came in with an asthma attack were incoherent with the cotinine levels of the urine samples of these children; therefore, the information provided by families about cigarette exposure cannot be reliable. The study by Kahvecioğlu et al. (20) shows that 25% of children whose parents claimed that they did not smoke were exposed to cigarette smoke. This shows that parents are not objective when reporting data on cigarette smoking and explained these results by saying that children were exposed to cigarette smoke outside the house (20). In our study, based on urine cotinine levels, 52.8% of smoking parents' children were positive for passive smoking, and 58.3% of non-smoking parents' children were passive smokers as well. Therefore, even though it is not statistically meaningful, the fact that the passive smoking rate in children whose parents claim that they do not smoke is high, we believe that the answers provided by families do not reflect the truth. This study verifies that to show passive cigarette smoking, the survey method alone is not sufficient.

When the relationship between the education level of the parents and cigarette smoking is considered, it is shown that with a higher mother's education, the percentage of cigarette smoking increases; with a higher father's education, the percentage of cigarette smoking decreases (21). Karakoç et al. (22) showed that 60.5% of smoking mothers and 81.2% of smoking fathers are middle school graduates. The study by Kahvecioğlu et al. (20) showed that 63% of smoking mothers are primary school graduates, and there was no relationship found between the education levels of mothers and the frequency of smoking. Floyd et al. (23) showed that the higher the education level, the lower the cigarette smoking frequency. In another study conducted in France, it was reported that as the education level increases, so does the cigarette smoking frequency (24). In our study, 30.6% of smoking mothers were middle school graduates, and 33.3% of fathers were primary school graduates. In our study, there was no significant difference between the groups when education status and cigarette smoking were compared. Our study also showed that working mothers' being smokers was found to be statistically meaningfully higher.

A study by Arvas et al. (25) states that children with a smoker in the household get lower respiratory system infections more frequently than children with non-smokers in the house. Another study by Habesoglu et al. (26) found that mucociliary clearance is decreased in children with cigarette smoke exposure. Moreover, cigarette exposure causes hyperplasia in goblet cells, mucus hypersecretion, and dysfunction in phagocytic antibacterial defense, facilitating viral infections and causing Eustachian tube dysfunction by causing adenoid hypertrophy (26). According to a study by Uyan et al. (27), cigarette smoke exposure is highly effective in the recurrence of respiratory symptoms. Another study showed a positive relationship between the mother's being a smoker and the number of cigarettes smoked and the frequency of lower respiratory tract infections (28). A study on passive cigarette smoking and otitis media infections showed that the effect of passive smoking is mostly seen in the first year of life (29). A study by Cook et al. (30) showed that a mother's being a smoker is more effective in the first three years of life compared to a father's being a smoker and that

Table 4. Evaluation of passive cigarette smoking based on urine cotinine levels

		n (%)
Urine cotinine (ng/mL)	**Not effected (<10 ng/mL)**	32 (44.4)
	Passive smoker (10-500 ng/mL)	40 (55.6)

Table 5. Evaluation of urine cotinine and cotinine/creatinine levels

		Study Group	Control Group	p-value
Urine cotinine (ng/mL)	Median (Min.-Max.)	20.94 (0-491.16)	16.62 (0-121.7)	[a]**0.646**
Urine cotinine/creatinine (ng/mg)	Median (Min.-Max.)	0.476 (0-17.565)	0.20 (0-4.11)	[a]**0.439**

[a]Mann-Whitney U test, [b]Pearson chi-square test, Min.: Minimum, Max.: Maximum

hospitalization due to lower respiratory tract infections is three times higher in this population. An extensive study in the United States of America and Canada showed that in children 8-11 years old, upper respiratory tract infection is seen 1.7 times higher in children with a smoking parent (31). Groneberg-Kloft et al. (32) showed in their compilation that passive cigarette exposure increases respiratory illnesses and symptoms, and this is seen more obviously in the pre-school years. Our study also found that the frequency of respiratory tract infections in the last two years is statistically meaningfully higher in children who are exposed to cigarette smoke. When the two groups were compared on the basis of the type of infection, tonsillitis, pharyngitis, and bronchiolitis were similar in both groups, whereas bronchopneumonia and sinusitis were statistically meaningfully higher in children who were exposed to cigarette smoke.

Saliva, serum, and urine cotinine levels are the most widely accepted biological markers to evaluate passive cigarette exposure. Cotinine is the major metabolite of nicotine and has a higher half-life compared to other metabolites (22). In our study, the cut-off value of urine cotinine level was set at 10 ng/mL. A study by Ekerbiçer et al. (33) also accepted the cut-off value as 10 ng/mL, and 92.2% of those in the passive cigarette exposure group had urine cotinine levels higher than 10 ng/mL. In our study, based on a 10 ng/mL cut-off value, 52.8% of those with cigarette exposure and 58.3% of those with no cigarette exposure had urine cotinine levels higher than 10 ng/mL. Our study found that the most specific and sensitive cut-off value is 16.62 ng/mL. The mean cotinine level in the study group was found to be 20.94 ng/mL. The study by Boyaci et al. (21) showed that the mean cotinine level of the group with passive cigarette exposure was found to be 58 ng/mL (3), whereas the study by Arvas et al. (25) found the mean value to be 37.5 ng/mL.

The study by Puig et al. (34) found that urine cotinine levels in children with a smoking mother were significantly higher. They state that the reason behind this increase is that children spend most of their time with their mothers during pre-school ages. The study by Arvas et al. (25) compared those with smokers' mothers and other groups and found no significant difference. Yilmaz et al. (35) showed that urine cotinine levels in babies with smoking mothers are statistically meaningfully higher than in babies with non-smoking mothers. Our study also compared the smoking mothers' children with others and found no meaningful difference in urine cotinine levels. However, our study had only 6 children with a smoking mother.

The study in children between the ages of 2-5 by İnci et al. (36) found no significant difference in the urine cotinine levels of children who were exposed to cigarettes and unexposed. They reported a difference in the urine cotinine/creatinine ratios and stated that in children who could not provide a 24-hour urine sample, cotinine/creatinine ratios are more reliable compared to urine cotinine levels (36). A study with 609 children who had acute bronchiolitis and healthy controls found urine cotinine/creatinine ratios to be higher in children with bronchiolitis (37). Our study showed using the survey method that when urine cotinine levels of children with passive cigarette exposure and children without any exposure were compared, even though it was not meaningful, the cotinine levels of those who were exposed were higher. Urine cotinine/creatinine ratios were also higher in the study group, but the difference was not statistically meaningful. These results contradict the information that urine cotinine/creatinine ratios are more reliable than cotinine levels in cases where 24-hour urine samples cannot be collected.

Study Limitations

The most important limitation of our study was that the number of samples gathered was not high due to families refusing to attend the survey because it is hard to take urine samples from children. The lack of a significant difference in urine cotinine levels between the study and control groups indicates that families were hesitant to provide accurate smoking information.Passive smoking is high in those who are not exposed to cigarette smoke based on cotinine levels, implying that families were secretive about smoking and did not care if the child was exposed to cigarette smoke outside the house.Despite the limitations of our study, we think that we have contributed to the current literature since there are not many studies on passive smoking exposure in children.

Conclusion

Passive cigarette exposure is a current health problem because of its preventability and danger. Our study evaluated cigarette exposure in the house both by survey and measurement of urine cotinine levels. Our study supports the literature on the insufficiency of answers by parents alone in determining cigarette smoke exposure by showing the difference between urine cotinine levels and the survey answers.

In our study, the history of respiratory tract infection in children with cigarette smoke exposure was statistically meaningfully higher. Frequent respiratory tract infections and hospitalizations can be prevented by informing families and creating a smoke-free environment for children. To create a healthy society, raising awareness of the importance of quitting smoking is critical.

It is mandatory to provide children with an environment free of cigarette smoke. Further legal precautions must be

taken, further laboratory techniques must be developed and used to determine the problems, and all health professionals working with children must inform the public about the dangers of passive smoking.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital Clinical Studies Ethical Board on September 11th, 2020, with the number 2020.09.2.07.124.

Informed Consent: A written consent form was obtained from all the families.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.A., M.E., Design: S.A., M.E., A.O., Data Collection and/or Processing: S.A., M.E., O.B.G., S.M.I., Analysis and/or Interpretation: S.A., M.E., O.B.G., O.B., Literature Research: S.A., M.E., O.B., S.M.I., Writing: S.A., M.E., S.M.I., O.B., A.O.

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Abdominal Obesity and Metabolic Parameters in Chronic Spontaneous Urticaria

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Abstract

Aim: Abdominal obesity (AO) can affect some disease developments such as diabetes, cardiovascular diseases, or thyroid autoimmunity. To date, there is no data on the anthropometric parameters' impact on the development of refractory chronic spontaneous urticaria (CSU). We evaluated the impact of AO on the course of the presence of refractory CSU and to determine the possible associated risk factors for having refractory CSU.

Methods: This study was designed as a retrospective study and data was collected from January 2021 to April 2022. For determining AO, the waist-to-height ratio (WHtR) was used and calculated by the physicians, retrospectively. WHtR>0.5 was considered AO. Patients were divided into two groups [Group 1= refractory CSU (n=87) and Group 2= non-refractory CSU (n=83)]. Demographics, clinical characteristics of patients, and laboratory test findings were recorded from patients' medical files, retrospectively.

Results: A hundred and seventy CSU patients were included in the study. The mean age of the patients was 38.95±13.08 years. The number of patients accompanying angioedema was significantly higher in refractory CSU than in non-refractory CSU [65 (74.7%) vs 45 (54.2%), p=0.005]. Exacerbation of urticaria plaques with stress was more common in refractory CSU than in non-refractory CSU (p=0.030). WHtRs were similar in both groups. Baseline C-reactive protein (CRP) and blood neutrophil count were significantly higher in refractory CSU (p=0.008 and p=0.024, respectively).

Conclusion: High baseline CRP levels, baseline blood neutrophil count, stress and angioedema accompanying CSU are the associated risk factors of refractory CSU in the Turkish population. Furthermore, AO may not have an impact on the development of antihistamine refractory CSU.

Keywords: Refractory urticaria, abdominal obesity, angioedema, stress, autoimmunity

Introduction

Urticaria is characterized by transient pruritic wheals with or without angioedema, and if urticaria plaques persist for more than six weeks, it is defined as chronic urticaria (CU) (1). Although CU symptoms are related to activated skin mast cell mediators such as histamine, the underlying mechanism of mast cell activation is still unknown (1). CU is more common in females than in males. Usually, CU can be self-limited. However, it can persist for years in 20% of patients (2). More than 50 million patients could have been affected by CU in their lifetime and it deteriorates patients' quality of life (QoL) and social activities (3). According to the International EAACI/GA2LEN/WAO, CU is divided into two groups: (a) chronic spontaneous urticaria (CSU), which has no identified eliciting factors, and (b) chronic inducible urticaria, which has a specific stimulation to occur, such as cold, heat, pressure, or vibration (1). Although CSU has no trigger for the symptoms, some specific factors can exacerbate the urticaria plaques like drugs (e.g. non-steroidal anti-inflammatory drugs), infections, emotional stress, or some foods (e.g. species) (1,4). In the recent urticaria guidelines, CSU is classified as type 1 [autoallergic, related to immunoglobulin E (IgE) to

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self-antigens] and type IIb (autoimmune, related to mast-cell activating autoantibodies) (1).

Using a standard dose of second-generation H1 antihistamines is suggested as the first-line therapy for CSU (1,4). Up-dosing to fourfold antihistamine can be used as a second-line therapy if CSU persists in the patients (1,4). Nevertheless, if the CSU persists under the four-dose H1 antihistamine therapy, omalizumab treatment, which is an anti-IgE monoclonal antibody, could be suggested to control refractory CSU (1,4). However, it is still unclear to predict in which patients do not respond to antihistamine therapy.

Although it is well known that patients' diets, conditions, and abdominal obesity (AO), which is related to anthropometric parameters including body mass index (BMI), waist circumference (WC), or hip circumference, can affect some disease development such as diabetes, cardiovascular diseases, or thyroid autoimmunity (5-8). In the literature, there is no data on the anthropometric parameters' impact on the development of refractory CSU. Additionally, to date, there is limited data on which patients with CSU could have refractory disease and are unresponsive to antihistamine therapy. Therefore, in this study, we aimed to evaluate the impact of AO on the course of the presence of refractory CSU. Additionally, we aimed to determine the possible risk factors for having refractory CSU.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Derince Training and Research Hospital's Ethics Committee (date: 12.05.2022, approval number: 2022-40) and written informed consent was obtained from all included patients.

Patient Selection and Study Design

This study was designed as a retrospective study, and data was collected from January 2021 to April 2022. A hundred and seventy CSU patients who were more than 18 years old and were followed at the Adult Immunology and Allergic Diseases outpatient clinic were included in this retrospective study. CSU was diagnosed according to the International EAACI/GA2LEN/WAO and Turkish National Society Urticaria guidelines, and refractory CSU was defined as patients who did not respond to four-fold antihistamine therapy for one month (1,4). Patients with known autoimmune diseases, accompanying physical urticaria, and those using omalizumab treatment were excluded from the study. To determine the differences between refractory or non-refractory CSU, patients were divided into two main groups as Group 1, which had refractory CSU under four-fold antihistamine treatment for one month (n=87, 51.2%), and Group 2, which had well-controlled CSU under the antihistamine treatment for one month (n=83, 48.8%).

Clinical Data Collection

Demographics and clinical features of the patients, including age, gender, smoking and alcohol habits, disease duration time, presence of angioedema accompanying CSU or other disease history, triggers (food, drugs, infection or stress) for CSU, and used antihistamine doses were collected from the patients records. To evaluate the AO impact on the development of refractory CSU, anthropometric measurements including weight, height, BMI, and WC were collected from patients' records, retrospectively. To determine the AO, the waist-to-height ratio (WHtR) was used (9), and it was calculated by the physicians, retrospectively. According to the literature, a WHtR>0.5 was considered as having AO (9).

Data for the standard diagnostic evaluation of the patients, baseline laboratory testing including neutrophil, lymphocyte, basophil, eosinophil count, fasting blood glucose, LDL cholesterol, triglyceride, anti-thyroid peroxidase, and C-reactive protein (CRP) were recorded from patients' medical files. The neutrophil/lymphocyte ratio (N/Lr) was calculated retrospectively. Turkish validated seven-day urticaria activity score (UAS7) was used for evaluating the disease activity before and 1 month after the antihistamine treatment (1). Accordingly, the UAS7=28-42, UAS7=16-27, UAS7s=7-15, and UAS7≤6 are considered as severe, moderate, mild, and well-controlled, respectively (1). Stress level was collected from patients' records which was evaluated with visual analogue scale (VAS)" if VAS was >5, it was considered as having high stress level (3).

Statistical Analysis

The Statistical Package for Social Sciences version 25.0 (SPSS Inc., Armonk, NY, USA) was used to analyze the data, and GraphPad Prism software (San Diego, CA, USA) was used for graphics.The patients' descriptive characteristics are presented as mean standard deviation, median, and interquartile range (IQR) percentile of 25-75. A Kolmogorov-Smirnov test was conducted to evaluate the normality of data. The chi-square test and Mann-Whitney U test were used to compare categorical and continuous variables, respectively. A binary logistic regression test was used for the analysis of risk factors for having refractory CSU. A p-value of 0.05 or lower is generally considered statistically significant.

Results

Results of Demographics and Clinical Characteristics, and Laboratory Findings of the Patients

While the mean age of the patients was 38.95±13.08 years, the median (IQR) CSU duration time was 24 (8.5-48) months. One hundred and twenty-two (71.8%) patients were female and less than half of the patients had smoking habits (n=72, 42.4%). Whilst the number of patients accompanying angioedema history was 110 (64.7%), 114 (67.1%) patients had AO. Before the antihistamine treatment, the mean UAS7 was 34.91±5.81. Stress was the most common trigger for exacerbation of urticaria plaques in the patients (n=114, 67.1%) (Figure 1A). Before the antihistamine treatment, 160 (94.1%) patients had severe CSU and 10 (5.9%) patients had moderate CSU. While the mean BMI of the patients was 26.42±5.10 kg/m^2, the mean WC and WHtR of the patients were 90.08±13.83 cm and 0.83±0.09, respectively. One hundred and fourteen (67.1%) patients had a WHtR of more than 0.5. Baseline demographics, clinical characteristics, and laboratory findings of the patients are summarized in Table 1.

Comparison Analysis Between Refractory and Non-refractory CSU Patients

The mean ages were 40.41±13.03 years and 37.43±13.04 years in Group 1 and Group 2, respectively (p>0.05). More than half of the patients were female in both groups [n=61 (70.1%) vs n=61 (73.5%), p>0.05]. The number of patients with angioedema accompanying CSU was significantly higher in Group 1 than in Group 2 [65 (74.7%) vs 45 (54.2%), p=0.005]. Exacerbation of urticaria plaques with stress was more common in Group 1 than in Group 2 (p=0.030) (Figure 1B). BM, WC, and WHtR were similar in both groups (p>0.05 for each). While 56 (64.4%) patients had AO in Group 1, 58 (59.9%) patients had AO in Group 2 (p>0.05). Group 1 had significantly higher CRP and neutrophil counts (p=0.008 and p=0.024, respectively). The comparison analysis between Group 1 and Group 2 is summarized in Table 2.

Analysis of Associated Possible Risk Factors for Having Refractory CSU

The regression analysis, which was performed to determine associated risk factors for refractory CSU, showed that having stress and accompanying angioedema were associated risk factors for refractory CSU [odds ratio (OR)=2.05, (95% confidence interval (CI) 1.06-3.93), p=0.031 and OR=2.49, (95% CI 1.30-4.77), p=0.006, respectively]. Furthermore, higher CRP levels and neutrophil counts were associated with the presence of refractory CSU (Table 3).

Discussion

This study demonstrated that having stress and angioedema accompanying CSU are related to having refractory to antihistamine treatment in patients with CSU in the Turkish population. Furthermore, higher blood neutrophil counts and CRP levels have been linked to refractory CSU. Additionally, our current study showed, for the first time, that there is no significant relationship between having AO and having refractory CSU.

In recent years, it has been frequently reported that AO has increased and become a global problem with the changes in food consumption habits (10-13). Moreover, it is well-known that AO can play a role in the development of severe diseases, including cardiovascular disease, diabetes, musculoskeletal disorders, or autoimmune diseases such as autoimmune thyroiditis (8,11,14-17). Normally, in

Table 1. Baseline demographics, clinical characteristics, and laboratory findings of the patients

Demographic, clinical and laboratory features of patients	Patients (n=170)
Age (years, mean ± SD)	38.95±13.08
Gender Female (n,%) Male (n,%)	 122 (71.8%) 48 (28.2%)
Current smokers (n,%)	72 (42.4%)
Disease duration time (years, median-IQR)	24 (8.5-48)
Accompanying angioedema (n,%)	110 (64.7%)
BMI (kg/m^2, mean ± SD)	26.42±5.10
WC (cm, mean ± SD)	90.08±13.83
WHtR (mean ± SD)	0.83±0.09
Having AO (n,%)	114 (67.1%)
Baseline UAS7 (mean ± SD)	34.91±5.81
CSU severity before antihistamine treatment Moderate (n,%) Severe (n,%)	 160 (94.1%) 10 (5.9%)
CBC Neutrophil (10^3/µL, median-IQR) Lymphocyte (10^3/µL, median-IQR) Basophil (10^3/µL, median-IQR) Eosinophil (10^3/µL, median-IQR) N/Lr (mean ± SD) **Fasting Blood Glucose (mg/dL, mean ± SD)** **Lipid profile** HDL (mg/dL, mean ± SD) LDL (mg/dL, mean ± SD) Triglyceride (mg/dL, mean ± SD) **CRP (mg/dL, median-range)** **Anti-TPO (IU/mL, median-range)** **Total IgE (IU/mL, median-range)**	 3200 (2700-5100) 1860 (1750-2300) 0 (0-0) 170 (100-250) 2.0±0.88 91.0±23.99 47.19±10.94 120.84±33.39 129.05±58.95 2.10 (1.46-4.99) 28 (9-48) 126 (56-273.5)

AO: Abdominal obesity, Anti-TPO: Anti-thyroid peroxidase, BMI: Body mass index, CBC: Complete blood count, CRP: C-reactive protein, HDL: High densitiy lipoprotein, IgE: Immunoglobin E, LDL: Low density lipoprotein, N/Lr: Neutrophil/lymphocyte ratio, UAS7: Seven days urticaria activity score, SD: Standard deviation, WC: Waist circumference; WHtR: Waist-to-height ratio

Table 2. Comparison analysis of the refractory and non-refractory CSU patients			
Features	**Group 1 (n=87)**	**Group 2 (n=83)**	**p-value**
Age (years, mean ± SD)	40.41±13.03	37.43±13.04	NS
Gender Female (n,%) Male (n,%)	 61 (70.1%) 22 (29.9%)	 61 (73.5%) 22 (26.5%)	 NS
Current smokers (n,%)	42 (48.3%)	45 (51.7%)	NS
Accompanying angioedema (n,%)	65 (74.7%)	45 (54.2%)	**0.005***
Disease duration time (years, median-IQR)	24 (9-48)	18 (8-48.5)	NS
Having AO (n,%)	56 (64.4%)	58 (69.9%)	NS
BMI (kg/m^2, mean ± SD)	26.55±4.72	26.28±5.49	NS
WC (cm, mean ± SD)	89.81±13.75	90.37±13.99	NS
WHtR (mean ± SD)	0.54±0.86	0.54±0.86	NS
Baseline UAS7 (mean ± SD)	35.03±5.74	34.78±5.90	NS
CBC Neutrophil (10^3/µL, median-IQR) Lymphocyte (10^3/µL, median-IQR) Basophil (10^3/µL, median-IQR) Eosinophil (10^3/µL, median-IQR) N/Lr (mean ± SD) **Fasting Blood Glucose (mg/dL, mean ± SD)** **Lipid profile** HDL (mg/dL, mean ± SD) LDL (mg/dL, mean ± SD) Triglyceride (mg/dL, mean ± SD) **CRP (mg/dL, median-IQR)** **Anti-TPO (IU/mL, median-IQR)** **Total IgE (IU/mL, median-IQR)**	 3700 (2800-5100) 1900 (1750-2420) 0 (0-0) 170 (100-200) 2.04±0.88 97.84±28.49 48.15±11.05 123.4±34.31 125.6±56.4 3.03 (1.6-7.37) 28 (2-43) 195 (51-232)	 2800 (2700-5100) 1800 (1750-2100) 0 (0-0) 190 (100-270) 1.96±0.89 94.96±18.26 46.21±10.81 118.1±32.39 132.6±61.66 2 (1.42-3.68) 18 (1-25.2) 140 (63.2-360)	 **0.024**** NS NS NS NS NS NS NS NS **0.008**** NS NS

AO: Abdominal obesity, Anti-TPO: Anti-thyroid peroxidase, BMI: Body mass index, CBC: Complete blood count, CRP: C-reactive protein, HDL: High densitiy lipoprotein, IgE: Immunoglobin E, LDL: Low density lipoprotein, N/Lr: Neutrophil/lymphocyte ratio, NS: Not significant, UAS7: Seven days urticaria activity score, SD: Standard deviation, WC: Waist circumference, WHtR: Waist-to-height ratio
*T-test was used and p<0.05
**Mann-Whitney U test was used and p<0.05

healthy fit people, visceral adipose tissue is important for the immune system due to the metabolism of adipocytes, which regulate immune cell function and produce antibacterial peptides or proinflammatory cytokines (8). However, the uncontrolled increase in visceral adipose tissue (such as AO) may trigger autoimmune diseases by causing an excessive increase in proinflammatory cytokines (18). In our study, in which we investigated the possible impact of AO on refractory CSU, contrary to expectations, we did not observe a difference in terms of AO in patients with and without refractory CSU. However, when we evaluated the all-study population, we observed that more than half of the patients (114) had AO before the antihistamine therapy. Therefore, we may not have been able to show the effect of AO on refractory CSU since most of the patients already had AO. Further studies with a control group without AO and larger numbers of CSU patients are needed to demonstrate the real AO impact on the refractory CSU.

Previously, in the literature, Alen Coutinho et al. (19) characterized the phenotypes of CU refractory to antihistamine treatment and they observed that

Table 3. Factors in association with presence of refractory CSU according to the binary regression analysis			
	OR	**95% CI for OR (Lower-upper)**	**p-value**
Factors			
Angioedema accompanying CSU	2.49	1.30-4.77	**0.006**
Having stress	2.05	1.06-3.93	**0.031**
Baseline CRP level	1.09	1.01-1.18	**0.016**
Baseline blood neutrophil count	1	1.0-1.19	**0.045**

Binary logistic regression analysis is used for all p-values and p<0.05. Parameters that are not found to be statistically significant are not included in the table
CRP: C-reactive protein, NS: Not significant, CSU: Chronic spontaneous urticaria

angioedema accompanying CSU and higher baseline UAS7 are possible predictors of poor control of CSU and treatment should be chosen crucially in the Portugal study. In another study, Sussman et al. (20) reported that angioedema accompanying CSU has a negative effect on QoL. Similar to the literature, in our study, we determined that angioedema accompanying CSU is an

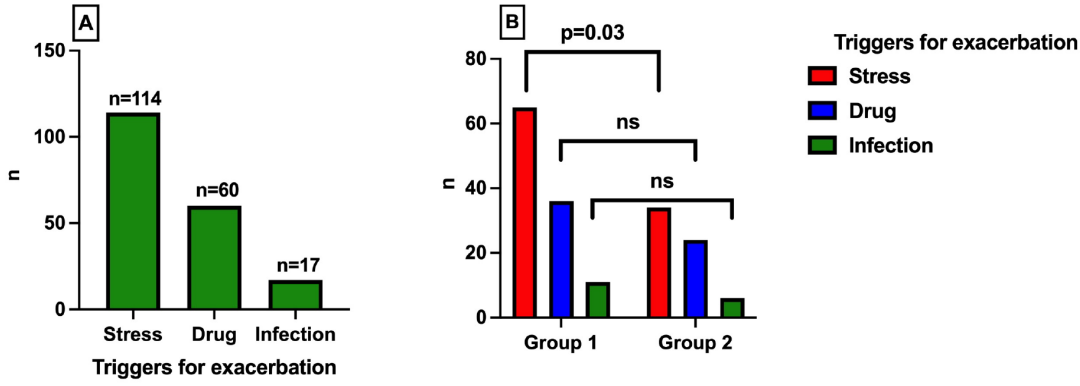

Figure 1. A) Triggers for exacerbation of urticaria plaques in all patients with CSU B) Comparison of triggers for exacerbation of urticaria plaques in Group 1 and Group 2
CSU: Chronic spontaneous urticaria

associated risk factor for having refractory antihistamine therapy in CSU patients. CSU is a mast-cell related disease, furthermore, mast cells can play a role in the development of angioedema (1,21). In line with this knowledge, we may speculate that in the presence of angioedema accompanying CSU, standard and four-fold antihistamine therapy may not be sufficient for symptom control, since the mast cell load will be higher compared to the presence of both diseases alone. In contrast to Alen Coutinho et al.'s (19) study, we did not observe any relationship between baseline UAS7 and poor control of CSU. The reason for this difference between our and Alen Coutinho et al.'s (19) study may be that most patients who applied to us had severe CSU (n=160, 94.1%) than in their study.

Psychological stress stimulates corticotropin releasing hormone (CRH). Furthermore, mast cells can synthesize CRH and express CRH receptors. Thus, psychological stress can cause mast cell degranulation (22,23). Previously, the relationship between psychological stress and increased symptoms in urticaria and mastocytosis was shown in Turkish patients (24,25). Although we collected the stress history from the anamnesis, we observed that stress is a possible associated risk factor for developing refractory CSU similar to the study. In line with this finding, we may think that stress-reducing psychological support may be needed to control refractory CSU and that multidisciplinary approaches to the CSU patients can improve the patients' QoL and control the disease activity.

Although autoimmunity, which is a result of exacerbated systemic inflammatory response, can be a reason for CU (19,26), there is limited data about the impact of autoimmunity on the control of refractory CSU in the Turkish population. In the past, it was reported that high CRP is related to poor disease control in CU (19,27). Similar to the literature, in our study, refractory CSU was associated with a higher CRP level. Although CRP has proinflammatory and anti-inflammatory features, it can be pathogenic when it is activated by autoantibodies in autoimmunity (28). CRP can also rise during an infection or an autoimmune disease (28). Blood neutrophil count can rise in infections, urticaria, and autoimmune diseases, just like CRP (29-31). Furthermore, a high blood neutrophil count may indicate the presence of urticarial syndromes such as urticarial vasculitis (UV) or cryopyrin-associated periodic syndromes (CAPS). If patients with CU undergo antihistamine treatment and have special symptoms for UV or CAPS, urticaria plaque biopsy should be performed (1,31). In our study, we observed a higher baseline neutrophil count in refractory CSU. In line with this information and our findings, we may think that in CSU patients in whom other autoimmune diseases have been excluded, those with a high baseline CRP level and a high blood neutrophil count may be predictors of the antihistamine refractory CSU, and these patients should be followed up more closely.

Study Limitations

Although this study demonstrated the possible risk factors for antihistamine refractor CSU in the Turkish population, we had some limitations. As a first limitation, we could not use a validated stress scale for evaluating the stress level. We could collect the stress history from patients' anamnesis and VAS. We believe that it will be important to conduct further larger studies, including more patients with validated scales, to support our findings. Secondly, we did not have a control group to compare the anthropometric parameters with healthy and CSU patients in the Turkish population. Therefore, we could not comment on the course of anthropometric measurement on the development of CSU; we could just comment on the AO impact on refractory CSU. Another limitation of

our study was the lack of an autologous serum skin test, which is a clue for autoimmunity in CSU patients. But we think that CRP and blood neutrophil counts are good predictors of biomarkers for autoimmunity and the autologous serum skin test.

Conclusion

AO may not have an impact on the presence of antihistamine refractory CSU. However, high baseline CRP and blood neutrophil count, stress and angioedema accompanying CSU are the associated risks of refractory CSU in the Turkish population. Multidisciplinary approaches, including psychiatric evaluation, should be required in refractory CSU. While investigating CSU, accompanying angioedema should be questioned in all patients. Further studies with a larger number of patients are needed to support our findings.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Derince Training and Research Hospital's Ethics Committee (date: 12.05.2022, approval number: 2022-40).

Informed Consent: Written informed consent was obtained from all included patients.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: S.B., N.O., Design: S.B., N.O., Data Collection, or Processing: C.O., Analysis, or Interpretation: N.O., Literature Research: N.O., Writing: N.O.

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Investigation of Cardiovascular Disease and Metabolic Syndrome Risk with Copeptin in Psoriasis Patients: A Case-Control Study

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Abstract

Aim: Psoriasis is thought to result in vascular diseases, atherogenesis, peripheral insulin resistance, and cardiac comorbidities by causing metabolic function disorders, hypertension, and type 2 diabetes. To our best knowledge, there has not yet been a study evaluating psoriasis patients with regard to copeptin. The present study assesses cardiovascular disease in psoriasis patients based on metabolic function and copeptin levels.

Methods: The presented case-control study, which is a type of analytical observational study, included 45 psoriasis patients and an age-sex matched control group admitted to University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Dermatology, between March 2016 and May 2017. Patients' blood pressure, height, weight, body mass index, and waistline were measured for both groups. All subjects were also given complete blood count, fasting blood glucose (FBG), uric acid, lipid profile, insulin, C-reactive protein (CRP), copeptin levels, neutrophil-lymphocyte rate, and thrombocyte-lymphocyte rate were analysed. Copeptin was measured by an ELISA kit.

Results: Insulin and CRP averages were statistically significantly higher in psoriasis patients than in the control group (p=0.001 for both). The neutrophil-lymphocyte and thrombocyte-lymphocyte rates were significantly higher in psoriasis patients (p=0.008). Insulin resistance was also higher in psoriasis patients (p=0.001). In both the patient and control groups, there was no statistically significant relationship found between copeptin level, general characteristics, and laboratory parameters.

Conclusion: To our best knowledge, this is the first study evaluating psoriasis patients with regard to copeptin. Psoriasis patients should be followed up with easily accessible parameters such as neutrophil-lymphocyte rate, thrombocyte-lymphocyte rate, insulin levels, FBG, and uric acid levels.

Key Words: Psoriasis, copeptin, metabolic disease, cardiovascular disease

Introduction

Psoriasis is a T-cell-mediated inflammatory disease with an incidence rate of 2-3% (1,2). While in the past it was believed only to affect the skin and joints, (3) in recent years it has been frequently researched that psoriasis causes cardiac diseases by affecting the metabolic system, blood pressure, and sugar-insulin resistance that causes atherosclerosis (4-6). Its an increasingly accepted

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opinion that the comorbidities should be considered when planning therapy and follow-ups for psoriasis (7,8).

Arginine vasopressin (AVP) is a neurohormone secreted from the neurohypophysis, protecting homeostasis by ensuring water reabsorption from the kidneys. As its half-life is low in plasma, the c-terminal fragment of the AVP precursor (copeptin) is used to determine AVP levels. It has a long half-life and is thought to be a marker of cardiac disease and mortality risk in population-based studies (9,10). Copeptin is also a good diagnostic and prognostic marker in metabolic diseases (diabetes mellitus, metabolic syndrome, insulin resistance) (11) and cardiovascular events in clinical practice (12). El Dayem et al. (13) declare that copeptin can be used as a marker for early detection of atherosclerosis in type 1 diabetic patients.

Extensive studies on biomarkers of psoriasis have identified some promising markers at the genome, transcriptome, proteome, and metabolome levels. These discoveries have provided new insights into the underlying molecular mechanisms and signaling pathways of psoriasis pathogenesis. There are also various abnormalities in lipid metabolism as well as oxidative stress in patients with psoriasis. In addition, decreased antioxidant enzyme activity and high lipid levels in the blood and lipid peroxidation, such as total cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoprotein, were found in psoriasis patients. This knowledge may be useful in the management of high-need patients with psoriasis. As copeptin levels do not change with age, it is beneficial for patients of any age group but not for patients with electrolyte imbalance disorders.

Different results regarding the relationship between metabolic syndrome and psoriasis have been reported (5). Our study presents independent data using inflammation indicators and metabolic function parameters. Thus, we attempted to predict which parameters are more affected in psoriasis patients, and this study compared cardiovascular disease (CVD) psoriasis with a healthy control group by evaluating metabolic functions and copeptin levels. We could not find any other studies in the literature evaluating psoriasis patients based on copeptin levels.

Materials and Methods

Compliance with Ethical Standards

All patients signed an informed consent form, and the study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Non-Drug Clinical Research Ethics Committee (382-22/06/2016).

Study Design

This study enrolled 45 patients who were admitted to the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Dermatology, between March 2016 and May 2017. All patients had had psoriasis for at least six months and had not received any therapy for at least three months before the study. The ages ranged from 18-63. Patients enrolled in the study were diagnosed by the same dermatologist, and psoriasis area and severity index (PASI) was used to determine psoriasis severity. Severe psoriasis patients (with a PASI ≥10) were studied. The control group consisted of 44 healthy individuals of the appropriate age and gender. For both groups, subjects with known coronary artery disease, hypertension, diabetes mellitus, renal failure, valvular heart disease, acute vascular involvement, malignancy, inflammatory disease, or acute or chronic infection were excluded. The demographics of the patients and the control group (name, surname, and gender) were recorded. Disease onset, age, disease duration, and medications used were recorded for patients. Arterial blood pressure, height, weight, body mass index (BMI), waist circumference, fasting blood glucose (FBG), insulin levels, lipid values, hemogram, C-reactive protein (CRP), and uric acid were measured for both groups.

Copeptin Measurement

The copeptin levels were also studied by waiting at -80° in simultaneously taken blood. The Human Copeptin ELISA test kit (Sunred Copeptin ELISA Kit, Germany) measured copeptin using a sandwich test method.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. The defining statistics are presented as numbers and percentages for categorical variables, and a mean, standard deviation, and median are included for numeric variables. A comparison of numeric variables in two independent groups was carried out using Student's t-test for normal distribution and the Mann-Whitney U test for non-normal distribution. The relationships between numeric variables were examined using the Pearson correlation analysis when parametric test conditions were met, and the Spearmen correlation analysis when these conditions were not met. The statistical alpha significance level was assumed to be $p<0.05$.

Results

The general characteristics of the patient group are found in Table 1. While almost all the patients had scalp involvement, nail involvement was seen in 38 patients, and psoriatic arthritis was found in 16 patients. In addition, the patient group had more males than the control group.

As a result, the male gender rate, average height, and waist circumference were statistically significantly higher in the patient group than in the control group (p=0.044, p=0.045, and p=0.011, respectively).

Of the laboratory parameters evaluated, insulin and CRP averages were statistically significantly higher in psoriasis patients compared to the control group (p=0.001 for both). Insulin resistance was higher in patients with psoriasis (p=0.001) (Table 2). Compared with Homa-IR, the levels were average. While there was no difference between the groups regarding uric acid levels, uric acid was markedly higher in patients diagnosed for more than ten years.

There was no statistically significant correlation between the patient and control groups found between the copeptin level, general characteristics, and laboratory parameters. The neutrophil-lymphocyte rate was significantly higher in psoriasis patients (p=0.012). While thrombocytes were numerically higher in the study group, this study detected statistical significance with regard to thrombocyte/lymphocyte between patients and the control group (Table 3) (Figure 1).

Discussion

Studies have found altered CV biomarkers in patients with psoriasis. These biomarkers may help characterize a subgroup of patients who are at risk of developing CVD and/or monitor the effectiveness of therapeutic antipsoriatic strategies on concomitant diseases. This knowledge may be useful in the management of high-need patients with psoriasis. In the pathophysiology of psoriasis, inflammation of the skin is thought to lead to systemic inflammation that contributes to comorbidities. Thus, cardiac disease, metabolic syndrome, type 2 diabetes, lipid disorders, hypertension, and obesity are more frequent in these patients (14). This study evaluated metabolic function parameters in psoriasis patients and investigated their relationship with copeptin.

Although there have been many studies on psoriasis and CVD, whether these comorbidities result from inflammation, genetics, or other factors is still being debated (14,15). There have also been studies indicating no relation (16,17). Various cardiac biomarkers have

Table 1. Patient group characteristics

	Mean ± SD	Min.-Max.
Age at Diagnosis (years)	28.1±11.5	6-52
Disease Duration(years)	13.5±9.6	0.5-41.0
Smoking (years)	13.8±15.3	0-60
PASI	16.9±7.4	10-44
HBA1C	5.55±0.58	3.60-8.06
HOMA-IR	1.96±0.83	0.82-4.34
	n	%
Psoriasis family history	10	22.2
Alcohol use	5	11.1
Psoriatic arthritis	16	35.6
Nail involvement	38	84.4
Scalp involvement	44	97.8

PASI: Psoriasis area and severity index, HBA1C: HOMA-IR: Homeostatic model assessment for insulin resistance

Table 2. Comparison of laboratory values for patient and control groups

	Patients		Control		
	Mean ± SD	**Min.-Max. (Avr)**	**Mean ± SD**	**Min.-Max. (Avr)**	**p-value**
FBS	94.0±19.8	74-207 (93)	91.2±9.4	80-121 (90)	0.516
Uric acid	5.2±1.2	3.4-8.0 (5)	6.1±7.8	2.8-56.0 (4.9)	0.414
Cholesterol	191.4±37.6	104-279 (186)	181.2±47.0	22-276 (176)	0.263
Triglyceride	134.4±52.7	59-278 (123)	130.6±68.6	41-330 (117.5)	0.398
HDL	48.5±24.9	23.9-198.0 (45)	49.1±14.8	31-109 (46.35)	0.409
LDL	113.5±36.0	8.6-203.0 (113)	113.3±30.3	67-170 (108)	0.977
Insulin	9.8±11.9	1.93-81.00 (7.2)	5.8±3.5	2.3-22.4 (5.4)	0.001
WBC	8.1±2.2	4.5-15.7 (7.95)	7.3±1.9	3.8-12.2 (7.09)	0.081
PLT	258.8±65.1	142-448 (256)	258.1±57.7	167-427 (253)	0.955
NEU	58.7±17.6	3.61-90.00 (60.9)	60.0±4.4	48.4-68.1 (60.2)	0.446
LYMH	25.4±10.6	1.06-44.9 (26.2)	30.9±3.9	21.3-40.9 (31)	0.001
CRP	6.61±12.24	0.5-78.0 (3.6)	2.31±2.90	0.13-16.40 (1.45)	0.001
Copeptin	6.81±8.36	0.76-24.00 (3)	4.87±6.31	0.73-24.00 (3)	0.997

FBS: Fasting blood sugar, NEU: Neutrophil, LYMH: Lymphocyte, PLT: Platelet, SD: Standard deviation, Min.: Minimum, Max.: Maximum
Insulin and CRP averages statistically significantly higher in psoriasis patients
Insulin resistance higher in psoriasis patients
Student's t-test and Mann-Whitney U test

Table 3. Comparison of neutrophil-lymphocyte, thrombocyte-lymphocyte ratio in the patient and control groups					
	Patient		Control		
	Mean ± SD	Min.-Max.	Mean ± SD	Min.-Max.	p-value
Neutrophil number	4.79±2.35	0.23-14.09	4.40±1.22	2.12-7.56	0.385
Lymphosit number	1.97±0.85	0.11-3.85	2.26±0.68	1.17-4.27	0.208
Neutrophil-lymphocyte	2.85±2.03	0.96-13.24	1.99±0.37	1.18-3.06	0.012
Thrombocyte-lymphocyte	300.0±668.3	58.3-3780.3	121.8±39.6	57.1-262.2	0.047

The neutrophil, thrombocyte-lymphocyte rate was significantly higher in psoriasis patients
Student's t-test and Mann-Whitney U test
SD: Standard deviation, Min.: Minimum, Max.: Maximum

been used to determine the inflammation marker in psoriasis patients (18,19). There is no entirely determined biomarker. Our study investigated copeptin in addition to classical cardiac biomarkers (20).

One of the critical comorbidities of psoriasis is obesity. Obesity is a risk factor with regard to metabolic function, and it is thought to have a complex association with abdominal obesity, glucose intolerance, atherogenic lipid disorder, and hypertension (21). In our study, waist circumference in male patients was found to be high in terms of BMI. The fact that there was no difference for female patients may have been because of the low proportion of females in the group. The high incidence of central obesity in psoriasis patients and whether it triggers psoriasis are still controversial. While obesity is reported to be an outcome in a study, some studies have reported that obesity increases psoriasis (22,23). In our study, there were no characteristics found in obesity and BMI. However, insulin levels were higher in the patient group.

A high CRP level is thought to increase the risk of cardiac disease on its own. CRP is often high in psoriasis patients, and it triggers insulin resistance and adiposity (24-26). In a study of the relationship between PASI values and CRP, no ratio was determined between these two variables. However, there were regressions and decreases in normal CRP levels after treatment (27). In this study, consistent with the literature, CRP levels were higher in the study group than in the control group. As patient therapy was excluded in this study, the values after treatment are not discussed.

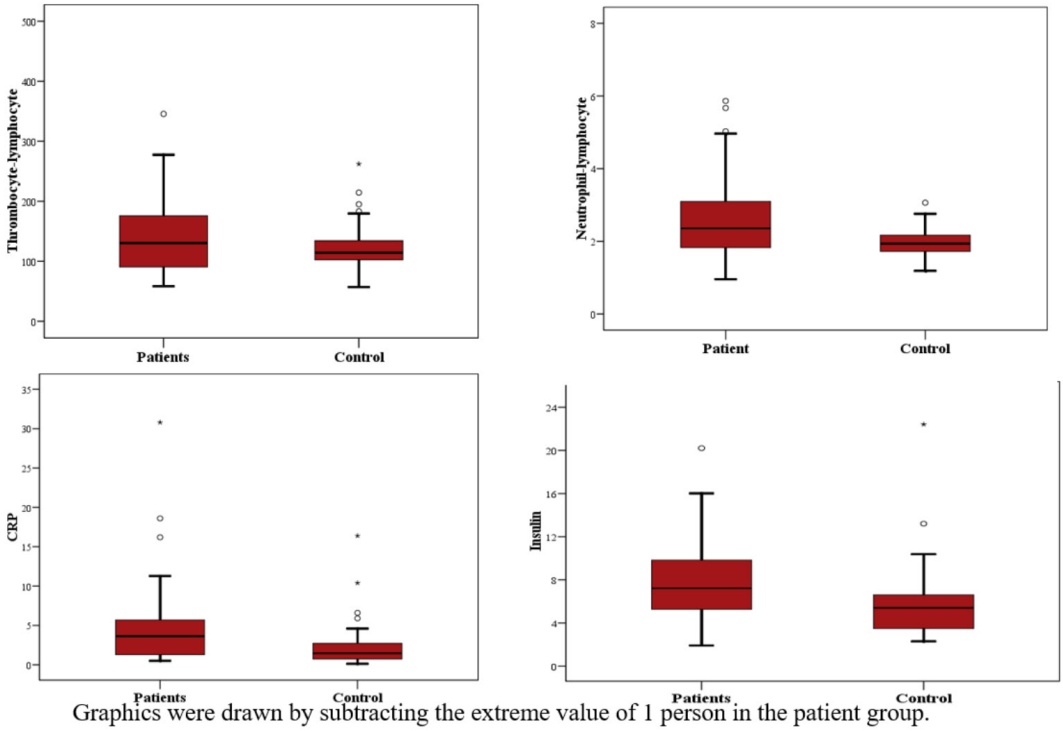

Figure 1. Neutrophil-lymphocyte rate, thrombocyte-lymphocyte rate, insulin, CRP level graphics were drawn by subtracting the extreme value of 1 person in the patient group
CRP: C-reactive protein

Neutrophil-lymphocyte and thrombocyte-lymphocyte rates are recommended as cardiac disease indicators (28). In the study by Kim et al. (29), neutrophil-lymphocyte and thrombocyte-lymphocyte ratios were evaluated and were determined to be associated with PASI scores. The authors also thought that there was an important relationship between these levels and psoriatic arthritis. This study worked with a severe patient group, and the neutrophil-lymphocyte and thrombocyte-lymphocyte rates were high in this group, in agreement with the literature.

In our study, there was no difference between the groups in terms of lipid values or hypertension. That our study did not find any difference for patients with severe psoriasis is inconsistent with the literature (30). This may be caused by the small sample size and the fact that only a single measure was evaluated.

Studies have found high levels of uric acid in psoriasis patients, especially those with psoriatic arthritis. These increased levels were related to the increase in uric acid production due to high turnover in keratinocytes (31). Uric acid levels are also high in cardiac disease and metabolic syndrome patients, as well as patients with rheumatoid arthritis and psoriatic arthritis (32). Our study found no difference between the control group and psoriasis patients in terms of uric acid levels.

The Koebner phenomenon, which is thought to be mediated by neurohormones, is also seen in patients with psoriasis (33). Copeptin is used to indicate the severity and progression of psoriasis heart failure. In several studies, copeptin was shown to be associated with insulin resistance, obesity, and metabolic disturbances (9,34). This study is the first to evaluate copeptin in psoriasis patients. Our study did not observe a statistically significant difference in copeptin levels between the two groups. This may be due to the fact that patients with CVD and acute vascular damage were excluded from our study, so the participating patients had not yet reached the level of cardiac failure.

Study Limitations

In our study, copeptin was studied in moderate-severe patients. The limited number of patients may be the lack of a statistical difference. Recently, the change in the development of cardiovascular disease with biological treatments has been the subject of frequent research. In our study, presenting the metabolic disease data of moderate-to-severe patients who did not receive treatment for three months provides data that can be used to compare new treatments.

Conclusion

Psoriasis patients are at risk of metabolic dysfunction and CVD. These patients should be monitored with easily accessible parameters such as neutrophil-lymphocyte rate, thrombocyte-lymphocyte rate, insulin level, FBG, and uric acid levels. Studies have found altered CV biomarkers in patients with psoriasis. These biomarkers may help characterize a subgroup of patients at risk of developing CVD and/or monitor the effectiveness of therapeutic antipsoriatic strategies on concomitant diseases. This knowledge may be helpful in the management of high-need patients with psoriasis. We believe that further evaluation of copeptin in patients with psoriasis will provide more information about the disease. Large-series studies are needed on this subject.

Ethics

Ethics Committee Approval: Ethical committee approval was obtained from University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Non-Drug Clinical Research Ethics Committee (382-22/06/2016)

Informed Consent: All patients signed an informed consent form.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Design: S.A., T.O.A., E.C., A.G., M.A., C.C., Data Collection and/or Processing: S.A., E.C., M.A., C.C., Analysis and/or Interpretation: M.A., Literature Research: S.A., T.O.A., F.T.D., A.G., M.A., C.C., Supervision: Z.T., Writing: S.A., T.O.A., E.C., F.T.D., A.G., M.A., Z.T., C.C.

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Original Article

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Role of Percutaneous Cholecystostomy in the Treatment of Grade-2 Acute Cholecystitis

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Abstract

Aim: Acute cholecystitis (AC) is one of the most common causes of emergency abdominal pain admissions. Its treatment is laparoscopic cholecystectomy. However, the disease's severity, duration, and the patient's general condition may necessitate effective alternative methods such as percutaneous cholecystostomy. This study aimed to analyze the place and importance of percutaneous cholecystostomy in the treatment of AC.

Methods: The records of 122 patients who were interned with an AC diagnosis between January 2018 and July 2021 were retrospectively scanned. The demographic data of the patients, Tokyo grades, laboratory values, imaging findings, and treatments were comparatively analyzed. The patients determined as grade 3 AC were excluded from the study. The data of the patients with grade 1 and grade 2 AC were comparatively analyzed.

Results: Fifty-four of 122 patients were grade 1; 66 of them were diagnosed as grade 2, and 2 of them were grade 3 AC. While 60 patients received only antibiotic treatment, 31 underwent percutaneous cholecystostomy, of whom 22 of them were from the grade 2 group. White blood cell, C-reactive protein, alanine transaminase, aspartate transaminase, Gamma-glutamyltransferase levels of grade 2 patients were statistically significantly higher than grade 1 patients ($p<0.001$; $p<0.001$; $p=0.029$; $p=0.031$; $p=0.043$). There were no significant differences between the groups in the values of alkaline phosphatase, bilirubin, time from admission to surgery, and follow-up time ($p=0.077$, $p=0.908$, $p=0.119$, and $p=0.127$, respectively). Age, mean fever duration, and chronic lung disease rates of grade 2 patients were statistically significantly higher than those of grade 1 patients ($p<0.001$, $p<0.001$, and $p=0.002$, respectively).

Conclusion: Percutaneous cholecystostomy is an effective and the least invasive method for treating grade 2 AC.

Keywords: Acute cholecystitis, treatment choice, percutaneous cholecystostomy

Introduction

Acute cholecystitis (AC) is one of the most common causes of abdominal pain and admission to the emergency department. Its frequency increases with age, and its treatment becomes more difficult with the addition of co-morbid diseases. In the etiology of AC, the most common cause is gallstones. In addition, ischemia, motility disorders, direct chemical trauma, infections, protozoa and parasites, collagen tissue diseases, and allergic reactions can also cause AC. 90-95% of the cases are cholecystitis with stones and 5-10% are without stones (acalculous) (1,2).

Severe symptoms or complications (AC, acute cholangitis, jaundice, and pancreatitis) occur in 1-2% of patients with asymptomatic gallstones. Mild or moderate symptoms are 1-2% per year (3). The prevalence of complications in AC varies between 1 and 22.7% (4). While the mortality rate in AC is 0.6-13.5% in large and multicenter studies, this rate is higher in postoperative and acalculous cholecystitis patients. Elderly patients (75 years and older) have a higher mortality rate than younger patients. In addition, the presence of a co-morbid disease, such as diabetes, increases the risk of death (5-8).

Although laparoscopic cholecystectomy is the standard treatment in AC, it is not always easy to apply it successfully, particularly in grade 2 AC patients. In addition, the presence of comorbid diseases in the patient makes laparoscopic surgery and even general anesthesia high-risk

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procedures. At this point, percutaneous cholecystostomy in selected patients could be an excellent alternative to laparoscopic surgery as it is minimally invasive and could be performed under local anesthesia.

Our study presented our AC treatment approaches and proposed percutaneous cholecystostomy treatment for AC.

Materials and Methods

Compliance with Ethical Standards and Study Design

This study was conducted with the approval of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee (ref no: 2021/166 date: 17.06.2021). The records of 122 patients admitted to the general surgery department with an AC diagnosis between January 2018 and July 2021 were scanned retrospectively through the hospital's electronic database.

Two patients determined as grade 3 were excluded from the study. The data of 120 patients, 54 with grade 1 AC and 66 with grade 2 AC, were comparatively analyzed.

Gender, age, signs, symptoms, duration of fever, comorbid diseases (diabetes mellitus, hypertension, chronic lung disease, chronic cardiac disease, cerebrovascular disease, chronic renal disease, malignancy, asthma), previous endoscopic retrograde cholangiopancreatography (ERCP), etc., ultrasonography, magnetic resonance imaging, and computed tomography findings needed for emergency surgery, treatment combinations, laboratory blood values [White blood cell (WBC), C-reactive protein (CRP), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, Gamma-glutamyltransferase (GGT), bilirubin], surgical timing, and follow-up times were analyzed statistically.

Statistical Analysis

The SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics are listed as numbers and percentages of categorical variables. Numerical variables were studied as mean, standard deviation, minimum, maximum, and median. Comparisons of two independent groups were performed using Student's t-test when the numerical variable satisfied the normal distribution condition. When the condition was not met, the Mann-Whitney U test was used. The rates in the groups were compared with the chi-square test. The statistical alpha significance level was deemed as $p<0.05$.

Results

One hundred and fifty-one patients were admitted to the hospital from the emergency room. Excluding 29 patients who reached a definitive diagnosis other than AC, 54 of the remaining 122 patients had grade 1 AC, whereas 66 were diagnosed with grade 2 and two with grade 3 acute cholecystitis (Table 1). The number of female patients (n=30) in grade 1 and male patients in grade 2 (n=36) was higher. Age, mean fever duration, and the rate of chronic lung disease in grade 2 patients were statistically significantly higher than those in the grade 1 patient group ($p<0.001$ $p<0.001$ $p=0.002$). Emergency surgical intervention was performed in 22 cases, of which 13 were from the grade 2 patient group (Table 2). While 60 patients received only antibiotic treatment, 31 patients underwent percutaneous cholecystostomy; 22 of them were in the grade 2 acute cholecystitis group (Table 3). The WBC, CRP, ALT, AST, and GGT levels of grade 2 patients were statistically significantly higher than those of grade 1 patients ($p<0.001$ $p<0.001$ $p=0.029$ $p=0.031$ $p=0.043$). No statistically significant difference was found in the mean alkaline phosphatase and bilirubin levels ($p=0.077$ and $p=0.908$) (Table 4).

There was no statistically significant difference between grade 1 and 2 patients in post-attack operation time (time from admission to surgery) or follow-up time ($p=0.119$ $p=0.127$) (Table 5).

Discussion

Acute cholecystitis is an acute inflammatory disease of the gallbladder that is the most common cause of gallstones. In patients with clinically suspected acute cholecystitis, the diagnosis should be confirmed by radiological imaging methods. Acute cholecystitis can be classified as mild, moderate, or severe in clinical severity. The Tokyo 2018 criteria is the latest revision in treating acute cholecystitis in grade (9).

Grade 2 (moderately acute) cholecystitis is when an extensive disease of the gallbladder without any organ dysfunction makes it difficult to perform cholecystectomy safely. Its treatment is still not standardized. Therefore, grade 2 AC is a situation that requires more invasive procedures. However, the attempt should be made when and under what conditions is related to the patient's timing of admission and the severity of the physical and laboratory examination findings. Nowadays, laparoscopic cholecystectomy is accepted as a safe treatment method for treating acute cholecystitis in the presence of sufficient experience. Laparoscopic cholecystectomy has a lower complication rate, shorter hospital stay, early recovery,

Table 1. The distribution of patients according to grades

		n	%
Grade	1	54	45
	2	66	55
	Total	120	100

Table 2. The comparison of grade 1 and 2 patients					
		Total	**Grade 1**	**Grade 2**	**p-value**
Gender n (%)	Male	60 (50.0)	24 (44.4)	36 (54.5)	0.271*
	Female	60 (50.0)	30 (55.6)	30 (45.5)	
Age Mean ± SD (Min.-Max.)		55.4±16.2	49.6±14.7	60.0±15.9	**<0.001#**
		(24-90)	(24-82)	(26-90)	
Findings n (%)	Nausea	11 (9.2)	6 (11.1)	5 (7.6)	0.540*
	Vomiting	15 (12.5)	10 (18.5)	5 (7.6)	0.071*
	Abdominal ache	104 (86.7)	45 (83.3)	59 (89.4)	0.331*
	Diarrhea	1 (0.8)	0 (0.0)	1 (1.5)	1.000*
	Jaundice	2 (1.7)	0 (0.0)	2 (3.0)	0.501*
	Fever	1 (0.8)	0 (0.0)	1 (1.5)	1.000*
Fever duration (Day) Mean ± SD		3.2±2.7	2.2±1.5	4.0±3.2	**<0.001¥**
Median (Min.-Max.)		2 (1-15)	2 (1-7)	3 (1-15)	
Comorbidities n (%)		78 (74.3)	29 (70.7)	49 (76.6)	0.505*
	Diabetes mellitus	21 (20.0)	7 (17.1)	14 (21.9)	0.548*
	Hypertension	39 (37.1)	11 (26.8)	28 (43.8)	0.088*
	Chronic lung disease	13 (12.4)	0 (0.0)	13 (20.3)	**0.002***
	Chronic cardiac disease	3 (2.9)	1 (2.4)	2 (3.1)	1.000*
	Cerebrovascular disease	1 (1.0)	0 (0.0)	1 (1.6)	1.000*
	Chronic renal disease	4 (3.8)	0 (0.0)	4 (6.3)	0.154*
	Malignity	5 (4.8)	2 (4.9)	3 (4.7)	1.000*
	Asthma	2 (1.9)	1 (2.4)	1 (1.6)	1.000*
	Previous ERCP	4 (3.8)	2 (4.9)	2 (3.1)	0.643*
	Others	21 (20.0)	10 (24.4)	11 (17.2)	0.368*
Positive sign in USG n (%)		90 (75.0)	38 (70.4)	52 (78.8)	0.289*
Positive MRI n (%)		16 (13.3)	10 (18.5)	6 (9.1)	0.131*
Positive sign in CT n (%)		106 (88.3)	49 (90.7)	57 (86.4)	0.457*
Acute emergency surgery n (%)		22 (18.3)	9 (16.7)	13 (19.7)	0.670*

*Chi-square test, #Student's t-test, ¥Mann-Whitney U test: Age, mean fever duration, and rate of chronic lung disease significantly higher in grade 2 patients than the grade 1 patient group
SD: Standard deviation, Min.: Minimum, Max.: Maximum, ERCP: Endoscopic retrograde cholangiopancreatography, USG: Ultrasonography, CT: Computed tomography

and early return to work than open cholecystectomy. Percutaneous transhepatic gallbladder drainage is a treatment method that can be preferred in elderly patients defined as presenting high-risk surgically. However, laparoscopic cholecystectomy is the preferred treatment method in all eligible patients.

The treatment method used more than expected in our series was percutaneous cholecystostomy. Percutaneous cholecystostomy was performed in 31 patients (25.83%), and we think this high rate is related to the coronavirus disease-2019 pandemic, at least in our approach. It is noteworthy that interventional radiology has started to occur in surgical treatments with the developing technology. While open cholecystostomy was rarely used as a bridge treatment on the road to elective surgery in the previous decades, the rate of benefit from percutaneous cholecystostomy increased from 2.5% to 12.2% in the same clinic between 2011 and 2015 in a retrospective study in which 4311 patients were evaluated in 2016 (10). The rate of percutaneous cholecystostomy continues to increase worldwide, and the most intense application in this regard was published in 2019. Percutaneous cholecystostomy performed in 97 (48.2%) of 201 patients in that study shows a changing trend (11).

Emergency cholecystectomy was seen to be 18.3% in both groups in our study. This rate, which we found in our study to be 16.7% for group 1 and 19.7% for group 2, when compared with rates between 15.7% (England) and 52.7% (USA) in various studies, is consistent with the literature (12).

There was no evidence that the application of emergency cholecystectomy increased complications or shortened the length of hospital stay (13). We obtained similar results for patients who underwent surgery in our

Table 3. Treatment options carried out in regard to grade 1 and 2 patients and their percentages				
	Total (120)	Grade 1 (54)	Grade 2 (66)	p*
	n (%)	n (%)	n (%)	
Antibiotics only	60 (50.0)	31 (57.4)	29 (43.9)	0.283
Percutaneous cholecystostomy	1 (0.8)	0 (0.0)	1 (1.5)	
Antibiotics + ERCP	7 (5.8)	5 (9.3)	2 (3.0)	
Antibiotics + surgery (colecystectomy)	5 (4.2)	1 (1.9)	4 (6.1)	
Antibiotics + Percutaneous cholecystostomy	28 (23.4)	9 (16.7)	19 (28.8)	
Antibiotics + Percutaneous cholecystostomy + ERCP	2 (1.7)	0 (0.0)	2 (3.0)	
Surgery (colecystectomy) only	17 (14.2)	8 (14.8)	9 (13.6)	

*Chi-square test
ERCP: Endoscopic retrograde cholangiopancreatography

Table 4. The comparison of laboratory values of grade 1 and 2 patients										
Grade										
	Total			1			2			p¥
	Mean ± SD	Min.-Max.	Median	Mean ± SD	Min.-Max.	Median	Mean ± SD	Min.-Max.	Median	
WBC	13.5±5.7	3-34	13	10.9±3.9	3-17	12	15.6±6.0	5-34	15	<0.001
CRP	80.9±94.4	2-357	30.5	33.7±47.1	2-178	12	119.6±105.5	3-357	101	<0.001
ALT	10.5±242.7	3-970	58.5	229.1±268.6	4-969	125	122.5±209.3	3-970	40	0.029
AST	159.6±225.0	9-1200	45	211.4±244.1	14-1031	111	118.0±200.7	9-1200	41.5	0.031
Alkaline phosphatase	182.2±168.6	32-1222	127.5	191.6±178.1	32-1222	141	174.4±161.4	54-927	102.5	0.077
GGT	216.5±221.3	11-1056	141	254.3±222.4	19-784	208	185.6±217.3	11-1056	90.5	0.043
Bilirubin	2.03±1.92	0.2-10.8	1.4	1.94±1.51	0.2-6.4	1,495	2.11±2.21	0.27-10.8	1	0.908

¥Mann-Whitney U test: WBC, CRP, ALT, AST, GGT levels of grade 2 patients were statistically significantly higher than grade 1 patients
WBC: White blood cell, CRP: C-reactive protein, ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: Gamma-glutamyltransferase, SD: Standard deviation, Min.-Max.: Minimum-Maximum

Table 5. The comparison of surgery timing and follow-up periods of grade 1 and 2 patients										
Grade										
	Total			1			2			p-value
	Mean ± SD	Min.-Max.	Median	Mean ± SD	Min.-Max.	Median	Mean ± SD	Min.-Max.	Median	
Surgery timing (in weeks)	3.84±3.00	0-12	3	4.53±3.10	0-12	4	3.25±2.84	1-12	2.5	0.119
Follow-up period	5.61±4.80	2-47	4.5	4.98±2.91	2-15	4	6.12±5.88	2-47	5	0.127

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

study. We did not find a statistically significant difference in complications between the treatment options used.

In our series, we found that emergency cholecystectomy was performed within the first 3 days of the onset of symptoms. We have seen that we benefit from percutaneous cholecystostomy, ERCP, antibiotic therapy, and their combinations in more delayed patients. The World Emergency Surgery Association reports that early surgery can be performed safely for up to 10 days as a guideline (14).

Study Limitations

There are some limitations to our study. The major limitation is that our study has a retrospective design. Therefore, we could not detect all of the prognostic factors of the patients included because we conducted the study on patient files. Another limitation is the limited number of patients. Our study wanted to emphasize the use of percutaneous cholecystostomy, especially in patients with grade 2 cholecystitis. Therefore, a prospective study in which treatment modalities are comparatively analyzed in a larger population of only patients with grade 2 acute cholecystitis would be more valuable. Despite these limitations, we believe that our study will contribute to the literature as it provides an idea about the use of percutaneous cholecystostomy in patients with grade 2 acute cholecystitis, where the optimal treatment approach is still sought.

Conclusion

Grade 2 acute cholecystitis is a condition that requires more invasive interventions. However, which attempt should be made when and under what conditions is related to the patient's timing of admission and the severity of the physical examination and laboratory findings in addition to imaging modalities. The least invasive and most effective treatment is percutaneous cholecystostomies performed under antibiotic therapy in grade 2 acute cholecystitis.

Ethics

Ethics Committee Approval: This study was conducted with the approval of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee (ref no: 2021/166 date: 17.06.2021).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.K., F.E., Design: H.Ü.G., A.K., Data Collection, or Processing: S.C.O., M.S.D., Analysis, or Interpretation: H.Ü.G., F.E., Literature Search: S.C.O., M.S.D., Writing: A.K., M.S.D., Revision: M.S.D.

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Case Report

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Rhinorrhea due to Infusion of Dexmedetomidine during Rhinoplasty: A Case Report and Current Literature Review

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Abstract

Dexmedetomidine can be used to achieve controlled hypotension during surgery. A 26-year-old female with no medical history underwent rhinoplasty. The maintenance of the anesthesia was achieved with propofol and dexmedetomidine (1 mcg kg-1 as a loading dose for 10 minutes, followed by 0.5 mcg kg-1 hr-1 as maintenance) infusion as total intravenous anesthesia. Propofol and dexmedetomidine infusion doses were adjusted to maintain a bispectral index of 40-60 and a mean arterial pressure of 55-65 mmHg. During surgery, rhinorrhea developed, which disrupted the view of the surgical field. An intravenous antihistamine and a topical decongestant were administered. However, rhinorrhea persisted, suggesting that it developed as a drug-related adverse effect. Dexmedetomidine was halted. Subsequently, the rhinorrhea decreased, and the quality of the surgical field improved. That was a temporary and reversible side effect, which resulted in no long-term sequela. To the best of our knowledge, this is the first patient who developed rhinorrhea as a side effect of dexmedetomidine infusion during rhinoplasty.

Keywords: Controlled hypotension, dexmedetomidine, rhinoplasty, rhinorrhea

Introduction

Rhinoplasty is one of the most commonly performed aesthetic surgical procedures. The nasal cavity is an area with a rich blood supply. Thus, bleeding is expected during surgery, which undermines the outcome of rhinoplasty. Reduction of bleeding and achieving the best visual acuity in the surgical field are critically important. Intraoperative controlled hypotension is one of the most common measures to reduce nasal bleeding during surgery. Several medications can be used to achieve controlled hypotension, including beta-blockers, magnesium sulfate, calcium-channel blockers, and many total intravenous and inhalational anesthetics. In this regard, interest in dexmedetomidine has increased recently, and we have used dexmedetomidine in rhinoplasty to achieve controlled hypotension. Many studies have evaluated the role of dexmedetomidine in the induction and maintenance of controlled hypotension (1,2). However, to our knowledge, none of these studies has reported rhinorrhea as a side effect associated with dexmedetomidine.

Here, we present a case of rhinorrhea that developed as a side effect of dexmedetomidine infusion during rhinoplasty and discuss its management.

Case Report

A 26-year-old female patient with no medical history was referred to our institution for rhinoplast. She was premedicated with 2 mg of midazolam. After standard monitoring, the patient was given oxygen via a face mask for 3 minutes. Intravenous anesthesia induction was performed with propofol (2-2.5 mg kg-1), rocuronium bromide (0.6-mg kg-1) and fentanyl (2 mcg kg-1). After muscle relaxation, the patient was intubated. The maintenance of the anesthesia was achieved with propofol (0.1 mg kg-1 min-1) and dexmedetomidine (1 mcg kg-1

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as a loading dose for 10 minutes, followed by 0.5 mcg kg-1 hr-1 as maintenance) infusion as total intravenous anesthesia. Propofol and dexmedetomidine infusion doses were adjusted to maintain a bispectral index of 40–60 and a mean arterial pressure of 55-65 mmHg.

The quality of the surgical field (1= bad, 2= acceptable, 3= good) and the satisfaction level of the surgeon (1= dissatisfied, 2= satisfied, 3= very satisfied) were evaluated throughout the surgery. At the 30th minute of the surgery, the quality of the surgical field was reported as 1, and the satisfaction level of the surgeon was reported as 1. The reason for this was rhinorrhea, which disrupted the visual acuity in the surgical field. Intravenous antihistamine (pheniramine maleate, 45.5 mg) and topical decongestant (oxymetazoline, 2 puffs on each side) were administered to manage rhinorrhea. Since rhinorrhea did not decrease after waiting for 30 minutes with these measures, a drug-related adverse effect was suspected. First, dexmedetomidine infusion was stopped, and remifentanil infusion was started instead. After 15 minutes, the rhinorrhea terminated, the quality of the surgical field improved, and the operation was successfully completed. At the end of the procedure, the remifentanil infusion was stopped, and the patient was given ibuprofen 400 mg for analgesia. The demographic and intraoperative data of the patient are provided in Table 1. Postoperative recovery was uneventful, and she was discharged with no other complications 1 day after rhinoplasty.

Discussion

Average blood pressure is a significant factor influencing bleeding during surgical procedures. In healthy individuals, the induction of controlled hypotension to a mean arterial pressure of 50 mmHg is not expected to have a substantial side effect. Dexmedetomidine, a potent and highly selective α-2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic features, can also induce hypotension. Dexmedetomidine was evaluated for hypotension in middle ear surgery, endoscopic sinus surgery, rhinoplasty, spine surgery, and laparoscopic colectomy (3). It was demonstrated that dexmedetomidine more effectively induces hypotension than esmolol, magnesium sulfate, and nitroglycerin (3). Therefore, we started to use dexmedetomidine to reduce bleeding in patients undergoing rhinoplasty.

Table 1. Demographic and intraoperative data of the patient

	Patient
Age (years)	26
Gender	Female
Weight (kg)	63
ASA physical status	1
Total dexmedetomidine dose (mcg)	73
Mean arterial pressure (mmHg)	60
Mean heart rate (bpm)	75
Estimated blood loss (ml)	150
Duration of surgery (minutes)	150
Duration of anesthesia (minutes)	165

bpm: Beats per minute, ASA: American Society of Anesthesiologists

The reported adverse effects of dexmedetomidine are excessive sedation, hypotension, hypertension, bradycardia, hypoxemia, nausea, vomiting, urine retention, respiratory depression, headache, shivering, pruritis, blurred vision, and neurological complications (4). However, these side effects are rare, and rhinorrhea has not been reported previously as a side effect of dexmedetomidine. In a systematic review by Lee et al. (5), dexmedetomidine, and placebo showed no difference in the incidence of perioperative side effects. However, considering the limited number of randomized studies reporting complications, the authors concluded that evidence for complications associated with dexmedetomidine was weak (5).

Rhinorrhea is a symptom in which the nasal cavity is filled with excessive amounts of mucus produced by the mucous membranes. It is a common symptom of allergies and some viral infections. Nasal irritation or inflammation can also cause rhinorrhea. It can be a side effect of crying, cocaine abuse, various genetic disorders, or medication. For managing rhinorrhea, antihistamines, decongestants, and saline nasal sprays may be used. These medications help either to cease the discharge of mucus or to limit its overflow. In this case, the first-line treatment for rhinorrhea was intravenous antihistamine and nasal decongestant. However, rhinorrhea did not stop, and we suspected a drug-related adverse effect. We terminated the infusion of dexmedetomidine and then the rhinorrhea halted. Rhinorrhea in this patient was a temporary and reversible side effect and resulted in no long-term sequela.

The autonomic nervous system controls the blood flow to the nasal mucosa and mucus secretion. The sympathetic system mediates the diameter of the vessels in the nose. Dexmedetomidine produces sedation by agonizing the central α2-receptors. Stimulation of α2-receptors also leads to decreased sympathetic nervous system activity and plasma norepinephrine concentrations. Dexmedetomidine-induced bradycardia is attributed to centrally mediated sympathetic withdrawal (6). The underlying mechanisms of rhinorrhea are not clear. It can be suggested that a decrease in sympathetic innervation causes venous dilatation and swelling of the nasal mucosa, hence leading to congestion and rhinorrhea. The total dose of dexmedetomidine and infusion duration may affect this side effect.

To the best of our knowledge, this is the first reported

case of rhinorrhea developing after a dexmedetomidine infusion used to induce controlled hypotension. We conclude that rhinorrhea as a side effect of dexmedetomidine should be considered in the differential diagnosis of patients receiving dexmedetomidine and developing rhinorrhea. An antihistamine and a decongestant can be administered to reduce symptoms. Further studies are needed to assess the frequency of rhinorrhea after dexmedetomidine infusion.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.U.Y., Y.O.A., Design: T.U.Y., Y.O.A., Data Collection or Processing: P.K., H.G., Analysis or Interpretation: Y.O.A., J.D.T., Literature Research: H.G., J.D.T., Writing: T.U.Y., Y.O.A.

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Case Report

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Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease Presenting with ADEM-Like Encephalomyelitis: A Case Report and Current Literature Review

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Abstract

Myelin oligodendrocyte glycoprotein antibody-associated disease has recently been found to be a different nosological entity, with some clinical features overlapping with neuromyelitis optica spectrum disorders. We hereby describe the case of a patient who was first admitted in 2015 with a tingling sensation in both legs, severe lumbar pain, and gait problems, and later developed urinary retention, confusion, and seizure. Brain magnetic resonance imaging (MRI) showed multiple fluid attenuated inversion recovery hyperintense lesions with no gadolinium enhancement in the bilateral subcortical white matter, cerebellar peduncles, and cervical cord. Cerebrospinal fluid analysis demonstrated marked pleocytosis (116 cells/μL) and an elevated protein concentration (68 mg/dL). Neither oligoclonal bands nor the elevation of IgG index levels were detected (IgG index: 0.59). During the follow-up, he had 2 optic neuritis attacks in 4 years. Five years later, the patient was referred to our hospital with severe pain in both legs. Spinal MRI showed a longitudinally extending conus medullaris lesion with gadolinium enhancement. The patient showed full recovery after 7 days of 1000 mg/day IV methylprednisolone treatment, and the follow-up MRI showed no residual lesions. The anti-MOG IgG was found to be positive. In this case report, we would like to highlight the importance of MOG antibody testing in encephalitis.

Keywords: Anti-MOG, demyelinating disease, ADEM, optic neuritis, transverse myelitis

Introduction

Recently, it has been discovered that myelin oligodendrocyte glycoprotein antibodies (anti-MOG IgG) play a diagnostic role regarding acquired demyelinating diseases. MOG antibody-associated disease is now deemed a nosologically different entity, showing clinical and paraclinical differences from multiple sclerosis and neuromyelitis optica spectrum disorder (NMOSD) (1,2).

The average age of onset for MOG antibody-associated disease is in the third decade of life, with a male predominance (3,4).The most common core feature is optic neuritis (ON), followed by transverse myelitis (5). Although MOG IgG positivity is common in children with acute disseminated encephalomyelitis (ADEM), ADEM-like presentation in adults is rare.

Here, we report a patient who presented with ADEM-like encephalomyelitis, who has shown a relapsing disease course (two ON attacks and lastly, longitudinally extending TM).

Case Report

A 22-year-old man suffered from tingling sensations in both legs, severe lumbar pain, and gait problems in 2015. He was admitted to the hospital after developing urinary retention, confusion, and generalized onset tonic-clonic seizures. A neurological examination revealed horizontal nystagmus revoked by downward gaze, bilateral positive Babinski sign, hyperactive patellar and Achilles reflexes, and bilateral Achilles tendon clonus. Magnetic resonance imaging (MRI) showed multiple expanded high signal

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intensity lesions with no gadolinium enhancement in the subcortical white matter of both cerebral hemispheres, cerebellar peduncles, and cervical cord (Figure 1A, B).

Cerebrospinal fluid (CSF) analysis demonstrated marked pleocytosis (116 cells/μL) and elevated protein concentration (68 mg/dL). Neither the oligoclonal band nor the elevation of IgG index levels were detected (IgG index: 0.59). The electroencephalography showed no epileptogenic activity. Various vascular and serologic tests, including antinuclear antibody, anti-ds DNA, anti-SSA, anti-SSB, and HIV, were all negative. CSF culture showed no growth. During the disease course, the patient developed a fever. In conjunction with the CSF and MRI findings, the preliminary diagnosis was viral infectious encephalitis, and antiviral treatment was administered. Five days later, repeated MRI showed new hyperintense lesions in the mesencephalon and thalamus with no gadolinium enhancement (Figure 1C, D), which led to the alteration of the differential diagnosis to acquired demyelinating disease. Intravenous methylprednisolone (IVMP) 1 g/day was administered for five days. The symptoms regressed within a week, and the follow-up MRI demonstrated no residual lesions.

Seven months later, he was referred to our hospital with blurry vision and a neurological examination showed temporal visual field loss in the right eye. The fundoscopic examination was normal, which incited a diagnosis of retrobulbar ON, and 5 days of 1000 mg/day IVMP were administered. The patient fully recovered after the treatment and AQP4 IgG was found negative in the blood serum [enzyme-linked immunosorbent assay (ELISA)].

Four years later (09/2019), he suffered from temporary blurry vision for a month but didn't apply to a hospital. Five years after the first admission (03/2020), the patient was referred to our hospital with severe pain in both legs. A neurological examination showed bilateral Babinski sign positivity. Spinal MRI showed a longitudinally extending conus medullaris lesion with gadolinium enhancement (Figure 1E). Consent wasn't given for lumbar puncture, so CSF analysis couldn't be done. After 7 days of 1000 mg/day IVMP, the patient showed full recovery, and the follow-up MRI showed no residual lesions. The Anti-AQP4 IgG test was repeated and found negative. The anti-MOG IgG test was positive (Both tests were done with ELISA). Rituximab treatment was started and sustained clinical stability was reached. Written consent was obtained from the patient for this article.

Discussion

Myelin oligodendrocyte glycoprotein is found on the surface of myelinating oligodendrocytes and is considered to be a cell adhesion molecule. It also plays

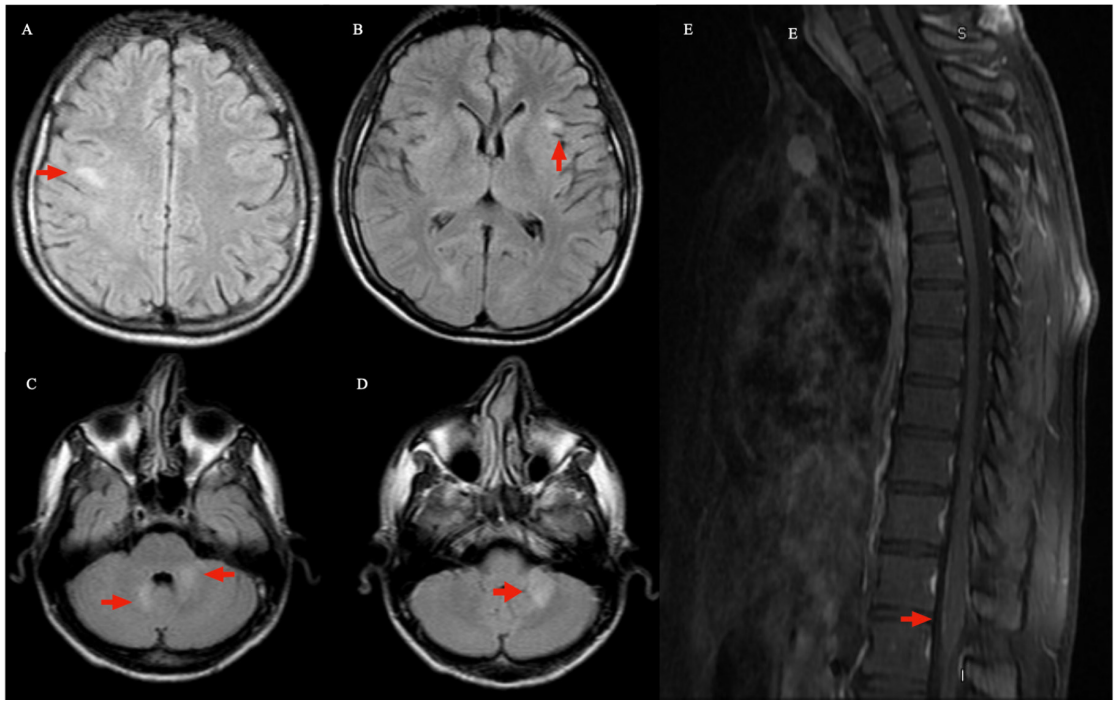

Figure 1. A, B) Fluid attenuated inversion recovery (FLAIR) axial image from the first admission. Bilateral subcortical FLAIR hyperintense lesions (lower left). C, D) High signal intensity lesions in both cerebellar peduncles (upper left). E) T2 hyperintense longitudinally extending conus medullaris lesion with gadolinium enhancement on T1-weighted MRI (right)
MRI: Magnetic resonance imaging

a role in the activation of the complement cascade, causing MS type 2 demyelination in mice and inducing T cell-mediated experimental autoimmune encephalitis (3). Over the years, a subgroup of patients, priorly diagnosed as seronegative NMOSD, was found to be positive for anti-MOG IgG1 and the lesions showed pathophysiological differences. Since anti-MOG IgG and AQP4 positivity very rarely coincide with these histopathological differences, it's hypothesized that these are two distinct diseases (3,6).

MOG-associated disease was first identified in pediatric patients with ADEM-like presentation. Further studies have shown distinct clinical features that include, most commonly in TM, brainstem involvement, and ADEM-like encephalomyelitis (5). During the disease course, acute supratentorial encephalitis prevalence has been reported as 14%, but only 4% of the patients had encephalitis at onset (1).

In previous literature, higher rates of epileptic seizures have been reported for anti-MOG positive cases in comparison with patients with NMO, and most of these MOG related encephalitis cases have been primarily diagnosed with viral or autoimmune encephalitis (7,8), similar to our case because it can mimic infectious encephalitis due to the similarity of CSF and MRI findings. Therefore, an important portion of encephalitis cases with seizures were treated with antibiotherapy before the final diagnosis (8,9). In this study, which also presented with encephalopathy and seizure, brain MRI and CSF findings led to the preliminary diagnosis of infectious encephalitis. The patient was initially treated with acyclovir. Recently, a novel clinical phenotype has been identified as FLAMES in patients who present with seizures and unilateral encephalitis with cortical FLAIR hyperintense lesions (10). Because of the lack of cortical lesions in this case, a retrospective diagnosis of FLAMES was made in this study.

In 2015, anti-MOG IgG testing was unavailable for clinical use in Turkey. During the follow-up, the patient had an ON attack, which brought MOG antibody-associated disease into prominence, but the non-compliance of the patient made the testing improbable. Finally, because of the longitudinally extending TM attack, MOG was near the top of the differential diagnosis, and the increasing use of anti-MOG IgG tests allowed the diagnosis to be completed.

MOG antibody-associated disease is an emerging diagnosis for patients who have been previously diagnosed with seronegative NMOSD. With this case report, we would like to highlight the importance of MOG antibody testing for adult patients presenting with acute demyelinating encephalomyelitis.

Ethics

Informed Consent: Written consent was obtained from the patient for this article.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: C.E.T., Design: C.E.T., Data Collection or Processing: M.D.B., E.B.D., B.P.B., B.B., Analysis or Interpretation: C.E.T., Literature Research: C.E.T., Writing: C.E.T.

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

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