E-ISSN: 2587-0262

NKMJ
NAMIK KEMAL MEDICAL JOURNAL

Volume: 12
Issue: 4
December 2024

ORIGINAL ARTICLES

CASE REPORT

galenos yayınevi

www.namikkemalmedj.com

NAMIK KEMAL MEDICAL JOURNAL

EDITORIAL BOARD

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey
Phone: +90 530 177 30 975
E-mail: info@galenos.com.tr/yayin@galenos.com.tr **Web:** www.galenos.com.tr **Publisher Certificate Number:** 14521
Online Publication Date: December 2024
E-ISSN: 2587-0262
International scientific journal published quarterly.

NAMIK KEMAL MEDICAL JOURNAL

Associate Editors

ADVISORY BOARD

ADVISORY BOARD

Please refer to the journal's webpage (**https://namikkemalmedj.com/**) for "Ethical Policy" and "Instructions to Authors".

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal conforms with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice). Namık Kemal Medical Journal (NKMJ) is indexed by **Emerging Sources Citation Index, Ulakbim Tr Index (TR DIZIN/ULAKBIM), EBSCO: CINAHL Complete, Türk Medline, Ideal Online, J-Gate, CAB International (CABI), Gale Academic OneFile, DOAJ, Embase, Chemical Abstracts Services** and **Turkey Citation Index**.

The journal is published online.

Owner: Erdoğan Gültekin on behalf of Tekirdağ Namık Kemal University Faculty of Medicine Dean

Responsible Manager: Burçin Nalbantoğlu

NAMIK KEMAL MEDICAL JOURNAL

CONTENTS

ORIGINAL ARTICLES

CASE REPORT

INDEX

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.00821
Nam Kem Med J 2024;12(4):243-251

Effects of Baicalein on Oxidative Stress and Apoptotic Process in Formaldehyde-Induced Lung Damage

Baicaleinin Formaldehitle İndüklenen Akciğer Hasarında Oksidatif Stres ve Apoptotik Süreç Üzerine Etkileri

Ebru TAŞTEKİN[1], Enis ULUÇAM[2], Elvan BAKAR[3], Menekşe KARAHAN[4], Emine MUT KEÇECİ[2]

[1]*Trakya University Faculty of Medicine, Department of Pathology, Edirne, Turkey*
[2]*Trakya University Faculty of Medicine, Department of Anatomy, Edirne, Turkey*
[3]*Trakya University Faculty of Pharmacy, Department of Basic Pharmaceutical Sciences, Edirne, Turkey*
[4]*Kırklareli University Faculty of Medicine, Department of Anatomy, Kırklareli, Turkey*

ABSTRACT

Aim: In this study, the effect of baicalein (BAI) on lung damage caused by formaldehyde (FA) is aimed to be examined via immunohistochemistry and gene expression techniques.

Materials and Methods: Within the scope of the study, 24 male Wistar-Albino rats were provided from experimental animal unit. Animals were divided into three groups as two experimental and a control group, using the simple randomization method. Control group received saline intraperitoneally for 14 days, the FA group received 10 mg/kg dose of FA intraperitoneally for 14 days and the FA+BAI group received 10 mg/kg dose of FA intraperitoneally and 200 mg/kg BAI daily for 14 days. At the end of the experimental process, lung tissue samples of rats were taken and analyzed in terms of gene expression and immunohistochemistry.

Results: FA group had high degree of histopathologic lung damage, immunochemically low endothelial nitric oxide synthase (NOS) and high inducible NOS expression. The FA+BAI group had similar findings with the FA group and did not display significant improvement on pathological findings ($p<0.05$). Superoxide dismutase and catalase expression levels were significantly increased in the FA+BAI group compared to the FA group ($p<0.05$). Compared with the control group, it was determined that Cytochrome-c expression increased in both FA group and FA+BAI group ($p<0.05$).

Conclusion: As a result, BAI treatment has no positive effects on FA-induced lung tissue damage. FA induces apoptosis in rat lungs via the intrinsic mitochondrial pathway and BAI has no positive effects on apoptosis at the expression level. However, our study reveals that BAI has an ameliorating effect on oxidative stress parameters at the expression level.

Keywords: Formaldehyde, lung damage, baicalein, apoptosis, oxidative stress

ÖZ

Amaç: Bu çalışmada, baicaleinin (BAI) formaldehitin (FA) neden olduğu akciğer hasarı üzerindeki etkisinin immünohistokimya ve gen ekspresyonu teknikleri ile incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmada deney hayvanları biriminden temin edilen 24 adet erkek Wistar-Albino sıçan kullanıldı. Hayvanlar, basit randomizasyon yöntemi kullanılarak iki deney ve bir kontrol grubu olmak üzere üç gruba ayrıldı. Kontrol grubuna 14 gün boyunca intraperitoneal yolla serum fizyolojik, FA grubuna 14 gün boyunca intraperitoneal yolla 10 mg/kg dozda FA, FA+BAI grubuna intraperitoneal yolla 10 mg/kg dozda FA ve günlük 200 mg/kg BAI verildi. Deney sonunda toplanan akciğer doku örnekleri gen ekspresyonu ve immünohistokimya için analiz edildi.

Bulgular: FA grubunda yüksek derecede histopatolojik akciğer hasarı, immünokimyasal olarak düşük endotelyal nitrik oksit sentaz (NOS) ve yüksek indüklenebilir NOS ekspresyonu vardı. FA+BAI grubu FA grubu ile benzer bulgulara sahipti ve patolojik bulgularda anlamlı iyileşme sağlamadı ($p<0,05$). Süperoksit dismutaz ve katalaz ekspresyon düzeyleri FA+BAI grubunda FA grubuna kıyasla anlamlı olarak artmıştı ($p<0,05$). Kontrol grubu ile karşılaştırıldığında, Sitokrom-c ekspresyonunun hem FA grubunda hem de FA+BAI grubunda arttığı tespit edildi ($p<0,05$).

Address for Correspondence: Enis ULUÇAM MD, Trakya University Faculty of Medicine, Department of Anatomy, Edirne, Turkey
E-mail: eulucam@trakya.edu.tr **ORCID ID:** orcid.org/0000-0002-4686-7350
Received: 07.05.2024 **Accepted**: 13.08.2024

Sonuç: Sonuç olarak, BAI tedavisinin FA kaynaklı akciğer dokusu hasarı üzerinde olumlu etkileri yoktur. FA, sıçan akciğerlerinde intrinsik mitokondriyal yol üzerinden apoptozu indükler ve BAI'nın ekspresyon düzeyinde apoptoz üzerinde olumlu bir etkisi yoktur. Ancak, çalışmamız BAI'nin ifade düzeyinde oksidatif stres parametreleri üzerinde iyileştirici bir etkiye sahip olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Formaldehit, akciğer hasarı, baicalein, apoptosis, oksidatif stress

INTRODUCTION

Formaldehyde (FA) is an aldehyde that dissolves well in water, colorless, irritating in its pure form and has a pungent odor. FA is a commonly utilized chemical agent in a multitude of settings, including anatomy laboratories for the fixation of cadavers, histology and pathology laboratories for the fixation of tissues, disinfection processes within the medical field, and extensively within the food industry as a preservative (E240). However, due to its inherent properties, FA is classified as an irritating and poisonous chemical. It can exist in a gaseous state at room temperature in any environment, which poses a significant health hazard[1].

After an exposure, FA metabolizes to methanol and formic acid in the liver and erythrocytes. It excretes out of the body via urine and feces or with the respiratory tract by oxidizing to carbon dioxide. Numerous studies have shown that exposure to FA causes various symptoms such as sensory irritation, salivation, dyspnea, headache, insomnia, convulsions, behavioral disorders, and abnormal sperm production. The exposure of experimental animals to FA results in its rapid metabolic incorporation into DNA, RNA, and proteins[2-4]. In experimental animal studies, FA induces a variety of toxic effects, possibly because of these macromolecular interactions. In studies conducted for many years, the toxic effect of FA on different tissues and potential protective agents has been investigated. Especially the respiratory tract and lungs are major damaged tissues due to the first affected area by inhalation[4-11].

In the literature, numerous studies have shown that increased oxidative stress and apoptosis are involved in the damage-inducing mechanism of FA. It causes a decrease in lung epithelial cell viability and induction of apoptosis. Different mechanisms have been reported in the mechanism of apoptosis induced by FA, such as change in the Bax/Bcl-2 expression ratio, mitochondrial damage, emergence of toxic metabolites, and activation of the mitochondrial pathway of the apoptosis mechanism. Changes in the expression of Bcl-2 family proteins are generally thought to induce apoptosis by the intrinsic pathway. In addition, higher reactive oxygen species levels have been associated with cell death and pathological conditions caused by oxidative stress, in which excess ROS oxidizes DNA, lipids, proteins and cellular macromolecules, causing damage[10-14].

Apoptosis involves the activation, expression and regulation of certain genes[15]. Tumor suppressor gene p53, Bcl-2 family, and caspase family are among the genes associated with apoptosis. The mechanism of apoptosis includes receiving the apoptotic signal, interaction between molecules and caspase activation, which leads to a continuous reaction process[16]. Apoptosis, a dynamic process, activates caspases by releasing protein from mitochondria[17]. One of these proteins is cytochrome-c (Cyt-c), which is a component of the electron transport chain[18]. Cyt-c is localized between the inner and outer membranes of mitochondria. The release of Cyt-c from the outer membrane into the cytosol is the most important event triggering apoptosis[19]. The release of Cyt-c into the cytosol activates caspase. Caspases that play a role in apoptosis are divided into initiator caspase and effector caspase[20]. Activated by Cyt-c, caspase-9 induces caspase-3. Thus, the caspase cascade begins, which will end with cell death. P53 is a tumor suppressor protein that controls the cell cycle, DNA replication and uncontrolled cell division. In healthy cells, p53 proteins are switched off. It is activated when cells are exposed to stress and uncontrolled division. However, when this protein is damaged or mutated, it cannot perform functions. This causes uncontrolled cell division and tumorigenesis[21].

Nitric oxide (NO) is a signaling molecule synthesized from L-arginine by nitric oxide synthase (NOS), which has three isoforms; endothelial NOS (eNOS), neuronal NOS and inducible NOS (iNOS). It is synthesized by eNOS and is required for the normal functions of cells. In the caspase of tissue damage or stresses, extra NO is produced via iNOS. Due to increased NO production, an increase occurs in other free radicals such as peroxynitrite anion and hydroxyl, which are highly active. NO can also deplete antioxidants and inhibit their protective effects on organs against oxidative stress[22].

Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and non-enzymatic markers such as reduced glutathione (GSH) contribute to the healthy functioning of physiological processes by providing defense against ROS species. SOD, glutathione peroxidase (Gpx), and CAT are the most important antioxidant enzymes in the investigation of tissue damage caused by oxidative stress, and changes in their activities are considered as oxidative stress markers. FA triggers both apoptosis and oxidative stress in cells by reacting with many molecules. SOD, Gpx and CAT are the most important antioxidant enzymes in the investigation of tissue damage caused by oxidative stress, and changes in their activities are considered as oxidant stress markers in studies conducted with FA[23-27].

Baicalein (BAI) is derived from the roots of the Scutellaria baicalensis plant. Studies have shown that BAI has anti-bacterial, anti-virus, anti-allergic, anti-oxidant, and anti-inflammatory properties. In recent studies, it has been found out that BAI has anti-cancer activities upon its effect on various biological processes such as cell proliferation, metastasis, apoptosis, and autophagy[28-30].

Our objective was to use this data to find out an answer to these two questions relevant to the topic. Initially, a link between the damage caused by FA and the production of eNOS, iNOS, apoptotic processes, and antioxidant responses in lung tissues were discovered. Furthermore, we investigated the influence of BAI on the lung damage caused by FA.

MATERIALS AND METHODS

Chemicals

BAI (BLDpharm BD6298, China), FA (Tekkim, Turkey).

Animals

A total of 24 male Wistar albino rats (weighing 20-24 g) were obtained from the Experimental Animals Unit of Trakya, Faculty of Medicine. Animals were maintained under standard laboratory conditions (22±1 °C temperature, 55% humidity, 12-hour light/dark cycle) and fed with standard feed and tap water. Animals were brought to the laboratory environment 24 hours before the start of the experiment to ensure their adaptation to the experimental environment. The Trakya University Animal Experiments Local Ethics Committee granted approval for this study (decision no: 2019.03.01, date: 29.03.2019).

Experimental Design

The study was planned to have three groups, including two experimental and a control group. Each group was formed with eight rats that were randomly selected.

Control group: Intraperitoneal saline was given daily for 14 days.

FA group: Intraperitoneal FA was administered at a dose of 10 mg/kg diluted 1/10 with saline daily for 14 days. FA + BAI group: Intraperitoneal FA at a dose of 10 mg/kg diluted 1/10 with saline and BAI at a daily intraperitoneal dose of 200 mg/kg were given daily for 14 days. When subacute studies were examined in the literature to establish experimental FA toxicity, it was seen that intraperitoneal administration of FA was preferred. The doses of both FA and BAI were selected according to the literature[30-32].

At the end of the experiment, all rats were euthanized by removing lung tissues under 10 mg/kg xylazine hydrochloride (HCl) and 50 mg/kg ketamine HCl anesthesia. Half of the tissues were soaked into 10% formalin solution for pathological examination. The other parts were stored in liquid nitrogen at -80 °C until mRNA isolation after they were frozen quickly.

Determination of Gene Expression Levels

Quantitative reverse transcriptase (qRT)-PCR analyses were conducted on complementary DNA (cDNA) samples produced from total RNA extracted from lung tissue. Specially designed primers for the GSH, SOD, CAT, Cyt-c, P53, Caspase-3, Caspase-9, iNOS, and eNOS genes were utilized.

RNA Isolation

RNA isolation from lung tissues was performed using the Invitrogen by Thermo Fisher Scientific isolation kit. The isolation procedure was performed according to this kit's method as described below. 1 mm diameter zirconium silicate r beads were placed in the samples for better homogenization. It was then kept in liquid nitrogen and passed through a tissue shredder. 1% mercaptoethanol and lysis buffer were added to the samples to accelerate the protein denaturation process in order to isolate the RNA easily. The same volume of 70% ethanol was added to the cell homogenates to remove water. It was centrifuged at 21380 G to remove the beads. 700 µL of the liquid from the centrifuge was taken into the columnar tubes included in the kit. The samples in these tubes were centrifuged at 12000 g for 15 seconds and then the filter sections of the tubes were transferred to the collection tubes. 700 µL of washing buffer 1 was added to the samples and centrifuged at 12000 g for 15 seconds, and the filter parts of the columnar tubes were taken into new tubes. 500 µL of washing buffer 2 was added to them and centrifuged at 12000 g for 15 seconds. 500 µL of washing buffer 2 was added again and centrifuged for 2 minutes, and then the tubes were taken into capped tubes and 50 µL of the RNase-free water composition was added to the tubes. The reason for adding 50 µL was that it was determined as the optimum volume in the studies. The mixture was centrifuged at 12000 g for 2 minutes, 30 seconds after incubation for 2 minutes. Filter parts were discarded and the lower parts were taken for measurement. 2 µL of the obtained RNA samples were taken, pipetted on the Nanodrop device and the purity and absorbance values were determined by reading at 260-280 nm. The measured purity values were measured in the range of 1.8-2.0, and c-DNA synthesis was performed from these samples.

Complementary Deoxyribonucleic Acid (cDNA) Synthesis

The cDNA synthesis was carried out from the isolated RNAs using the High-Capacity cDNA reverse transcription synthesis kit (Catalog no: 4368814) by following the appropriate protocol steps. The synthesized cDNAs were stored at -20 °C. Polymerase chain reaction (PCR) conditions step 1: 25 °C, 09:53 min; step

2: 37 °C, 120 min; step 3: The cDNA synthesis was performed by programming at 85 °C for 5 minutes. The cDNA synthesis protocol is shown in Table 1.

Real-Time Polymerase Chain Reaction (qRT-PCR) Expression

Active GSH, SOD, CAT, P53, Cyt-c, Caspase-3, Caspase-9, iNOS and eNOS gene expression levels were determined by qRT-PCR method. In gene expression studies, cDNAs obtained from RNA isolated as described in the "RNA isolation" section was used. In our study, the Quant Studio 6 Flex qRT-PCR system, which can read 384-well microplates, was used. qRT-PCR' genes used and their sequences are listed in Table 2. Glyceraldehyde 3-phosphate dehydrogenase was used as calibration and correction factor and samples were analyzed. Expression levels of genes were determined using the SYBR Green method. qRT-PCR mix; cDNA contains SYBR Green and related genes. The contents of the qRT-PCR reaction mix consist of 6 µL of SYBR Green Master Mix, 2 µL of cDNA and 2 µL of RNase free water, and 0.5 µL of primer forward, 0.5 µL of reverse for each well of a 384-well plate. PCR program: 1 cycle of 2 min at 50 °C and 10 min at 95 °C, followed by 40 cycles of denaturation (95 °C for 15 s) and annealing and extension (1 min at 60 °C).

Table 1. cDNA synthesis protocol

Substance	Volume
Total RNA	10
10 X RT buffer	2 µL
25 X dNTP mix (100 mM)	0.8 µL
10 X RT Random Primer	2 µL
MultiScribe reverse transcriptase	1 µL
Nuclease free water	4.2 µL
Final volume	20 µL

RNA: Ribonucleic acid, RT: Reverse transcription, dNTP: Deoxynucleotide triphosphate

Histopathological and Immunohistochemical Evaluation

After the tissue samples were fixed in 10% formalin solution for 24 hours at room temperature, they were embedded in paraffin blocks and passed through an increasing rate of alcohol series (60%, 70%, 80%, 90.99.9%). Paraffin blocks were prepared after the tissues were exposed to 2 exchange xylene and paraffinization steps for transparency. After the deparaffinization process of the 4µ sections taken from the blocks, hematoxylin-eosin (H&E) staining was applied to one of them primarily for general tissue histological examination, and iNOS (Thermo Invitrogen PA3-030A) and eNOS (Thermo Invitrogen MA5-15559) antibodies were applied to the others. Ventana BenchMark XT Ultra IHC/ISH system platform was used for immunohistochemistry staining. Tissue slides were incubated at 37 °C overnight and 56 °C for 2 hours. Here, a 10-minute xylene series, 96%, 80%, 70% alcohol series and three times distilled water series were applied to the slides at 60°C. "Citrate buffer 10 X pH 8.0" (code: 15-M820, Lot. 50930) was used for antigen retrieval (20 minutes at 95-100 °C and 20 minutes at room temperature/cooling). Phosphate-buffered saline was administered 10 minutes after endogenous peroxide blockade with 3% H_2O_2. Slides were incubated with iNOS and eNOS antibodies for 45 minutes at room temperature. Then, standard immunoperoxidase staining method steps were applied. While evaluating the stainings in the sections, the pathologist made an unbiased evaluation without knowing the group characteristics. The prepared preparations were evaluated under the Nikon Eclipse E600 model light microscope. Images were taken from the sections in the Visia imaging program and saved. All H&E sections were evaluated in 10 randomly selected high magnification fields (x400) of the microscope. Inflammatory cellular infiltration and foamy macrophages accumulation in the pulmonary interstitium, thickening, hemorrhage and epithelial cell shedding in the bronchiolar wall were observed. All rat's sections were scored according to these findings from 0 to 4 on a predefined

Table 2. Genes and their sequences used in qRT-PCR

Target gene	Forward primer sequence (5'- 3')	Reverse primer sequence (5'- 3')
SOD	AGCTGCACCACAGCAAGCAC	TCCACCACCCTTAGGGCTCA
CAT	TCCGGGATCTTTTTAACGCCATTG	TCGAGCACGGTAGGGACAGTTCAC
GSH	ACTTGGCACTCCTCTCCTGA	AGGCACTAGAACCTGCTGGA
Cyt-c	AGTGGCTAGAGTGGTCATTCATTTAC	TCATGATCTGAATTCTGGTGTATGAG
P53	CACAGTCGGATATGAGCATC	GTCGTCCAGATACTCAGCAT
Caspase-3	AGTTGGACCCACCTTGTGAG	AGTCTGCAGCTCCTCCACAT
Caspase-9	AGCCAGATGCTGTCCCATAC	CAGGAACCGCTCTTCTTGTC
iNOS	GAGACAGGGAAGTCTGAAGCAC	CCAGCAGTAGTTGCTCCTCTTC
eNOS	ACCAGCACCTTTGGCAATGGAG	GAGACGCTGTTGAATCGGACCT

SOD: Superoxide dismutase, CAT: Catalase, GSH: Glutathione, Cyt-c: Cytochrome-c, P53: Tumor protein 53, iNOS: Inducible nitric oxide synthase, eNOS: Endothelial nitric oxide synthase

semi-quantitative scale. The degree of lung damage scored as 0: normal tissue; 1: minimal damage (<1-25% uptake); 2: moderate damage (25-75% involvement); and 3: severe necrosis (>75% involvement)[33]. For the evaluation of eNOS and iNOS antibodies, the extension and density of positively stained cells were determined in each Caspase. The extent of staining was graded as 0 (0-5%), 1 (6-24%), 2 (25-49%), 3 (50-74%), and 4 (≥75%). Staining intensity was graded as 0 (negative), 1 (mild), 2 (moderate), and 3 (strong). The immunoreactivity score ranging from 0 to 300 was determined by multiplying the two obtained degrees[34].

Statistics Analysis

To define descriptive statistics, mean and standard deviation values were used. The conformity of the data to the normal

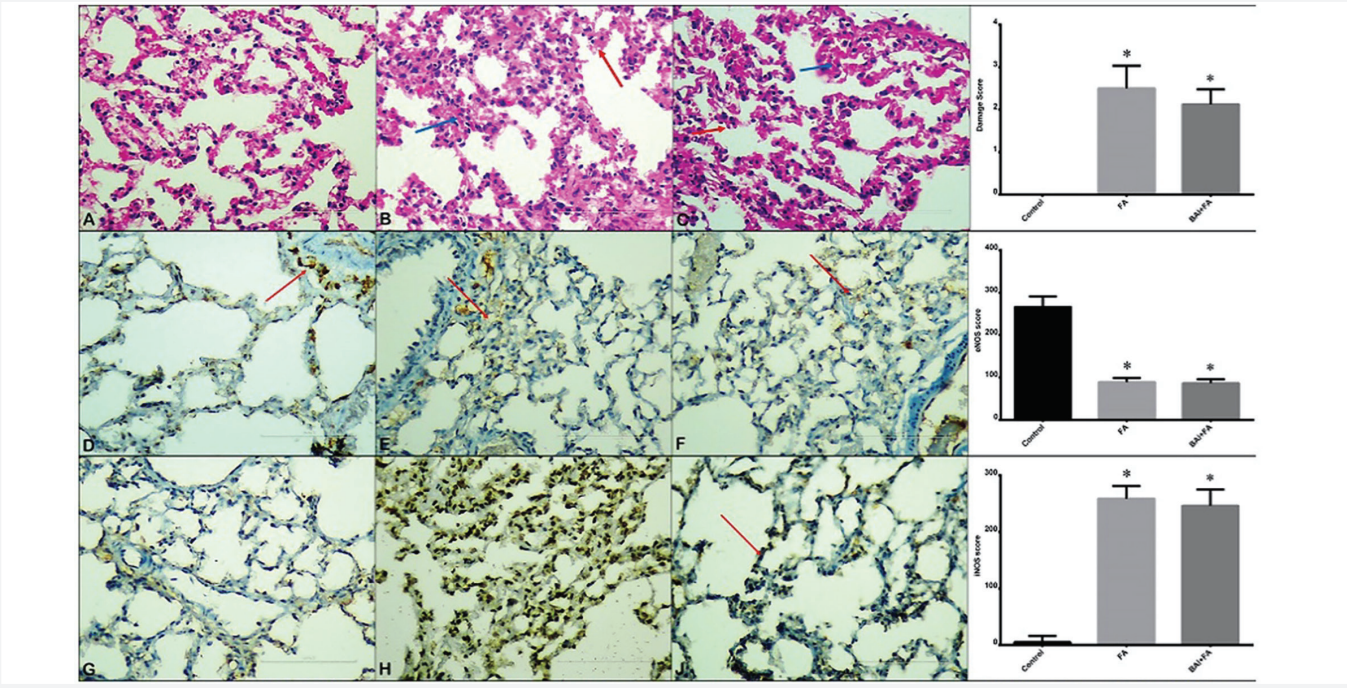


Figure 1. Lung tissue light microscopy and immunohistochemistry findigs. A) Control; normal morphology (HEX200). B) FA; moderate to severe lung damage (blue arrow: interstitial hemorrhage, red arrow: sloughed epithelial cells and macrophages) (HEX200). C) FA+BAI; moderate lung damage (blue arrow: interstitial hemorrhage, red arrow: sloughed epithelial cells and macrophages) (HEX200). D) eNOS control; moderate to severe staining (X200). E) eNOS FA; light staining (x200). F) eNOS FA+BAI; mild staining (X200). G) iNOS control; no staining (X200). H) iNOS FA; severe staining X200). J) iNOS FA+BAI; moderate staining (X200). Lung tissue histopathology findigs. *: Control group comparison p<0.005

Table 3. Lung tissue gene expression levels tissue

Parameters	Control	FA	FA+BAI
SOD	3.22± 0.60	3.10±0.85	7.77±0.85*,γ
GSH	2.78±0.52	0.24±0.17*	0.28±0.14*
CAT	7.17±1.76	2.62±0.48*	4.03±1.18*,γ
P53	1.52±0.46	0.06±0.04*	0.02±0.01*,γ
Cyt-c	1.73±0.56	9.65±1.94*	22.80±4.88*,γ
Caspase-3	2.69±1.05	0.50±0.23*	0.43±0.23*
Caspase-9	0.06±0.08	0.23±0.27*	0.14±0.13
iNOS	5.55±0.42	7.12±1.69*	26.13±4.59*,γ
eNOS	413.78±51.96	73.30±3.71*	37.93±3.35*,γ

Values are given as mean ± standard deviation. For all groups, n=8. *: Control group comparison p<0.05, γ: Comparison of FA and Baicalein groups, p<0.05.

FA: Formaldehyde, BAI: Baicalein, SOD: Superoxide dismutase, CAT: Catalase, GSH: Glutathione, Cyt-c: Cytochrome-c, P53: Tumor protein 53, iNOS: Inducible nitric oxide synthase, eNOS: Endothelial nitric oxide synthase

distribution was determined by the one-sample Kolmogorov-Smirnov test. One-way ANOVA test was applied if the variables fit the normal distribution. The "Bonferoni post-hoc" test was performed for multiple comparisons between variables. The Kruskal-Wallis test was used for multiple comparisons between non-normally distributed variables. Pairwise comparisons between groups were evaluated with the Mann-Whitney U test. The significance limit for all statistics was considered as $p<0.05$. IBM SPSS Statistics 20.0 program was used for statistical analysis. GraphPad Prism 6 Windows Software was used to create the graphs.

RESULTS

Light Microscopy Findings

In control group, morphology of lung tissues of rats was similar to normal morphology. Microscopic findings of the FA group were quite remarkable since interstitial hemorrhage, inflammatory cells, macrophages and edema were seen in the FA group's lungs. Terminal bronchioles with moderate or severe shedding of epithelial cells, thickening and bleeding were detected in all rats. Although the histopathologic findings of the FA+BAI group are less prominent than the FA group, there was statistically no significant difference between these two groups ($p>0.05$) (Figure 1).

Immunohistochemistry Findings

eNOS staining was moderate to severe in the control group and mild in the FA group. On the contrary, iNOS staining was not detected in the control group but it was moderate to severe in the FA group. The staining features in the BAI+FA group were similar with the FA group ($p<0.05$) (Figure 1).

In our study, while control group had normal range of findings, the FA group had higher degree of histopathologic lung damage, immunuchemically low eNOS and high iNOS expression. FA+BAI provided minimal reduction on lung damage and iNOS expression level in addition to the minimal increase on eNOS expression levels. However, these findings were not statistically significant ($p<0.05$).

Gene Expression Levels

Compared to the control group, it is seen that GSH and CAT levels were lower in the FA group. SOD and CAT expression levels were significantly increased in the FA+BAI group compared to the FA group ($p<0.05$). The P53 expression level was lower in the FA group compared to the control group. When compared with the control group, it was observed that the expression level of sit-c, iNOS and eNOS increased in both FA and FA+BAI groups ($p<0.05$). The gene expression levels we obtained as a result of our study are given in Table 3.

DISCUSSION

FA is a colorless, flammable gas that is widely used in medical science and industrial sectors, and unfortunately it is one of the major air pollutants. Due to FA exposure in some professions such as pathologists, anatomists, and technicians, it is observed that there is an increase in the incidence of leukemias, brain tumors, liver, testes and lung cancers compared with the normal population. FA is well-known as mucosal irritant, serious respiratory system toxic agent and carcinogenic chemical, classified as Group 1 by International Agency for Research on Cancer[35,36]. FA is also associated with depressive symptoms mediated by systemic inflammation[37]. In this study, we aimed to observe the connection between FA induced lung damage and eNOS, iNOS expression, antioxidant response and apoptotic process in lung tissues. On the other hand, we wanted to investigate the effects of baicaline on FA damage, which have never been studied before.

FA, which is taken exogenously or formed by metabolic reactions, causes various toxic effects in tissues. FA exposure mostly appears with inhalation through exogenous and biosynthetic sources such as methanol metabolism, demethylation, histone/DNA/RNA demethylation in the body form FA as an intermediate product. Toxic effects of FA and its metabolites can be observed especially in parenchymal tissues. Previous studies confirmed the role of FA in biomolecular profile alterations and highlighted that the low occupational exposure on health care professionals could also result in measurable biological outcomes[38,39].

The objective of this study was to ascertain the histopathologic effects of the toxic metabolites of FA metabolized in the liver on the lung parenchyma, as well as the apoptosis pathway, and to delineate the underlying causes of the observed damage, which included inflammation and oxidative stress. A rat model was established by direct (intraperitoneal) administration of FA to rats at doses previously determined in other studies. The results demonstrated that direct subacute FA exposure caused lung injury by inducing severe inflammation, apoptosis, and increased oxidative stress. These injury mechanisms resulted in histopathologic findings.

The decrease in eNOS level due to FA exposure indicates that the cell loses its normal functions. The increase in iNOS can be seen as a sign of tissue damage development. The decrease in GSH and CAT levels also shows that the deterioration in oxidative balance is a factor that facilitates tissue damage and prevents the healing of the damage.

Although FA is caused cytotoxicity with cell death or apoptosis and genotoxicity via DNA and chromosomal damage, limited data suggested that oxidative stress caused by reactive oxygen species may contribute to damage. Excessive exposure to ROS

is known to cause developmental toxicity through damage to cellular components such as DNA, lipids, and proteins[40]. Both the induction and suppression of antioxidant enzymes by FA has been demonstrated in different tissues. While GPx, SOD, CAT and GSH protect cells against oxidative damage, malondialdehyde is an oxidative biomarker that their activity levels may use for indicating the level of oxidative damage[41]. Some studies have shown that FA induces the antioxidant defense mechanism in rodent testicular tissue and may impair its effects[42]. Lim et al.[9] showed that FA induced an increase in lipid peroxidation formation, a marker of oxidative stress.

NO is generated through the action of iNOS in response to tissue injury or stress. The iNOS level increases but eNOS level decreases as an indicator of tissue damage. NO production causes an increase in free radicals. Another effect of NO is to reduce antioxidants such as SOD, Gpx, and CAT. As a result, tissue damage occurs due to oxidative stress. There were numerous studies about FA induced tissue damage, NO and oxidative stress mechanisms. First, the activator effect of FA on oxidative stress was evaluated[43]. They were followed by studies showing the iNOS, eNOS, ROS, oxidative stress stimulating the effects of FA, degree of tissue damage and SOD, CAT, GPx levels in different tissues (brain, liver, kidney, lung, etc.). Mohammed et al.[44] evaluated genotoxic and heamatotoxic damage of FA. Zararsız et al.[31] planned their study on lung tissue. Results of these studies are compatible with our data supporting the FA, NO and ROS relationship[31,43-45].

Teng et al.[46] reported that even low concentrations of FA caused oxidative damage on isolated rat hepatocytes in their experimental study. Similarly, Sarsılmaz et al.[47] found that CAT activity decreased and SOD activity increased in liver tissue by administering FA to rats by inhalation. Zararsız et al.[31] studied on lung tissue and they found out that CAT enzyme levels decreased and SOD enzyme activities increased in lung tissue of rats exposed to FA.

There is no study in the literature investigating the protective effects of BAI, an antioxidant, against FA toxicity at the expression level. However, there are studies evaluating the protective effects of BAI on different cell lines by in vitro studies at the expression level[9,43,45].

In our study, qRT-PCR results demonstrated that GSH and CAT expressions were downregulated as a result of damage to the lung tissue due to FA toxicity. This result shows that antioxidant defense is negatively affected. SOD and CAT expression levels were significantly increased in the FA+BAI group compared to the FA group. This situation was evaluated as a positive effect of BAI on providing antioxidant defense through SOD and CAT.

Two major pathways lead to apoptosis activation. First one is the extrinsic (death receptor-mediated) pathway that is initiated by tumor necrosis factor family members, as an activating complex for pro-caspase-8, and second one is the intrinsic (mitochondria-mediated) pathway with apoptosome, as an activating complex for procaspase-9. The intrinsic pathway is regulated by Bcl-2 family proteins. Several signaling molecules lead to the initiation of intracellular inflammatory mediator synthesis and/or apoptosis. Numerous studies have shown that apoptosis is one of the mechanisms of cell death during the FA induced lung injury[12,14,44]. In our study, we investigated major members of the intrinsic pathway as Cyt-c, CASPASE-3, and CASPASE-9 via qRT-PCR.

The decrease in P53 expression level in the FA group compared to the control group was interpreted as the TP53 gene, which is a tumor suppressor gene. It was damaged due to oxidative stress and therefore the P53 expression level decreased. P53 expression level was found to be significantly lower in the FA+BAI group than in the control and FA groups. This was interpreted as BAI did not have an effect on the apoptotic process. As a result of oxidative stress due to FA toxicity, it was considered that the apoptotic process was triggered via the mitochondrial pathway. The increased expression of Cyt-c in the FA group compared to the control group may be an indicator of this. It is thought that raisedcellular stress may cause membrane damage due to DNA damage and lipid peroxidation, and as a result, Cyt-c release from mitochondria to the cytoplasm may have increased. Apoptotic effector or "executive" proteins in the apoptosome (Cyt-c, Apaf-1 and procaspase) and caspase cascade play roles in the mitochondrial-dependent apoptotic process. It is observed that the expression of Cyt-c increases to trigger cell death against the harmful effects of FA and triggers the formation of active caspase-9. Active caspase-9, as an initiator caspase, cleaves and activates effector caspase such as caspase-3 and caspase-7. This situation increases the degree of cellular damage and DNA damage. There was no increase in caspase-3 expression levels in both the FA and FA+BAI groups. This suggested that the level of inactive caspase-3 in the cell was sufficient to trigger apoptosis. However, Cyt-c expression level was found to be high in the FA+BAI group. This suggests that BAI has no therapeutic effect on mitochondrial damage.

When compared to the control group, it was observed that the iNOS expression level increased in the FA group. In a different study with lung tissue, it was stated that iNOS expression increased due to FA toxicity. This result is compatible with our study[44]. In our study, iNOS expression level was also higher than in the FA+BAI group when compared to the other two groups ($p<0.05$). NO reacts with the superoxide radical and forms peroxynitrite, which causes DNA damage. The increase in iNOS expression level in the FA+BAI group can be interpreted as the activation of the antioxidant system via NO. As a result of immunostaining, it was observed that iNOS immunoreactivity increased significantly in the FA group. This suggests that the

response to cellular damage to this toxicity might be via NO. Similarly, iNOS immunoreactivity was found high in the FA+BAI group, but there was no significant difference compared to FA. It was determined that the eNOS expression level decreased significantly due to FA toxicity. Immunohistochemical staining also supports this result. It was considered that the decrease in eNOS immunoreactivity might be associated with epithelial tissue damage due to FA toxicity. A decrease in eNOS expression level and immunoreactivity intensity was observed in both FA and FA+BAI groups when compared to the control. This situation interpreted as BAI not efficient on eNOS.

At high concentrations of FA exposure, pulmonary effects such as cough, shortness of breath, wheezing at 10-20 ppm levels, edema and spasm in the larynx were observed. On microscopic examination, it is seen that even acute inhalation of low doses of FA causes inflammatory cell changes in the upper respiratory tract and lung parenchyma in humans and animals. Pulmonary inflammation, edema and pneumonia develop at doses of 50-100 ppm[37-38]. Other important microscopic findings were an increase in thickness of the wall, hemorrhage and epithelial cell shedding of bronchioles. In literature, numerous studies showed FA induced damage and protective effect of various substances[11,32,43-48]. In our study, easy identified microscopic lung damage was detected as a FA application.

Wogonin and BAI, extracted from S. baicalensis, exhibit similar pharmacological properties with respect to apoptotic, inflammatory, and oxidative effects. In vivo and in vitro studies have demonstrated that BAI protects organs such as the pancreas, liver, and kidney from inflammatory mediators and immune system damage[49,50].

Study Limitations

That the parameters of the experimental study could not be examined biochemically and western blot analysis could not be performed in the tissue samples were the limitations of this study.

CONCLUSION

In this study, it was aimed to research the BAI, whose antioxidant and anti-inflammatory properties on different tissues have been proven, with experimental studies as a protective agent on lung tissue against FA damage. Bie et al.[28] investigated the anti-cancer effects of BAI against hepatocellular carcinoma and they found favorable results. In addition, Sowndhararajan et al.[29] highlighted the neuroprotective effects of BAI. However, we could not detect positive effects of BAI on FA induced lung damage. In rat lungs, FA induces apoptosis via the intrinsic mitochondrial pathway and BAI has no positive effects on apoptosis at the expression level. On the other hand, our study reveals that BAI has a curative effect on oxidative stress parameters at the expression level.

Ethics

Ethics Committee Approval: The Trakya University Animal Experiments Local Ethics Committee granted approval for this study (decision no: 2019.03.01, date: 29.03).

Informed Consent: Animal experimentation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.U., M.K., E.M.K., Concept: E.U., E.B., Design: E.T., E.U., E.B., Data Collection or Processing: E.U., E.B., M.K., E.M.K., Analysis or Interpretation: E.T., E.U., E.B., Literature Search: M.K., E.M.K., Writing: E.T., E.U., E.B.

Conflict of Interest: One author of this article, Ebru TAŞTEKİN is a member of the Editorial Board of the Namık Kemal Medical Journal. However, she did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

Financial Disclosure: Financial support of the study was provided by Trakya University Scientific Research Projects Unit (TUBAP-2020/30).

REFERENCES

1. Suh HH, Bahadori T, Vallarino J, Spengler JD. Criteria air pollutants and toxic air pollutants. Environ Health Perspect. 2000;108:625-33.
2. Condray R, Morrow LA, Steinhauer SR, Hodgson M, Kelley M. Mood and behavioral symptoms in individuals with chronic solvent exposure. Psychiatry Res. 2000;97:191-206.
3. Kum C, Kiral F, Sekkin S, Seyrek K, Boyacioglu M. Effects of xylene and formaldehyde inhalations on oxidative stress in adult and developing rats livers. Exp Anim. 2007;56:35-42.
4. Quievryn G, Zhitkovich A. Loss of DNA-protein crosslinks from formaldehyde-exposed cells occurs through spontaneous hydrolysis and an active repair process linked to proteosome function. Carcinogenesis. 2000;21:1573-80.
5. Bakar E, Ulucam E, Cerkezkayabekir A. Protective effects of proanthocyanidin and vitamin E against toxic effects of formaldehyde in kidney tissue. Biotech Histochem. 2015;90:69-78.
6. Gulec M, Gurel A, Armutcu F. Vitamin E protects against oxidative damage caused by formaldehyde in the liver and plasma of rats. Mol Cell Biochem. 2006;290:61-7.
7. Jakab MG, Klupp T, Besenyei K, Biró A, Major J, Tompa A. Formaldehyde-induced chromosomal aberrations and apoptosis in peripheral blood lymphocytes of personnel working in pathology departments. Mutat Res. 2010;698:11-7.
8. Uluçam E, Bakar E. The effect of proanthocyanidin on formaldehyde-induced toxicity in rat testes. Turk J Med Sci. 2016;46:185-93.
9. Lim SK, Kim JC, Moon CJ, Kim GY, Han HJ, Park SH. Formaldehyde induces apoptosis through decreased Prx 2 via p38 MAPK in lung epithelial cells. Toxicology. 2010;271:100-6.
10. Rahman I, Biswas SK, Kode A. Oxidant and antioxidant balance in the airways and airway diseases. Eur J Pharmacol. 2006;533:222-39.

11. Sandikci M, Seyrek K, Aksit H, Kose H. Inhalation of formaldehyde and xylene induces apoptotic cell death in the lung tissue. Toxicol Ind Health. 2009;25:455-61.
12. Chopra M, Reuben JS, Sharma AC. Acute lung injury:apoptosis and signaling mechanisms. Exp Biol Med (Maywood). 2009;234:361-71.
13. Klekotka PA, Santoro SA, Wang H, Zutter MM. Specific residues within the alpha 2 integrin subunit cytoplasmic domain regulate migration and cell cycle progression via distinct MAPK pathways. J Biol Chem. 2001;276:32353.
14. Levy M, Khan E, Careaga M, Goldkorn T. Neutral sphingomyelinase 2 is activated by cigarette smoke to augment ceramide-induced apoptosis in lung cell death. Am J Physiol Lung Cell Mol Physiol. 2009;297:125-33.
15. Latif M, Faheem M. Study of oxidative stress and histo-biochemical biomarkers of diethyl phthalate induced toxicity in a cultureable fish, labeo rohita. Pak Vet J. 2019;40:202-8.
16. Antonio LS, Jeggle P, MacVinish LJ, Bartram JC, Miller H, Jarvis GE, et al. The effect of fluoride on the structure, function, and proteome of a renal epithelial cell monolayer. Environ Toxicol. 2017;32:1455-67.
17. Goldstein JC, Kluck RM, Green DR. A single cell analysis of apoptosis. Ordering the apoptotic phenotype. Ann N Y Acad Sci. 2000;926:132-41.
18. Gogvadze V, Orrenius S, Zhivotovsky B. Multiple pathways of cytochrome c release from mitochondria in apoptosis. Biochim Biophys Acta. 2006;1757:639-47.
19. Goldstein JC, Muñoz-Pinedo C, Ricci JE, Adams SR, Kelekar A, Schuler M, et al. Cytochrome c is released in a single step during apoptosis. Cell Death Differ. 2005;12:453-62.
20. Ouyang Z, Yang B, Yi J, Zhu S, Lu S, Liu Y, et al. Exposure to fluoride induces apoptosis in liver of ducks by regulating Cyt-C/Caspase 3/9 signaling pathway. Ecotoxicol Environ Saf. 2021;224:112662.
21. Kanapathipillai M. Treating p53 mutant aggregation-associated cancer. Cancers (Basel). 2018;10:154.
22. Chatterjee A, Black SM, Catravas JD. Endothelial nitric oxide (NO) and its pathophysiologic regulation. Vascul Pharmacol. 2008;49:134-40.
23. Anbhazhagan S, Winkins SS. A biochemical study on variability of Superoxide dismutase, Catalase and Glutathione peroxidase in dry cleaners. Indian J Clin Biochem. 2008;23:198-9.
24. Chen Q, Xiao DS. Long-term aerobic exercise increases redox-active iron through nitric oxide in rat hippocampus. Nitric Oxide. 2014;361-10.
25. Eghbalzadeh K, Brixius K, Bloch W, Brinkmann C. Skeletal muscle nitric oxide (NO) synthases and NO-signaling in "diabesity"--what about the relevance of exercise training interventions? Nitric Oxide. 2014;37:28-40.
26. Miyauchi T, Maeda S, Iemitsu M, Kobayashi T, Kumagai Y, Yamaguchi I, et al. Exercise causes a tissue-specific change of NO production in the kidney and lung. J Appl Physiol. 2003;94:60-8.
27. Ramirez DC, Gimenez MS. Induction of redox changes, inducible nitric oxide synthase and cyclooxygenase-2 by chronic cadmium exposure in mouse peritoneal macrophages. Toxicol Lett. 2003;145:121-32.
28. Bie B, Sun J, Guo Y, Li J, Jiang W, Yang J, et al. Baicalein: a review of its anti-cancer effects and mechanisms in hepatocellular carcinoma. Biomed Pharmacother. 2017;93:1285-91.
29. Sowndhararajan K, Deepa P, Kim M, Park SJ, Kim S. Baicalein as a potent neuroprotective agent: A review. Biomed Pharmacother. 2017;95:1021-32.
30. Yalçınkaya Yavuz Ö, Aydoğdu N, Taştekin E, Süt N. The effects of baicalin on myoglobinuric acute renal failure in rats. Balkan Med J. 2018;35:68-76.
31. Zararsız İ, Kuş İ, Çolakoğlu N, Pekmez H, Yılmaz HR, Sarsılmaz M. Protective effects of melatonin hormone against exposure of formaldehyde-induced oxidative damage in lung of rats: light microscopic and biochemical study. Van Med J. 2004;11:105-12.
32. Türkoğlu AO, Sarsılmaz M, Çolakoğlu N, Zararsız İ, Kuloğlu T, Pekmez H, et al. Formaldehyde-induced damage in lungs and effects of caffeic acid phenethyl ester: a light microscopic study. Eur J Intern Med. 2008;5:152-6.
33. Sezer A, Guclu B, Kazanci B, Cakir M, Coban MK. Neuroprotective effects of agmatine in experimental peripheral nerve injury in rats: a prospective randomized and placebo-controlled trial. Turk Neurosurg. 2014;24:196-201.
34. Tastekin E, Palabiyik O, Ulucam E, Uzgur S, Karaca A, Vardar SA, et al. The effect of high protein diet and exercise on irisin, eNOS, and iNOS expressions in kidney. Ren Fail. 2016;38:1107-14.
35. Hauptmann M, Stewart PA, Lubin JH, Beane Freeman LE, Hornung RW, Herrick RF, et al. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. J Natl Cancer Inst. 2009;101:1696-708.
36. Mahboubi A, Koushik A, Siemiatycki J, Lavoue J, Rousseau MC. Assessment of the effect of occupational exposure to formaldehyde on the risk of lung cancer in two Canadian population-based case-control studies. Scand J Work Environ Health. 2013;39:401-10.
37. Guo J, Garshick E, Si F, Tang Z, Lian X, Wang Y, et al. Environmental toxicant exposure and depressive symptoms. JAMA Netw Open. 2024;7:e2420259.
38. Ghelli F, Bellisario V, Squillacioti G, Panizzolo M, Santovito A, Bono R. Formaldehyde in Hospitals Induces Oxidative Stress: The Role of GSTT1 and GSTM1 Polymorphisms. Toxics. 2021;9:178.
39. Ghelli F, Cocchi E, Buglisi M, Squillacioti G, Bellisario V, Bono R, Santovito A. The role of phase I, phase II, and DNA-repair gene polymorphisms in the damage induced by formaldehyde in pathologists. Sci Rep. 2021;11:10507.
40. Saito Y, Nishio K, Yoshida Y, Niki E. Cytotoxic effect of formaldehyde with free radicals via increment of cellular reactive oxygen species. Toxicology. 2005;210:235-45.
41. Zeng CE, Peng X, Qiao Y. Reproductive toxicity of formaldehyde to male mice. Chin J Hum Sex. 2003;12:1-4.
42. Ozen OA, Kus MA, Kus I, Alkoc OA, Songur A. Protective effects of melatonin against formaldehyde-induced oxidative damage and apoptosis in rat testes: an immunohistochemical and biochemical study. Syst Biol Reprod Med. 2008;54:169-76.
43. Arslan-Acaroz D, Bayşu-Sozbilir N. Ameliorative effect of boric acid against formaldehyde-induced oxidative stress in A549 cell lines. Environ Sci Pollut Res Int. 2020;27:4067-74.
44. Mohammed N, Ahmed SA, Hegazy NI, Kashishy K. Ameliorative effects of hesperidin and N-acetylcysteine against formaldehyde-induced-hemato- and genotoxicity. Toxicol Res (Camb). 2021;10:992-1002.
45. Squillacioti G, Bellisario V, Grosso A, Ghelli F, Piccioni P, Grignani E, et al. formaldehyde, oxidative stress, and FeNO in traffic police officers working in two cities of northern Italy. Int J Environ Res Public Health. 2020;17:1655.
46. Teng S, Beard K, Pourahmad J, Moridani M, Easson E, Poon R, et al. The formaldehyde metabolic detoxification enzyme systems and molecular cytotoxic mechanism in isolated rat hepatocytes. Chem Biol Interact. 2001;130-132:285-96.
47. Sarsılmaz M, Özen OA, Özyurt H. The Evaluation of the enzymatic antioxidan system of liver after the subacute and subchronic inhalation of formaldehyde in Rats. Van Med J. 2000;7:84-9.
48. Kriebel D, Myers D, Cheng M, Woskie S, Cocanour B. Short-term effects of formaldehyde on peak expiratory flow and irritant symptoms. Arch Environ Health. 2001;56:11-8.
49. Pan L, Cho KS, Yi I, To CH, Chen DF, Do CW. Baicalein, Baicalin, and Wogonin: protective effects against ıschemia-ınduced neurodegeneration in the brain and Retina. Oxid Med Cell Longev. 2021;2021:8377362.
50. Ren M, Zhao Y, He Z, Lin J, Xu C, Liu F, et al. B Baicalein inhibits inflammatory response and promotes osteogenic activity in periodontal ligament cells challenged with lipopolysaccharides. BMC Complement Med Ther. 2021;21:43.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.19327
Nam Kem Med J 2024;12(4):252-259

Investigation of Eating Disorders and Hypoglycemia Awareness in People with Type 2 Diabetes

Tip 2 Diyabetli Kişilerde Yeme Bozukluklarının ve Hipoglisemi Farkındalığının Araştırılması

Lütfiye KODAZ, Sibel TUNÇ KARAMAN, Okcan BASAT

University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey

ABSTRACT

Aim: This study aimed to investigate type 2 diabetics in terms of eating disorders (ED) and hypoglycemia awareness (HA).

Materials and Methods: This cross-sectional study was conducted with type 2 diabetics who applied to the Family Medicine Outpatient Clinic of a tertiary hospital between January and June 2022 and met the inclusion criteria. The Descriptive Information Form, Munich Eating and Feeding Disorder Questionnaire (Munich ED-quest), and The Gold Questionnaire (GQ) were used to obtain data. Measured fasting plasma glucose and HbA1c levels and anthropometric measurements were recorded.

Results: Of the 148 participants with an average age of 53.56±7.61 years (min: 28-max: 65), 62.8% (n=93) were female. Munich ED-(FPG) scores were 22.49±19.68 for overall condition. Subscale scores were 5.12±11.50 for "preoccupation with figure and weight", 17.16±10.93 for "bingeing and vomiting", and 0.22±0.95 for "inappropriate compensatory behavior". The average GQ score of participants who stated that they had previously experienced hypoglycemia (n=78; 52.7%) was 1.50±1.03 and impaired HA was detected in 7.7%. No significant correlation was found between GQ and Munich ED-quest scores. A significant relationship was observed between body mass index (BMI) and age and Munich ED-quest total score (r=0.215, p=0.009; r=-0.274, p=0.001, respectively). A significant difference was found between gender and Munich ED-quest total score (p=0.007).

Conclusion: The overall risk of ED was found to be low in people with type 2 diabetes. However, binge eating was the type of ED with the highest risk. Impaired HA was detected in 7.7% of those who stated that they had previously experienced hypoglycemia. Although no significant relationship was found between ED and HA in our study population, the possibility of ED development over time should be taken into consideration. Especially patients at risk for ED (young people, women and those with high BMI) should be followed more closely in this context.

Keywords: Diabetes mellitus, hypoglycemia, hypoglycemia awareness, eating disorders

ÖZ

Amaç: Bu çalışmada tip 2 diyabetlilerin yeme bozukluğu (YB) ve hipoglisemi farkındalığı (HF) açısından incelenmesi amaçlandı.

Gereç ve Yöntem: Bu kesitsel çalışma üçüncü basamak bir hastanenin Aile Hekimliği Polikliniği'ne Ocak-Haziran 2022 tarihleri arasında başvuran ve çalışmaya dahil etme kriterlerini karşılayan tip 2 diyabetliler ile gerçekleştirildi. Verilerin elde edilmesinde Tanıtıcı Bilgi Formu, Münih Yeme ve Beslenme Bozuklukları Anketi (MYBBA) ve Gold Anketi (GA) kullanıldı. Ölçülmüş açlık plazma glukozu ve HbA1c düzeyleri ile antropometrik ölçümler kaydedildi.

Bulgular: Yaş ortalaması 53,56±7,61 (min: 28-maks: 65) yıl olan 148 katılımcının %62,8'i (n=93) (APG) idi. MYBBA'dan alınan toplam puan genel durum için 22,49±19,68 idi. Alt boyut puanları; "şekil ve kilo ile meşgul olma'' için 5,12±11,50, "tıkınırcasına yeme ve kusma" için 17,16±10,93 ve "uygunsuz telafi edici davranış" için 0,22±0,95 idi. Daha önce hipoglisemi yaşadığını belirten katılımcıların (n=78; %52,7) GA ortalama puanı 1,50 ±1,03 olup %7,7'sinde Bozulmuş HF saptandı. GA ile MYBBA skorları arasında istatistiksel olarak anlamlı ilişki bulunmadı. Vücut kitle indeksi (VKİ) ve yaş ile MYBBA toplam puanı arasında anlamlı ilişki vardı (r=0,215 p=0,009; r=-0,274 p=0,001, sırasıyla). Cinsiyet ile MYBBA toplam puanı arasında anlamlı farklılık saptandı (p=0,007).

Sonuç: Tip 2 diyabetlilerde genel YB riski düşük bulundu. Ancak tıkınırcasına yeme, en yüksek riskli YB tipi idi. Daha önce hipoglisemi yaşadığını ifade edenlerin de %7,7'sinde bozulmuş HF saptandı. Her ne kadar bizim çalışma popülasyonumuzda YB ile HF arasında anlamlı ilişki bulunmamış olsa da,

Address for Correspondence: Sibel TUNÇ KARAMAN MD, University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey
E-mail: drsibeltunc@hotmail.com **ORCID ID:** orcid.org/0000-0003-1833-8758
Received: 08.05.2024 **Accepted**: 26.07.2024

zaman içerisinde YB gelişimi olabileceği göz önünde bulundurulmalıdır. Özellikle YB açısından riskli hastalar (genç yaştakiler, kadınlar ve VKİ yüksek olanlar) bu bağlamda daha sıkı takip edilmelidir.

Anahtar Kelimeler: Diabetes mellitus, hipoglisemi, hipoglisemi farkındalığı, yeme bozuklukları

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and the potential for acute and chronic complications to manifest during its progression[1]. Hypoglycemia, an acute complication of diabetes, is marked by a decrease in plasma glucose concentration and can arise from various factors such as glycemia-directed therapies, low-carbohydrate diets, and physical exertion[2].

The symptoms and manifestations of hypoglycemia can vary depending on its severity and individual factors. Timely recognition of hypoglycemia symptoms empowers individuals to take corrective measures to restore their blood glucose levels. However, impaired ability to detect hypoglycemia symptoms at its onset is termed impaired awareness of hypoglycemia (IAH)[3]. IAH is a complication associated with glucose-lowering therapies in individuals with both type 1 and type 2 diabetes[4]. Various assessment methods exist for evaluating IAH in people with diabetes, and the prevalence may differ based on the chosen methodology[5-7]. Recurrent, untreated episodes of non-severe hypoglycemia can lead to IAH, predisposing individuals to severe hypoglycemic events[8]. Therefore, activities aiming at raising awareness about hypoglycemia recognition and prevention are crucial[9].

Eating disorders (ED) are psychiatric disorders characterized by severe disturbances in eating behavior and body weight[10]. Diabetes has been previously linked to a heightened risk of ED[11]. Binge eating disorder (BED) is particularly prevalent among individuals diagnosed with type 2 diabetes[12]. Inappropriate caloric intake in these individuals may compromise insulin activity and secretion, leading to glycemic fluctuations consequently impacting diabetes management[13]. As a result, ED can exacerbate complications, mortality rates, and overall morbidity in individuals with diabetes[14].

It is noteworthy that it is emphasized in the literature that hypoglycemia awareness (HA) is observed more frequently in type 1 diabetics and in diabetics who use long-term insulin. This study aimed to examine people with type 2 diabetes in terms of ED and HA.

MATERIALS AND METHODS

Study Design

This study employed a cross-sectional design. It was conducted between January 24, 2022 and June 5, 2022, with type 2 diabetic individuals aged 18 years and over, who applied to the family medicine outpatient clinic of a tertiary hospital for any reason and met the inclusion criteria for the study.

Selection and Description of the Cases

The study comprised of 148 volunteers aged 18 years and above, having the diagnosis of type 2 diabetes for at least 1 year, with no known diagnosis of ED, no serious psychiatric illnesses, and not taking any medication. Exclusions were made for individuals under 18 years, those with less than 1 year of type 2 diabetes duration, gestational diabetes, type 1 diabetes, communication barriers (such as hearing and speech impairments, cognitive dysfunction, inability to cooperate), and for illiterate individuals.

Data Collection Tools

For data collection, a Descriptive Information Form, the Turkish version of the Munich Eating and Feeding Disorders Questionnaire (Munich ED-quest), and the Gold Questionnaire were utilized.

Descriptive Information Form

The form, developed based on existing literature, inquired about sociodemographic details (age, gender, educational status) and diabetes-related factors (type, duration, treatment, presence of complications, diet compliance, hypoglycemia, and frequency and timing of blood glucose monitoring). Height, weight measurements, and body mass index (BMI) calculations were recorded. Additionally, fasting plasma glucose (FPG) and HbA1c levels were measured and recorded.

Turkish Version of the Munich Eating and Feeding Disorders Questionnaire

The Munich ED-quest was developed by Fichter et al.[15] in 2015 to assess ED symptoms in individuals aged 12-65 years. It was translated into Turkish by Öngün-Yılmaz[16] in 2020. The scale evaluates symptoms over two-time frames, as "current" (in the last three months) and "worst case in the past." The original version includes three subscales: "preoccupation with figure and weight," "bingeing and vomiting," and "inappropriate compensatory behavior." Total scores, derived from subscale items, indicate symptom severity, with a higher score indicating more severe symptoms. The scale demonstrated a Cronbach's alpha value of 0.940.

The Gold Questionnaire

In our study, we utilized The Gold Questionnaire, developed by Gold et al.[5] in 1994, to assess the HA of participants who reported previous experiences with hypoglycemia. This questionnaire employs a visual analog measurement scoring system, consisting of a single question: "Do you notice when your blood glucose drops below 60 mg/dL?" Responses are rated on a 7-point Likert scale. Scores of four and above indicate the presence of IAH. Ethical permission to perform this study was approved by the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Local Ethics Committee (decision no: 14, date: 19.01.2022). The study adhered to the principles outlined in the Declaration of Helsinki. All participants provided informed consent before inclusion in the study, and necessary permissions were obtained.

Statistical Analysis

Statistical analyses was conducted using IBM SPSS Statistics 25.0. Descriptive statistics (frequency, mean, standard deviation) were utilized for data presentation. As the continuous data did not follow a normal distribution (Kolmogorov-Smirnov values $p<0.05$), Non-parametric tests including the Mann-Whitney U test and the Kruskal-Wallis H test were employed to assess significant differences between total and sub-dimension scores of the scale and sociodemographic variables. The Games-Howell Post-Hoc test was applied to identify significant differences between groups where applicable. Spearman correlation analysis was used to examine relationships between continuous variables, while the chi-square test was utilized for comparing categorical variables. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

This study involved 148 participants with a mean age of 53.56±7.61 years (range: 28-65). The average duration of diabetes was 8.72±5.86 years, with mean FPG levels at 160.59±66.51 mg/dL and mean HbA1c levels at 7.77±1.97%. Sociodemographic and diabetes-related characteristics of the participants are summarized in Table 1.

Participant responses regarding blood glucose monitoring and hypoglycemia are detailed in Table 2. Among the participants, 78 (52.7%) reported experiencing hypoglycemia at some point. The prevalence of self-reported mild and severe hypoglycemia within the past year was 3.4% and 1.4%, respectively.

Descriptive statistics of total and sub-dimension scores from the scales are presented in Table 3. Munich ED-quest total scores averaged 22.49±19.68 (range: 0-122), with "last three months" scores at 12.14±8.68 (range: 0-52) and "worst case in the past" scores at 10.35±12.63 (range: 0-77). Among those who experienced hypoglycemia, the average Gold Questionnaire score was 1.50±1.03, with 7.7% (n=6) exhibiting IAH.

Table 4 presents correlation analysis results examining relationships between scale scores and various variables. Positive, statistically significant correlations were observed between BMI and Munich ED-quest scores, both "last three months" and "worst case in the past" ($r=0.215$, $p=0.009$; $r=0.295$, $p<0.001$, respectively). Additionally, a significant negative correlation was found between age and Munich ED-quest total scores, as well as "last three months" and "worst case in the past" scores ($r=-0.274$, $p=0.001$; $r=-0.269$, $p=0.001$; $r=-0.255$, $p=0.002$, respectively).

Analysis results comparing scale scores across various variables are presented in Table 5. Significant differences were observed in

Table 1. Baseline characteristics of the study participants (n=148)

Variables	Groups	n	%
Gender	Female	93	62.8
	Male	55	37.2
Education level	Literate	22	14.9
	Primary school	89	60.1
	Middle school	10	6.8
	High school	20	13.5
	University	7	4.7
Groups according to body mass index	Weak (n=1) and normal (n=12)	13	8.8
	Overweight	54	36.5
	Obese	81	54.7
Diabetes treatment	Oral antidiabetic drug	99	66.9
	Insulin	7	4.7
	Combined treatment	42	28.4
Compliance with diet	Yes	49	33.1
	Partially	72	48.6
	No	27	18.2
Presence of complication	No	99	66.9
	Yes	49	33.1
	Median (min-max)	**Mean ± SD**	
Age (years)	55.0 (28.0-65.0)	53.56±7.61	
Body mass index (kg/m²)	30.42 (17.30-54.82)	31.55±5.57	
Fasting plasma glucose (mg/dL)	142.0 (68.0-404.0)	160.59±66.51	
HbA1c (%)	7.10 (5.30-16.10)	7.77±1.97	
Diabetes duration (years)	8.0 (1.0-26.0)	8.72±5.86	
Number of insulin units	42.0 (1.0-110.0)	42.49±27.04	
Number of oral antidiabetic drugs	1.0 (1.0-3.0)	1.58±0.69	

Data are given as n (%), median, min-max, mean ± SD values. SD: Standard deviation, min-max: Minimum-maximum

Table 2. Participants' characteristics regarding blood glucose monitoring and hypoglycemia

Variables	Groups	n	%
Frequency of blood glucose monitoring	1-2 times	48	32.4
	3 and above	10	6.8
	Never	27	18.2
	Irregular	63	42.6
Blood glucose monitoring time*	Random	66	22.5
	Before meal	79	27.0
	After meal	47	16.0
	Night	5	1.7
	When you feel bad	96	32.8
Frequency of hypoglycemia	None	70	47.3
	Rarely	42	28.4
	Sometimes	22	14.9
	Often/Always (n=2)	14	9.5
HA status according to the Gold Questionnaire (n=78)	Impaired HA	6	7.7
	Normal HA	72	92.3

Data are presented as n (%). HA: Hypoglycemia awareness. *Since the answers contain multiple answers, the number (n) exceeds the sample size: Participants could choose more than one option for the relevant question since blood sugar monitoring could occur at different periods

Table 3. Descriptive statistics of total and sub-dimension scores of the scales

	Median	Min-max	Mean ± SD
Gold Questionnaire score (n=78)	1.0	1.0-5.0	1.50±1.03
Munich ED-quest total score (n=148)	18.00	0-122	22.49±19.68
Preoccupation with figure and weight	0.00	0-77	5.12±11.50
Bingeing and vomiting	16.00	0-53	17.16±10.93
Inappropriate compensatory behavior	0.00	0-6	0.22±0.95
In the last three months (current)	10.00	0-52	12.14±8.68
Preoccupation with figure and weight	0.00	0-25	1.67±3.95
Bingeing and vomiting	10.00	0-27	10.45±6.11
Inappropriate compensatory behavior	0.00	0-3	0.02±0.24
The worst case in the past	6.50	0-77	10.35±12.63
Preoccupation with figure and weight	0.00	0-52	3.45±8.56
Bingeing and vomiting	6.00	0-30	6.70±6.11
Inappropriate compensatory behavior	0.00	0-6	0.20±0.86

Data are given as median, min-max, mean ± SD values. Munich ED-quest: Munich Eating and Feeding Disorders Questionnaire, SD: Standard deviation, Min-max: Minimum-maximum

Munich ED-quest total scores and "last three months" and "worst case in the past" scores between genders, with higher scores reported in women (p=0.007; p=0.003; p=0.038, respectively).

However, no significant correlation was found between BMI, FPG, HbA1c, diabetes duration, insulin treatment regimens, and Gold Questionnaire scores.

DISCUSSION

This study aimed to investigate ED and HA among individuals diagnosed with type 2 diabetes. While the risk of ED was found to be low based on the scale scores obtained, there was a heightened risk of binge eating. Among participants, 52.7% reported previous experiences with hypoglycemia, with IAH detected in 7.7% of these individuals. However, no significant relationship was found between HA and ED.

It is well-established that individuals with type 2 diabetes face an increased risk of developing ED, characterized by significant disruptions in eating behavior and body weight. The association between diabetes and the risk of BED is extensively documented in the literature[17-21]. In the development study of the Munich ED-quest, individuals with ED exhibited higher mean scores compared to community controls[15]. Similarly, in the adaptation of the Munich ED-quest into Turkish, the mean total scores were reported as 29.94±23.40 (current) and 28.88±23.72 (worst case in the past)[16]. In our study, the Munich ED-quest general total score was 22.49±19.68. Notably, all scores obtained from the scale were lower than the literature average. However, "bingeing and vomiting" sub-dimension scores were higher than other sub-dimensions, consistent with previous literature findings. Disparities in sociodemographic and clinical characteristics among participants across studies, variations in exclusion criteria, and the use of different revisions for diagnosis may contribute to the wide range of prevalence reported in the literature.

Numerous factors contribute to the heightened risk of ED among individuals with diabetes. Research focusing on the ED status in people with type 2 diabetes indicates that age plays a significant role in disordered eating behaviors, with a higher prevalence observed among individuals under the age of 50 years[21]. Specifically, among type 2 diabetics, those reporting binge eating tend to be younger compared to those without an ED diagnosis[17,18]. Furthermore, evidence suggests that binge eating often precedes the onset of diabetes, with diabetes onset occurring earlier in individuals with this behavior pattern[19]. Consistent with existing literature, our study revealed a similar trend, wherein a decrease in participants' age correlated with an increased risk of both overall ED and binge eating. Given that young age is a notable risk factor for BED, particularly prevalent among individuals with type 2 diabetes, early screening for type 2 diabetes is warranted for this demographic.

Table 4. Correlation analysis of the relationships between scale scores and various variables

		1	2	3	4	5	6	7	8	9	10	11
1) Gold Questionnaire (n=78)	r	1										
	p	.										
2) Munich ED-quest-total score (n=148)	r	0.016	1									
	p	0.893	.									
3) Munich ED-quest-in the last three months score	r	-0.046	0.929**	1								
	p	0.690	**<0.001**	.								
4) Munich ED-quest score-the worst case in the past score	r	0.027	0.897**	0.691**	1							
	p	0.813	**<0.001**	**<0.001**	.							
5) Age	r	0.006	-0.274**	-0.269**	-0.255**	1						
	p	0.957	**0.001**	**0.001**	**0.002**	.						
6) Fasting plasma glucose	r	-0.010	-0.067	-0.076	-0.064	0.012	1					
	p	0.928	0.422	0.356	0.438	0.889	.					
7) HbA1c	r	-0.010	-0.106	-0.151	-0.051	0.055	0.712**	1				
	p	0.929	0.199	0.067	0.535	0.505	**<0.001**	.				
8) Body mass index	r	0.026	0.215**	0.295**	0.095	-0.102	-0.095	-0.207*	1			
	p	0.819	**0.009**	**<0.001**	0.252	0.216	0.250	**0.011**	.			
9) Diabetes duration	r	0.059	-0.003	-0.069	0.056	0.235**	0.368**	0.473**	-0.150	1		
	p	0.605	0.970	0.405	0.497	**0.004**	**<0.001**	**<0.001**	0.070	.		
10) Numbers of oral antidiabetic drugs	r	-0.148	-0.051	-0.056	-0.041	0.118	0.192*	0.265**	-0.138	0.292**	1	
	p	0.209	0.549	0.512	0.63	0.162	**0.023**	**0.001**	0.102	**<0.001**	.	
11) Numbers of insulin units	r	0.383*	0.015	-0.055	0.119	0.016	0.128	0.037	0.134	0.204	0.131	1
		0.034	0.92	0.710	0.415	0.916	0.381	0.800	0.359	0.16	0.407	.

*Correlation is significant at the level of 0.05 (Spearman correlation test), **Correlation is significant at the level of 0.01, (Spearman correlation test), Munich ED-quest: Munich Eating and Feeding Disorders Questionnaire

Similar to the general population, females exhibit a higher prevalence of ED among individuals with type 2 diabetes[17,21,22]. However, contrasting findings have been reported by García-Mayor et al.[20], highlighting a more significant association between BED and type 2 diabetes in men, while Nicolau et al.[18] found no significant gender-based difference in BED prevalence among individuals with type 2 diabetes. In alignment with existing literature, our study indicated that women had higher ED scores compared to men.

Research has indicated a relationship between longer years of education and binge eating behaviors in individuals with type 2 diabetes[22,23]. Consistently, our study revealed higher Munich ED-quest scores (worst case in the past) among university graduates compared to other educational groups. This association may stem from increased awareness and knowledge regarding dietary habits among individuals with higher education levels.

Certain types of ED are associated with an increase in BMI due to individuals' eating behaviors. Notably, individuals with type 2 diabetes and BED tend to have higher BMI compared to those without BED. Obesity, often linked to ED, poses a significant challenge in managing type 2 diabetes[17,21,22,24]. In line with existing literature, our study found that Munich ED-quest total scores (for the last 3 months) increased with higher BMI values.

The impact of ED on the metabolic control of type 2 diabetes remains unclear and most studies have failed to establish a significant relationship[14,17,21,24,25]. Similarly, a study investigating the clinical, biochemical, and psychological effects of ED on individuals with type 2 diabetes found no significant differences in glycemic parameters between those with and without BED[18]. Consistent with the literature, no significant relationship was found in our study between metabolic control (assessed by FBG and HbA1c levels) and Munich ED-quest scores. However, irrespective of HbA1c levels, behaviors such as consuming large quantities of food in a short timeframe and prolonged fasting may induce short-term glycemic variability in individuals with

Table 5. Evaluation of the relationship between various variables and scale scores

		Munich ED-quest scores (n=148)			HA according to the GQ (n=78)	
Variables		**Total score**	**In the last three months**	**The worst case in the past**	**Impaired HA (n=6)**	**Normal HA (n=72)**
Gender	n	Mean ± SD	Mean ± SD	Mean ± SD	n (%)	n (%)
Female	93	24.73±18.79	13.53±8.66	11.20±11.70	6 (12.2)	43 (87.8)
Male	55	18.70±20.72	9.80±8.27	8.91±14.08	0 (0)	29 (100)
	p	[1]**0.007**	[1]**0.003**	**10.038**	0.079[a]	
Education level	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**n (%)**	**n (%)**
1) Literate	22	21.22±19.79	11.82±7.19	9.41±13.33	2 (22.2)	7 (77.8)
2) Primary school	89	21.42±16.52	12.45±8.76	8.98±9.03	4 (8.9)	41 (91.1)
3) Middle school	10	16.20±9.56	9.50±6.28	6.70±5.79	0 (0)	5 (100)
4) High school	20	22.40±20.02	10.55±7.12	11.85±13.87	0 (0)	13 (100)
5) University	7	49.28±42.18	17.57±16.24	31.71±29.00	0 (0)	6 (100)
	p	[2]**0.005**	20.754	[2]**0.026**	0.353[a]	
Groups according to body mass index	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**n (%)**	**n (%)**
1) Weak/normal	13	14.46±12.85	8.00±6.73	6.46±6.84	0 (0)	7 (100)
2) Overweight	54	21.85±22.18	10.81±8.21	11.04±15.24	1 (3.2)	30 (96.8)
3) Obese	81	24.21±18.64	13.69±8.98	10.52±11.39	5 (12.5)	35 (87.5)
	p	[2]**0.104**	[2]**0.020**	[2]**0.385**	0.345[a]	
Diabetes treatment	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**n (%)**	**n (%)**
1) Oral antidiabetic drugs	99	24.41±20.06	13.07±8.66	11.34±13.44	4 (8.3)	44 (91.7)
2) Insulin	7	24.86±15.08	13.00±8.19	11.86±7.03	0 (0)	4 (100)
3) Combined treatment	42	17.57±18.95	9.81±8.57	7.76±11.14	2 (7.7)	24 (92.3)
	p	[2]**0.062**	[2]**0.054**	[2]**0.103**	1.000[a]	
Compliance with diet	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**n (%)**	**n (%)**
1) Yes	49	19.08±11.06	10.61±6.02	8.47±6.25	3 (10)	27 (90)
2) Partially	72	24.28±19.30	13.21±8.48	11.07±12.48	1 (2.7)	36 (97.3)
3) No	27	23.93±30.24	12.07±12.46	11.85±19.88	2 (18.2)	9 (81.8)
	p	[2]0.137	[2]0.121	[2]0.236	0.143[a]	
Number of blood glucose monitoring	**n**	**Mean ± SD**	**Mean±SD**	**Mean ± SD**	**n (%)**	**n (%)**
1) 1-2 times	48	20.69±19.22	10.38±7.15	10.31±13.93	1 (3.2)	30 (96.8)
2) 3 and above	10	19.00±25.52	11.2±14.47	7.80±11.20	1 (16.7)	5 (83.3)
3) Never	27	28.59±26.28	15.07±10.91	13.52±16.37	0 (0)	8 (100)
4) Irregular	63	21.81±15.27	12.38±7.30	9.43±9.74	4 (12.1)	29 (87.9)
	p	[2]0.257	[2]0.109	[2]0.539	0.349[a]	
Frequency of hypoglycemia	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**n (%)**	**n (%)**
1) None	70	22.10±21.41	12.37±10.00	9.73±12.59	-	-
2) Rarely	42	25.00±18.92	12.21±7.14	12.79±14.09	3 (7.1)	39 (92.9)
3) Sometimes	22	17.73±10.1	11.05±6.43	6.68±5.52	2 (9.1)	20 (90.9)
4) Often/Always (n=2)	14	24.43±24.28	12.5±9.58	11.93±15.57	1 (7.1)	13 (92.9)
	p	[2]0.549	[2]0.936	[2]0.286	1.000[a]	

Data are given as n (%) and mean ± SD values. [1]Mann-Whitney U test, [2]KV: Kruskal-Wallis, [a]Fisher's exact test, p<0.05, Munich ED-quest: Munich Eating and Feeding Disorders Questionnaire, HA: Hypoglycemia awareness, GQ: Gold Questionnaire, SD: Standard deviation

BED. Hence, further exploration of the relationship between BED and glycemic variability is warranted.

Several methods have been developed to assess IAH[5,6,7]. IAH prevalence may vary depending on the diabetes-related variables of the patients as well as the methodology used. A

meta-analysis of 62 studies encompassing type 1 and type 2 diabetes reported a prevalence of 26.2% using the Gold score[4]. Additionally, multinational studies have documented prevalence rates ranging from 20.2% to 27.9% in type 2 diabetes[26,27]. Among type 2 diabetics treated with insulin, prevalence rates of up to 10% have been reported[28]. Studies conducted in our country have reported IAH prevalence rates among type 2 diabetics ranging from 10.7% to 38.5%[29,30]. In our study, 52.7% (n=78) of participants reported experiencing hypoglycemia at any frequency and severity, with IAH observed in 7.7% of these individuals. Although HA has been predominantly emphasized in type 1 diabetics and long-term insulin users, it is acknowledged that the incidence of hypoglycemia may rise in type 2 diabetics due to glycemia-directed therapies. Our study concluded that the rate of IAH was lower than reported in the literature, likely due to the relatively small number of individuals using insulin alone or in combination with oral antidiabetic drugs.

Study Limitations

Our study has two primary limitations. Firstly, the single-center and cross-sectional design, along with the relatively small sample size, may restrict the generalizability of the findings to the broader population. Secondly, the lack of participant follow-up poses a limitation. Although our initial evaluation found no relationship between ED and HA in our study population, the potential development of ED during follow-up should be considered. Future contributions to the literature should aim for larger sample sizes and multicenter studies with patient follow-up to address these limitations. The strength of our study lies in being the first in our country to explore the relationship between ED and HA in individuals with type 2 diabetes.

CONCLUSION

Our findings suggest that while the overall risk of ED was low, the risk of binge eating was elevated among individuals with type 2 diabetes. 7.7% of those reporting hypoglycemia experienced impaired awareness but no significant relationship was observed between HA and ED. However, the possibility of developing ED over time should still be considered. Clinicians should consider psychiatric consultation for patients with type 2 diabetes displaying disordered eating attitudes. Raising patient awareness about hypoglycemia may help deter disordered eating behaviors.

Ethics

Ethics Committee Approval: Ethical permission to perform this study was approved by the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Local Ethics Committee (decision no: 14, date: 19.01.2022).

Informed Consent: All participants provided informed consent before inclusion in the study, and necessary permissions were obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: L.K., S.T.K., O.B., Concept: L.K., S.T.K., O.B., Design: L.K., S.T.K., O.B., Data Collection or Processing: L.K., S.T.K., O.B., Analysis or Interpretation: L.K., S.T.K., Literature Search: L.K., S.T.K., Writing: L.K., S.T.K., O.B.

Conflict of Interest: One author of this article, (Okcan BASAT) is a member of the Editorial Board of the Namık Kemal Medical Journal. However, he did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interes.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Complications Diagnosis, Treatment and Monitoring Guide 2022. Available at: https://file.temd.org.tr/Uploads/publications/guides/documents/diabetes-mellitus_2022.pdf Access date: 24.09.2023
2. International hypoglycaemia study group. Minimizing hypoglycemia in diabetes. Diabetes Care. 2015;38:1583-91.
3. Frier BM. Impaired awareness of hypoglycaemia. In: Frier BM, Heller SR, McCrimmon RJ (eds), Hypoglycaemia in clinical diabetes. India: Wiley, 2014;114-44.
4. Yu X, Fan M, Zhao X, Ding Y, Liu X, Yang S, et al. Prevalence of impaired awareness of hypoglycaemia in people with diabetes mellitus: A systematic review and meta-analysis from 21 countries and regions. Diabet Med. 2023;40:e15129.
5. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994;17:697-703.
6. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care. 1995;18:517-22.
7. Pedersen-Bjergaard U, Agerholm-Larsen B, Pramming S, Hougaard P, Thorsteinsson B. Activity of angiotensin-converting enzyme and risk of severe hypoglycaemia in type 1 diabetes mellitus. Lancet. 2001;357:1248-53.
8. Li XN, Kan YS, Liu HY, Pang J, He YY, Liu L, et al. Prevalence and contributing factors of impaired awareness of hypoglycemia in patients with type 2 diabetes: a meta-analysis. Acta Diabetol. 2023;60:1155-69.
9. Farrell CM, McCrimmon RJ. Clinical approaches to treat impaired awareness of hypoglycaemia. Ther Adv Endocrinol Metab. 2021;12:20420188211000248.
10. Galmiche M, Déchelotte P, Lambert G, Tavolacci MP. Prevalence of eating disorders over the 2000-2018 period: a systematic literature review. Am J Clin Nutr. 2019;109:1402-13.
11. Winston AP. Eating disorders and diabetes. Curr Diab Rep. 2020;20:32.
12. Chevinsky JD, Wadden TA, Chao AM. Binge eating disorder in patients with type 2 diabetes: diagnostic and management challenges. Diabetes Metab Syndr Obes. 2020;13:1117-31.

13. Salvia MG, Ritholz MD, Craigen KLE, Quatromoni PA. Managing type 2 diabetes or prediabetes and binge eating disorder: a qualitative study of patients' perceptions and lived experiences. J Eat Disord. 2022;10:148.

14. Abbott S, Dindol N, Tahrani AA, Piya MK. Binge eating disorder and night eating syndrome in adults with type 2 diabetes: a systematic review. J Eat Disord. 2018;6:36.

15. Fichter MM, Quadflieg N, Gierk B, Voderholzer U, Heuser J. The Munich eating and feeding disorder questionnaire (Munich ED-Quest) DSM-5/ICD-10: validity, reliability, sensitivity to change and norms. Eur Eat Disord Rev. 2015;23:229-40.

16. Öngün-Yılmaz H. The Turkish Version of the Munich Eating and Feeding Disorder Questionnaire: Factor structure, validity, and reliability. Alpha Psychiatry. 2020;21(Suppl 2):29-36.

17. Çelik S, Kayar Y, Önem Akçakaya R, Türkyılmaz Uyar E, Kalkan K, Yazısız V, et al. Correlation of binge eating disorder with level of depression and glycemic control in type 2 diabetes mellitus patients. Gen Hosp Psychiatry. 2015;37:116-9.

18. Nicolau J, Simó R, Sanchís P, Ayala L, Fortuny R, Zubillaga I, et al. Eating disorders are frequent among type 2 diabetic patients and are associated with worse metabolic and psychological outcomes: results from a cross-sectional study in primary and secondary care settings. Acta Diabetol. 2015;52:1037-44.

19. Gagnon C, Aimé A, Bélanger C. Predictors of comorbid eating disorders and diabetes in people with Type 1 and Type 2 Diabetes. Can J Diabetes. 2017;41:52-7.

20. García-Mayor RV, García-Soidán FJ, Barreira AS. Prevalence of eating disorders in ındividuals with type 2 diabetes: a cohort comparison of patients and controls. Experimental and Clinical Endocrinology & Diabetes Reports. 2017;4:7-9.

21. Petroni ML, Barbanti FA, Bonadonna R, Bruno G, Caletti MT, Croci M, et al. Dysfunctional eating in type 2 diabetes mellitus: A multicenter Italian study of socio-demographic and clinical associations. Nutr Metab Cardiovasc Dis. 2019;29:983-90.

22. Chao AM, Wadden TA, Gorin AA, Shaw Tronieri J, Pearl RL, Bakizada ZM, et al. Binge eating and weight loss outcomes in ındividuals with type 2 diabetes: 4-year results from the Look AHEAD Study. Obesity (Silver Spring). 2017;25:1830-7.

23. Shakeri Z, Mardali F, Azizabadi Farahani M, Alemrajabi M, Mottaghi A. Comparison of eating disorders and eating behaviors in adults with and without type 2 diabetes prior to bariatric surgery. J Eat Disord. 2022;10:107.

24. Papelbaum M, de Oliveira Moreira R, Coutinho WF, Kupfer R, Freitas S, Raggio Luz R, Appolinario JC. Does binge-eating matter for glycemic control in type 2 diabetes patients? J Eat Disord. 2019;7:30.

25. Krishnamurthy A, Gupta Y, Bhargava R, Sharan P, Tandon N, Jyotsna VP. Evaluation of eating disorders and their association with glycemic control and metabolic parameters in adult patients with type 2 diabetes mellitus. Diabetes Metab Syndr. 2020;14:1555-61.

26. Ampudia-Blasco FJ, Artime E, Díaz S, Rubio M, Reviriego J, Mitchell B, et al. Conversations and Reactions Around Severe Hypoglycaemia (CRASH): Spanish results of a global survey of people with type 1 diabetes or insulin-treated type 2 diabetes and caregivers. Endocrinol Diabetes Nutr (Engl Ed). 2021;68:557-66.

27. Snoek FJ, Spaepen E, Nambu BA, Child CJ, Bajpai S, Balantac Z, et al. Conversations and reactions around severe hypoglycemia (CRASH) study: results from people with diabetes and caregivers in the United States. Clin Diabetes. 2022;40:477-88.

28. Macon EL, Devore MH, Lin YK, Music MB, Wooten M, McMullen CA, et al. Current and future therapies to treat impaired awareness of hypoglycemia. Front Pharmacol. 2023;24:1271814.

29. Emral R, Tetiker T, Sahin I, Sari R, Kaya A, Yetkin İ, et al. An international survey on hypoglycemia among insulin-treated type I and type II diabetes patients: Turkey cohort of the non-interventional IO HAT study. BMC endocr Disord. 2018;18:9.

30. Büyükkaya Besen D, Arda Sürücü H, Koşar C. Self-reported frequency, severity of, and awareness of hypoglycemia in type 2 diabetes patients in Turkey. PeerJ. 2016;4:e2700.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.12599
Nam Kem Med J 2024;12(4):260-265

Does Delta Hemoglobin-Albumin-Lymphocyte Platelet (HALP) Score Predict the Risk of Early Progression in Patients Treated with CDK4/6 Inhibitors?

Delta Hemoglobin-Albümin-Lenfosit-Trombosit (HALP) Skoru Metastatik Meme Kanserinde CDK4/6 İnhitibitörü ile Erken Progresyon Riskini Predikte Eder mi?

Burcu Belen GÜLBAĞCI[1], Miraç ÖZEN[2], Esra ÖZEN ENGİN[3], Fatma AKDAĞ KAHVECİOĞLU[3], Esra ÇİFTÇİ[4], İlhan HACIBEKİROĞLU[3]

[1]*Tekirdağ İsmail Fehmi Cumalıoğlu State Hospital, Clinic of Medical Oncology, Tekirdağ, Turkey*
[2]*Asklepios Clinic Triberg, Clinic of Hematology, Schwarzwald, Germany*
[3]*Sakarya University Training and Research Hospital, Clinic of Medical Oncology, Sakarya, Turkey*
[4]*Sakarya University Training and Research Hospital, Clinic of Nuclear Medicine, Sakarya, Turkey*

ABSTRACT

Aim: This study aims to determine the predictive value of dynamic change in hemoglobin-albumin-lymphocyte-platelet (HALP) score on treatment response in hormone-positive metastatic breast cancer patients receiving cyclin-dependent kinase (CDK) 4/6 inhibitors.

Materials and Methods: This study was designed retrospectively. Between January 1, 2020, and September 30, 2023, 104 patients diagnosed with metastatic hormone receptor-positive/human epidermal growth factor 2 receptor negative breast cancer were treated with CDK4/6 inhibitors plus endocrine therapies at Sakarya University Training and Research Hospital. Patients were divided into two groups according to whether there was progression at the initial response evaluation. Factors that could predict treatment response between the two groups were compared with regression analysis.

Results: The median HALP score in patients was 34.08 (23.46-45.08) before treatment and 28.3 (19.24-42.61) at first response evaluation. Delta HALP was ≤0 for sixty-four (61.5%) patients, >0 for 40 patients (38.5%). There was no statistical difference in delta HALP score between groups with and without progression at the first response evaluation (p=0.334). The presence of liver metastasis and treatment line significantly affect the early progression by univariate and multivariate regression analysis (p=0.031 and p=0.016, respectively).

Conclusion: Our study has found that the delta HALP score does not predict early progression. The presence of liver metastasis and later treatment line were found to be statistically significant with early progression. These data are compatible with the literature.

Keywords: Cyclin-dependent kinase (CDK) 4/6 inhibitors, delta HALP score, hemoglobin-albumin-lymphocyte-platelet (HALP) score

ÖZ

Amaç: Bu çalışma, siklin bağımlı kinaz (CDK) 4/6 inhibitörleri alan hormon reseptörü pozitif/insan epidermal büyüme faktörü 2 reseptörü negatif (HR+/HER2-) metastatik meme kanseri hastalarında hemoglobin-albümin-lenfosit-trombosit (HALP) skorundaki tedavi başlangıcına göre olan değişimin tedavi yanıtını predikte edip etmediğini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Retrospektif olarak tasarlanan çalışmamıza Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi'nde 1 Ocak 2020-30 Eylül 2023 tarihleri arasında HR+/HER2- metastatik meme kanseri tanısıyla CDK4/6 inhibitörü tedavisi alan 104 hasta dahil edildi. Hastalar ilk yanıt değerlendirmede progresyon durumuna göre iki gruba ayrıldı. İki grup arasında tedavi yanıtını predikte edebilecek klinik ve patolojik faktörler tek değişkenli ve çok değişkenli regresyon analizi ile karşılaştırıldı.

Bulgular: Hastaların ortalama HALP skoru CDK4/6 inhibitörü tedavisi öncesi 34,08 (23,46-45,08), ilk yanıt değerlendirmede 28,3 (19,24-42,61)

Address for Correspondence: Burcu Belen GÜLBAĞCI MD, Tekirdağ İsmail Fehmi Cumalıoğlu State Hospital, Clinic of Medical Oncology, Tekirdağ, Turkey
E-mail: burcubln@gmail.com **ORCID ID:** orcid.org/0000-0002-5720-8254
Received: 13.05.2024 **Accepted**: 06.08.2024

idi. Altmış dört (%61,5) hastanın delta HALP değeri ≤0; 40 hastanın (%38,5) >0 olduğu görüldü. İlk yanıt değerlendirmede progresyon görülen ve görülmeyen hastalar arasında delta HALP skoru açısından istatistiksel fark saptanmadı (p=0,334). Karaciğer metastazı varlığı ve tedavi basamağının, tek değişkenli ve çok değişkenli regresyon analizinde erken progresyonu anlamlı olarak etkilediği görüldü (sırasıyla p=0,031; p=0,016).

Sonuç: Çalışmamıza göre delta HALP skoru erken progresyonu predikte etmemektedir. Karaciğer metastazı varlığı ve ileri basamaklarda kullanım erken progresyon için önemli iki risk faktörüdür. Bu veriler literatürle uyumludur.

Anahtar Kelimeler: Delta HALP skoru, hemoglobin-albümin-lenfosit-trombosit (HALP) skoru, siklin bağımlı kinaz (CDK) 4/6 inhibitörü

INTRODUCTION

Hormone receptor-positive/human epidermal growth factor 2 receptor negative (HR+/HER2-) patients account for 70% of all metastatic breast cancers. The metastasis is most commonly seen in the bone, lung, liver, and brain, respectively[1]. In HR+/HER2- metastatic breast cancer, a significant progression-free survival (PFS) benefit has been obtained with cyclin-dependent kinase 4/6 (CDK4/6) inhibitor and endocrine therapy combinations in the first-line treatment. The objective response rates (ORRs) with CDK4/6 inhibitors are 76%, yet a subset of patients fail to respond despite being classified as hormone positive[2,3].

Immunonutritional markers are valuable tools for predicting and assessing cancer progression and treatment response[4-6]. The hemoglobin-albumin-lymphocyte-platelet (HALP) score is a laboratory parameter that shows nutritional and inflammatory status. The HALP score is calculated as HALP score = [hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)]/ platelets (/L), which was first described in gastric cancer in 2015 and has been shown to be effective as a biomarker in many types of cancer[7,8].

The HALP score, a composite index reflecting nutritional and inflammatory status, has emerged as a potential prognostic biomarker in various cancer types, including metastatic hormone-positive breast cancer. A lower HALP score has been correlated with more aggressive disease progression and poorer outcomes in metastatic breast cancer patients[9,10].

This study aims to determine the predictive value of dynamic change in HALP score and also clinicopathological characteristics on treatment response in hormone-positive metastatic breast cancer patients receiving CDK4/6 inhibitors.

MATERIALS AND METHODS

Study Population

This retrospective study included 104 patients diagnosed with metastatic HR+, HER2- breast cancer who received CDK4/6 inhibitor plus ET at Sakarya University Training and Research Hospital between January 1, 2020 and September 30, 2023. Patients were aged 18 years or older, with confirmed ER and or PR positivity and HER2- metastatic breast cancer. Inclusion criteria required treatment with CDK4/6 inhibitors as first to fourth-line therapy. Patients were allowed to switch between CDK4/6 inhibitors due to allergy, tolerability, or drug availability. Male breast cancer patients and those without completed treatment response assessments were excluded. The study protocol was approved by the Ethics Committee of Sakarya University Medical Faculty (decision no: 27.06.2024-71522473-050.04-372954-165, date: 27.06.2024) and conducted according to the principles of the Declaration of Helsinki. Given the retrospective study design, the need for informed consent was waived.

This retrospective study analyzed patient data (demographic, clinicopathological, outcome, treatment response, and laboratory parameters) obtained from medical oncology outpatient clinic records, patient files, and electronic health records. Due to local insurance regulations, patients received either oral ribociclib or palbociclib in combination with fulvestrant, an aromatase inhibitor, or tamoxifen as endocrine therapy. Tumor response was evaluated locally every 12 weeks using RECIST 1.1 criteria from treatment initiation. Patients were categorized into two groups based on disease progression status at the initial response assessment.

Patients were evaluated for hemogram and biochemical blood parameters simultaneously. The HALP score was calculated, as [hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)]/ platelets (/L) at the beginning of CDK4/6 inhibitors and first response evaluation. PFS was defined as the time from the date of initiation of ribociclib or palbociclib until the date of radiological progression. Overall survival (OS) was defined as the time from the date of initiation of ribociclib or palbociclib to the date of death from any cause.

Statistical Analysis

All analyses were performed on SPSS version 23 (SPSS Inc., Chicago, IL, USA). Histogram and Q-Q plots were used to determine whether variables were normally distributed. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. Between groups, an analysis of continuous variables was performed using the independent samples t-test or Mann-Whitney U test, depending on the normality of distribution. Age, gender, clinical

characteristics, laboratory results, and treatment methods were analyzed using univariate logistic regression. Then, the variables that were found significant were analyzed using the stepwise multivariate listening-reading method (enter method). The mean was employed to determine cut-off values for age. Survival times were calculated using the Kaplan-Meier method. Between groups, comparisons of survival times were performed using the log-rank test. ROC curve test was used to determine HALP's cut-off sign. P<0.05 values were accepted as statistically significant results.

RESULTS

A total of 104 patients were included in the study. The median age of the patients was 56±11.67 years (32-84). At the first response evaluation, 21 patients (%20) had progression. The median OS was 137.57 months [95% confidence interval (CI): 97.57-177.57]; the median PFS was 7.73 months (95% CI: 3.70-11.76) for all patients included in the study. All patients had a median HALP score of 34.08 (23.46-45.08) before treatment and 28.3 (19.24-42.61) at the first response evaluation Delta HALP was ≤0 for sixty-four (61.5%) patients and >0 for 40 patients (38.5%) was. There was no statistical difference in delta HALP score between groups with and without progression at the first response evaluation (p=0.334; Table 1). The cut-off value for the HALP score was 32.02 [area under the curve (AUC): 0.564]. At the beginning of treatment, 44 (42.3%) patients had a low HALP score, and 60 (57.7%) had a high score.

Patients who experienced early disease progression exhibited significantly higher mortality risk compared to those without progression (95% CI: 4.60-45.78, p<0.001). The median OS could not be calculated for patients without progression at the initial evaluation (95% CI: 100.15-256.56), while it was 13.43 months for patients with progression (95% CI: 12.65-99.21, p<0.001). A detailed comparison of patient characteristics between the two groups is presented in Table 1.

Survival Outcomes

The median OS was 110.87 months (95% CI: 56.62-166.12) for the palbociclib group and 137.57 months (95% CI: 100.81-174.33) for the ribociclib group. The median PFS was 8.2 months (95% CI: 3.14-13.26) for palbociclib and 7.6 months (95% CI: 5.30-9.9) for ribociclib. No statistically significant differences were observed in OS or PFS between the two treatment groups (p=0.888 and p=0.260, respectively) (Figure 1).

The presence of liver metastasis (LVM) and treatment line were statistically significant with early progression. The risk of early progression increased 4.03 times in patients with liver metastases (95% CI: 1.36-11.93; p=0.012). The progression risk was 6.24 times higher in patients receiving CDK4/6 inhibitors in the third and fourth lines (95% CI: 1.68-23.11; p=0.006).

Table 1. Comparison of clinical and pathological features of patients with and without progression at the first response evaluation

	Yes (n=21)	No (n=83)	p-value
	n (%)	n (%)	
Age (year)			
<56	12 (57.1)	40 (48.2)	0.464†
>56	9 (42.9)	43 (51.8)	
Menopause status			
Premenopause	10 (47.6)	32 (38.55)	0.572†
Postmenopause	11 (52.38)	51 (62.44)	
Delta HALP			
>0	10 (47.6)	30 (36.1)	0.334†
≤0	11 (52.4)	53 (63.9)	
Tumor location			
Left	9 (42.9)	47 (56.6)	0.528†
Right	11 (52.4)	33 (39.8)	
Left + Right	1 (4.8)	3 (3.6)	
Histology			
IDC	14 (66.7)	66 (79.5)	0.370†
ILC	5 (23.8)	10 (12.0)	
Others (IC. IDC+ILC. NOS)	2 (9.5)	7 (8.4)	
Progesterone receptor			
≥%1	21 (100.0)	75 (90.4)	0.139†
<%1	0 (0.0)	8 (9.6)	
HER2 status			
IHC score 1-2	5 (23.8)	25 (30.1)	0.568†
IHC score 0	16 (76.2)	58 (69.9)	
E-cadherin (IHC)			
Positive	11 (73.3)	29 (87.9)	0.210*
Negative	4 (26.7)	4 (12.1)	
Ki 67. labeling index. %			
<20	5 (35.7)	34 (54.0)	0.217†
≥20	9 (64.3)	29 (46.0)	
Nuclear grade			
1	3 (17.6)	20 (29.9)	0.241*
2	9 (52.9)	38 (56.7)	
3	5 (29.4)	9 (13.4)	
Neoadjuvant/ adjuvant treatment			
Yes	6 (28.6)	20 (24.1)	0.672†
No	15 (71.4)	63 (75.9)	
Operation primary tumor			
Yes	15 (72.4)	45 (54.2)	0.154†
No	6 (28.6)	38 (45.8)	
Bone metastasis			
Yes	15 (71.4)	70 (84.3)	0.17*
No	6 (28.6)	13 (15.7)	

Table 1. Continued

	Yes (n=21)	No (n=83)	
	n (%)	n (%)	p-value
Lung metastasis			
Yes	4 (19.0)	28 (33.7)	0.193†
No	17 (81.0)	55 (66.3)	
Liver metastasis			
Yes	8 (38.1)	11 (13.3)	**0.008***
No	13 (61.9)	72 (86.7)	
Brain metastasis			
Yes	1 (4.8)	3 (3.6)	0.807*
No	20 (95.2)	80 (96.4)	
Treatment line			
1-2	15 (71.5)	78 (94.0)	**0.003***
3-4	6 (28.5)	5 (6.0)	
CDK4/6 inhibitors			
Ribociclib	13 (61.9)	50 (60.2)	0.889*
Palbociclib	8 (38.1)	33 (39.8)	
Endocrine therapy			
Letrozole	9 (42.9)	50 (60.2)	0.34*
Fulvestrant	11 (52.4)	31 (37.3)	
Tamoxifene	1 (4.8)	2 (2.4)	
Dose reduction			
Yes	3 (14.3)	23 (27.7)	0.204†
No	18 (85.7)	60 (72.3)	
Exitus			
Yes	16 (76.2)	15 (18.1)	**<0.001†**
No	5 (23.8)	68 (81.9)	

HALP: Hemoglobin-albumin-lymphocyte-platelet, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, NOS: Not otherwise specified, HER2: Human epidermal growth factor receptor 2, IHC: Immunohistochemical, CDK: Cyclin dependent kinase. *Fisher's exact chi-square test, †Pearson chi-square test, bold mean p<0.05

The presence of LVM and treatment line also significantly affect the early progression by multivariate regression analysis (p=0.031; p=0.016; respectively) (Table 2).

DISCUSSION

CDK4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) are first-line treatments in HR+/HER2- metastatic breast cancer. In our study, progression was observed in 20% of a total of 104 patients diagnosed with metastatic breast cancer using CDK4/6 inhibitors at the first response evaluation. Early progression was significantly higher in patients who had LVM and received CDK4-6 inhibitors treatment at the 3-4th line (p=0.012, p=0.006, respectively). However, there is no statistical difference in delta HALP score between groups with and without progression at the first response evaluation (p=0.334).

HALP score is a biomarker that indirectly shows immunological and nutritional status that may affect treatment response in metastatic breast cancer. In early-stage breast cancer, a low HALP score was associated with poor recurrence-free survival, axillary lymph node involvement at the surgical stage, and poor neoadjuvant treatment response. Pancytopenia due to CDK4/6 inhibitor and a history of chemotherapy may have affected the HALP score. However, the cut-off value is compatible with the literature and is 32.02 in our study[7,9-11].

The delta HALP score reflects the dynamic change in the patient's status and is thought to be more sensitive than the HALP score. Yuce et al.[12] evaluated whether delta HALP score predicted neoadjuvant treatment response in locally advanced breast cancer and obtained significant results like our study in all subgroups (HR+/-, HER2+/-).

Evaluating the first-line effectiveness of CDK4/6 inhibitors and paclitaxel treatment in patients with/impending visceral crisis in data, the ORR in the CDK4/6 inhibitors arm was 77.8% and it was observed that a rate like that in our study (22.2%) did not respond to treatment[13]. In addition, the fact that similar results were obtained in the 4-month disease control rate (77.8 % vs. 59.4%; p=0.168) and the time to first improvement (3.9 vs 3.6 weeks; p=0.773) between the two groups in this study suggests that chemotherapy cannot be an alternative to CDK4/6 inhibitors for preventing early progression. There is no clinicopathological or immunological biomarker to predict this aggressive group, and there is no statistical difference in delta HALP score between both groups (p=0.334).

The presence of liver metastases appears to be an essential risk factor for CDK4/6 inhibitor therapy. In a meta-analysis, the presence of liver metastases resistant to endocrine monotherapies was associated with poor outcomes, as in our study. This meta-analysis showed better outcomes for OS, PFS, and clinical benefit rate in the non-visceral metastasis group. The presence of LVM was associated with worse outcomes than patients with visceral non-liver metastases[14].

The fact that hormone receptor status was confirmed by biopsy before treatment in 90.4% of our patients and that HER2 receptor status was similar in both groups suggests that, apart from the available molecular data, changes in tumor biology, mainly caused by liver metastases, may be effective in early progression. We think an alternative/combined treatment to CDK4/6 inhibitors is required for this patient group.

Study Limitations

The most important limitations of our study are the heterogeneity of treatment lines and endocrine treatments, the inability to evaluate endocrine resistance mutations, the small number of patients, and the retrospective design.

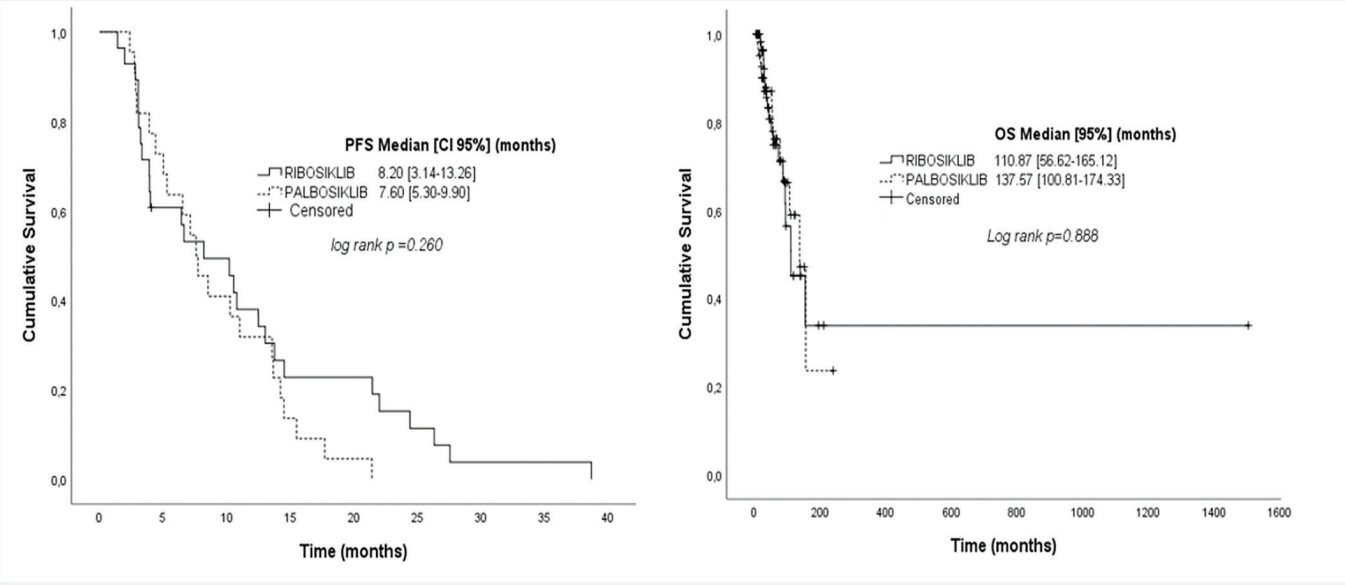


Figure 1. Comparison of PFS and OS Kaplan-Meier curves ribociclib and palbociclib

PFS: Progression-free survival, OS: Overall survival, CI: Confidence interval

Table 2. Univariate and multivariate regression analysis of clinical and pathological factors for early progression

	Univariate LR		Multivariate LR	
	OR (95% CI)	p	OR (95% CI)	p
Age >56 (ref ≤56)	0.69 (0.27-1.83)	0.465		
Delta HALP >0 (ref≤0)	1.61 (0.61-4.22)	0.337		
PR positive (ref: negative)	45.21 (0.01-155.15)	0.999		
HER2 score 1+ and 2+ (ref: score 0)	0.73 (0.24-2.19)	0.570		
Ki 67, % <20 (ref>20)	2.11 (0.64-7.01)	0.223		
Grade (ref: 1)		0.260		
2	1.58 (0.38-6.50)	0.527		
3	3.70 (0.72-18.97)	0.116		
Neoadjuvant/adjuvant chemotherapy history	1.26 (0.43-3.68)	0.673		
Operation with primary tumor	2.11 (0.75-5.98)	0.159		
Bone metastasis (ref: No)	0.46 (0.15-1.42)	0.178		
Lung metastasis (ref: No)	0.46 (0.14-1.51)	0.200		
Liver metastasis (ref: No)	4.03 (1.36-11.93)	**0.012**	3.50 (1.12-10.94)	**0.031**
Brain metastasis (ref: No)	1.33 (0.13-13.51)	0.808		
CDK treatment line 3-4 (ref: 1-2)	6.24 (1.68-23.11)	**0.006**	5.36 (1.37-20.89)	**0.016**
CDK type Ribociclib (ref: palbociclib)	0.93 (0.35-2.50)	0.889		
Dose reduction	0.44 (0.12-1.62)	0.214		

HALP: Hemoglobin-albumine-lymphocyte-platelet, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2, ref: Reference; CDK: Cyclin dependent kinase, LR: Logistic regression, CI: Confidence interval, OR: Odds ratio

CONCLUSION

This retrospective study investigated the predictive value of the delta HALP score for early progression in metastatic breast cancer patients treated with CDK4/6 inhibitors. Our findings indicate that the delta HALP score is not a reliable predictor for early progression in this patient population. However, the presence of liver metastases and later treatment lines were significantly associated with an increased risk of early progression in patients receiving CDK4/6 inhibitors. These

results align with previous research highlighting the challenges in managing patients with metastatic breast cancer and the need for alternative therapeutic strategies.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Sakarya University Medical Faculty (decision no: 27.06.2024-71522473-050.04-372954-165, date: 27.06.2024) and conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Given the retrospective study design, the need for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.B.G., Concept: B.B.G., M.Ö., E.Ö.E., F.A.K., E.Ç., İ.H., Design: B.B.G., M.Ö., E.Ö.E., F.A.K., E.Ç., İ.H., Data Collection or Processing: B.B.G., M.Ö., E.Ö.E., F.A.K., Analysis or Interpretation: B.B.G., E.Ç., İ.H., Literature Search: B.B.G., İ.H., Writing: B.G.

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

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Wu Q, Li J, Zhu S, Wu J, Chen C, Liu Q, et al. Breast cancer subtypes predict the preferential site of distant metastases: a SEER based study. Oncotarget. 2017;8:27990-6.
2. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375:1925-36.
3. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for hr-positive, advanced breast cancer. N Engl J Med. 2016;375:1738-48.
4. Ekinci F, Balcik OY, Oktay E, Erdogan AP. HALP score as a new prognostic index in metastatic renal cell cancer. J Coll Physicians Surg Pak. 2022;31:313-8.
5. Wang J, Jiang P, Huang Y, Tu Y, Zhou Q, Li N, et al. Prognostic value of the cut offs for halp in endometrial cancer. Am J Clin Oncol. 2023;46:107-13.
6. Zhang D, Chen S, Cao W, Geng N, Feng C. HALP score based on hemoglobin, albumin, lymphocyte and platelet can predict the prognosis of tongue squamous cell carcinoma patients. Heliyon. 2023;9:e20126.
7. Farag MC, Antar R, Akosman S, Ng M, Whalen MJ. What is hemoglobin, albumin, lymphocyte, platelet (HALP) score? A comprehensive literature review of HALP's prognostic ability in different cancer types. Oncotarget. 2023;14:153-72.
8. Chen XL, Xue L, Wang W, Chen HN, Zhang WH, Liu K, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. Oncotarget. 2015;6:41370-82.
9. Duran A, Pulat H, Cay F, Topal U. Importance of HALP Score in breast cancer and its diagnostic value in predicting axillary lymph node status. J Coll Physicians Surg Pak. 2022;32:734-9.
10. Zhao Z, Xu L. Prognostic significance of HALP score and combination of peripheral blood multiple indicators in patients with early breast cancer. Front Oncol. 2023;13:1253895.
11. Lou C, Jin F, Zhao Q, Qi H. Correlation of serum NLR, PLR and HALP with efficacy of neoadjuvant chemotherapy and prognosis of triple-negative breast cancer. Am J Transl Res. 2022;14:3240-6.
12. Yuce E, Karakullukcu S, Bulbul H, Alandag C, Saygin I, Kavgaci H. The effect of the change in hemoglobin-albumin-lymphocyte-platelet scores occurring with neoadjuvant chemotherapy on clinical and pathological responses in breast cancer. Bratisl Lek Listy. 2023;124:59-63.
13. Behrouzi R, Armstrong AC, Howell SJ. CDK4/6 inhibitors versus weekly paclitaxel for treatment of ER+/HER2- advanced breast cancer with impending or established visceral crisis. Breast Cancer Res Treat. 2023;202:83-95.
14. Robertson JFR, Leo AD, Johnston S, Chia S, Bliss JM, Paridaens RJ, et al. Meta-analyses of visceral versus non-visceral metastatic hormone receptor-positive breast cancer treated by endocrine monotherapies. NPJ Breast Cancer. 2021;7:11.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.81567
Nam Kem Med J 2024;12(4):266-272

The Effect of Patient Position on the Fluoroscopy Doses Received in Hip Fracture Surgery

Kalça Kırığı Ameliyatında Hasta Pozisyonunun Maruz Kalınan Floroskopi Dozları Üzerindeki Etkisi

Fatih UĞUR[1], Mehmet ALBAYRAK[2], Bedrettin AKAR[3], Mehmet Ali SABIR[1], Ahmet Eren ŞEN[4]

[1]*Kastamonu University Faculty of Medicine, Department of Orthopaedics and Traumatology, Kastamonu, Turkey*
[2]*İstanbul Rumeli University Vocational School of Health Services, İstanbul, Turkey*
[3]*Sakarya Yenikent State Hospital, Clinic of Orthopaedics and Traumatology, Sakarya, Turkey*
[4]*Konya City Hospital, Clinic of Nuclear Medicine, Konya, Turkey*

ABSTRACT

Aim: The study evaluates the impact of patient positioning on radiation doses received during fluoroscopy in proximal femoral nailing for hip fractures. With the increasing use of minimally invasive, imaging-guided procedures, it is crucial to assess radiation exposure risks to both patients and healthcare workers. Prior research indicates that various factors, including patient positioning, can influence radiation doses.

Materials and Methods: This study included patients who underwent proximal femoral nailing for hip fractures from January 2023 to May 2024. Patients' positions were supine on a traction table, lateral decubitus position on a radiolucent table. Fluoroscopy data, including fluoroscopy time, dose-area product (DAP), and radiation dose, along with patient demographics and body mass index (BMI), were analyzed.

Results: A total of 114 patients were included. There were no significant differences in demographic characteristics between the groups. The mean fluoroscopy time was 42.02±25.75 seconds, with no significant difference between positions. The mean radiation dose was 18.72±16.24 milligray (mGy), and the mean DAP was 3.50±3.07 Gy-cm², with no significant differences across positions. However, a statistically significant positive correlation was found between BMI values and dose mGy values (r=0.242, p=0.009). Similarly, a statistically significant positive correlation was observed between BMI values and DAP values (r=0.243, p=0.009). However, the mean number of fluoroscopic shots was significantly higher in the supine position compared to the lateral position.

Conclusion: Patient positioning did not significantly affect fluoroscopy time or radiation dose proximal femoral nailing procedures for hip fractures. However, the number of fluoroscopic shots was lower in the lateral position. High BMI was positively correlated with dose mGy and DAP values except for time. The findings highlight the importance of considering BMI in radiation dose management and suggest that the lateral position may be preferable for minimizing radiation exposure.

Keywords: Fluoroscopy, lateral, supine, traction

ÖZ

Amaç: Çalışma, kalça kırıkları için proksimal femur çivileme sırasında hastanın pozisyonunun floroskopi sırasında alınan radyasyon dozları üzerindeki etkisini değerlendirmektedir. Minimal invaziv, görüntüleme rehberliğindeki prosedürlerin artan kullanımı ile hem hastalar hem de sağlık çalışanları için radyasyon maruziyeti risklerini değerlendirmek önemlidir. Önceki araştırmalar, hasta pozisyonu da dahil olmak üzere çeşitli faktörlerin radyasyon dozlarını etkileyebileceğini göstermektedir.

Gereç ve Yöntem: Bu çalışmaya Ocak 2023 ile Mayıs 2024 tarihleri arasında kalça kırıkları için proksimal femur çivileme yapılan hastalar dahil edildi. Ameliyat sırasında hasta pozisyonları traksiyon masasında supin ya da radyolusent masada lateral idi. Floroskopi verileri, floroskopi süresi, doz-alan ürünü (DAP) ve radyasyon dozu ile hasta demografisi ve vücut kitle indeksi (VKİ) analiz edildi.

Bulgular: Toplamda 114 hasta dahil edildi ve gruplar arasında demografik özelliklerde anlamlı fark bulunmadı. Ortalama floroskopi süresi 42,02±25,75 saniye olup, pozisyonlar arasında anlamlı bir fark bulunmadı. Ortalama radyasyon dozu 18,72±16,24 miligri (mGy) ve ortalama DAP 3,50±3,07

Address for Correspondence: Fatih UĞUR MD, Kastamonu University Faculty of Medicine, Department of Orthopaedics and Traumatology, Kastamonu, Turkey
E-mail: fugur.md@gmail.com **ORCID ID:** orcid.org/0000-0001-6109-8425
Received: 26.06.2024 **Accepted**: 12.08.2024

Gy-cm² olup, pozisyonlar arasında anlamlı bir fark bulunmadı. Ancak, VKİ değerleri ile doz mGy değerleri arasında istatistiksel olarak anlamlı bir pozitif korelasyon bulunmuştur (r=0,242, p=0,009). Benzer şekilde, VKİ değerleri ile DAP değerleri arasında da istatistiksel olarak anlamlı bir pozitif korelasyon gözlenmiştir (r=0,243, p=0,009). Sırtüstü pozisyonda floroskopi çekim sayısı lateral pozisyona göre anlamlı derecede daha yüksekti.

Sonuç: Hasta pozisyonu, kalça kırıkları için proksimal femur çivileme prosedürlerinde floroskopi süresi veya radyasyon dozunu önemli ölçüde etkilemedi. Ancak, lateral pozisyonda floroskopik çekim sayısı daha düşüktü. Bulgular, radyasyon dozu yönetiminde VKİ önemini vurgulamakta ve radyasyon maruziyetini en aza indirmek için lateral pozisyonun tercih edilebileceğini önermektedir.

Anahtar Kelimeler: Floroskopi, lateral, sırtüstü, traksiyon

INTRODUCTION

Minimally invasive, imaging-guided interventional procedures are increasingly being used in medicine as their benefits to patients have been proven[1]. It has become a necessity to evaluate the risks that may occur in patients and healthcare workers due to the effect of ionizing radiation and to monitor the radiation dose in fluoroscopy equipment[1-3]. In 2009, the Society of Interventional Radiology defined radiation dose thresholds as peak skin dose > 3000 milligray (mGy), reference point air kerma > 5000 mGy, dose-area product (DAP) > 500 Gy-cm² or fluoroscopy time (FT) > 60 minutes[4].

The amount of radiation to which individual surgeons are exposed is influenced by many factors. These factors include the type and difficulty of the surgical procedure, the position of the patientand the radiation protection measures used[5,6]. It should be kept in mind that not only surgeons but also other health care providers in the operating room are at risk for scatter radiation exposure[6,7].

The use of C-arm fluoroscopy in intraoperative orthopedic procedures has become an important toolin modern orthopedic surgical practice. This method increases the surgeon's technical competence as well as reducing patient morbidity and length of hospital stay[8-10].

Radiation exposure among orthopedic surgeons varies widely; however, when radiation exposure is considered on a single case basis, an annual radiation exposure of 20 mSv is easily achievable without lead shielding. A cumulative radiation exposure of 1 Sv (1000 mSv) increases an individual's risk of developing a solid tumor at any age by 60%[11]. In logistic regression analysis, working as an orthopedic surgeon is known to significantly increase tumor risk[12]. Studies have shown that hematological and chromosomal abnormalities, dermatological conditions, cataract development and the spread of malignancies are linked to exposure to ionizing radiation, which causes free radical formation and DNA chain breakage[13]. Epidemiologic data collection is difficult for various reasons. According to data from the Life Span Study, the risks associated with low dose exposure are low; therefore, large sample sizes are required[14]. For this reason, the potential radiation risk should not be underestimated and safe working practices should be adopted by healthcare institutions[11-13].

Many studies have been conducted to reduce fluoroscopic radiation dose[9,10,15]. Significant reductions have been achieved by adjustments in operating modes compared to conventional modes, and different results have been obtained with mini C-arm fluoroscopy[9,13,15]. Virtual fluoroscopy can improve the accuracy of C-arm positioning and save time and radiation dose in the operating room[16]. It has been shown that real-time visualization of radiation exposure during the operation can reduce radiation exposure even in the highest exposure cases[17]. Surgical techniques, the approach (anteroposterior), the position of the patient during the procedure, the experience of the surgeon performing the procedure, and the patient's body structure have been shown to have an impact on fluoroscopy doses[18-21].

Proximal femoral nailing (PFN), one of the most commonly used applications of fluoroscopy in thesurgical treatment of hip fracture, can be performed in the supine position using a traction table[3,22], a radiolucent table, or a conventional surgical table[23] or in the lateral decubitus position[24].

Identifying procedures associated with significantly high radiation doses should allow for more tactical dose management strategies that can reduce the likelihood of radiation exposure to patients and limit the cumulative radiation exposure of physicians[1].

This study aims to determine the effect of ionizing radiation based on fluoroscopy in three different positions: under traction, supine and lateral positions on the radiolucent surgical table in PFN applications, which is one of the most common treatment modalities for the rapidly increasing elderly population worldwide and thus the predicted increase in hip fracture cases[3].

MATERIALS AND METHODS

Ethics committee approval for this retrospective study was obtained on with Kastamonu University Clinical Research Ethics Committee (decision no: 2024-KAEK-2 date: 17.01.2024). The study included patients who underwent PFN for hip fracture

in the orthopedics and traumatology clinic of Kastamonu Training and Research Hospital between January 2023 and May 2024, when fluoroscopy data were started to be recorded in the hospital system. Surgical procedures were performed in patients who underwent fluoroscopy-guided traction table, lateral decubitus position and supine position on radiolucent table.

We excluded patients with pathologic fractures that might increase the use of fluoroscopy, reoperation, non-union or implant revision, cases of multiple trauma and surgery for fractures at othersites (requiring two or more fluoroscopies in the same surgical procedure) as exclusion criteria. Other hip fracture surgical techniques were also specifically excluded from the analysis. The analysis included a comprehensive review of hospital records and electronic data. The intertrochanteric antegrade nail with integrated compression screws, 130°, 20 cm nail was used for proximal fixation for all patien.

Fluoroscopy data, FT in seconds, DAP, number of shots (NS) and dose were evaluated along with patient demographics and body mass index (BMI). FT was defined as the total time fluoroscopy was used during the intervention. DAP was defined as the dose in air in a given plane multiplied by the areaof the entire x-ray beam emitted from the x-ray tube and is gray (Gy)-cm². Dose is defined as the total dose amount and its unit is mGy. 1 mGy is equal to 0.001 Gy[1].

Gy refers to the absorbed dose and does not take into account energy type or tissue type. It can be used to express the biological effects of high dose exposure. Sievert (Sv) represents the biological equivalent dose and includes effects on specific tissues. Conversion from Gy to Sv is done using unitless weighting factors for energy and tissue type, the radiation weighting factor for all photon radiation, including x-rays, is 1[11].

The portable C-Arm fluoroscope used to acquire real-time images of the patient during the procedures was an OEC Brivo 785 Essential. The C-arm fluoroscopy system was set to automatic mode; all technical factors, including kilovolt peak and milliampere values, were automatically adjusted to optimize image quality[25].

Statistical Analysis

In this study, statistical analyses were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean, standard deviation, median, interquartile range), the distribution of variables was examined with the Shapiro-Wilk test, one-way analysis of variance was used for intergroup comparisons of normally distributed variables, and Tukey multiple comparison test was used for subgroup comparisons, Kruskal-Wallis test was used in intergroup comparisons of variables that did not show normal distribution, Dunn's multiple comparison test was used in subgroup comparisons, chi-square and Fisher's exact test were used in comparisons of qualitative data, and Pearson correlation test was used to determine the relationship between variables. The results were evaluated at a significance level of $p<0.05$.

RESULTS

A total of 114 patients participated in the study. The mean age of all patients was 78.81±10.52 years and 74 (64.9%) of them were female. The positions used in hip fracture operations were lateral, supine, and traction positions at the rates of 45.60%, 39.50%, and 14.90%, respectively. BMI values were 27.39±4.59 in the lateral group, 27.83±3.98 in the supine group, and 25.51±4.33 in the traction group. No statistically significant difference was observed between the lateral, supine and traction groups in terms of mean age, gender distribution and BMI (p=0.331, p=0.101, p=0.171, respectively).

The mean FT was 42.02±25.75 seconds in all patients. There was no statistically significant difference in the mean FT between the lateral, supine, and traction groups (p=0.062). The mean fluoroscopic dose was calculated as 18.72±16.24 mGy and DAP as 3.50±3.07 Gy-cm² in all patients. There was no statistically significant difference between the lateral, supine and traction groups in terms of mean dose and DAP (p=0.515, p=0.507, p=0.524 respectively).

The mean number of fluoroscopic shots was calculated as 67.01±31.01 when all patients were included. A statistically significant difference was observed between the lateral, supine and traction groups in terms of the mean NS taken (p=0.003). All these parameters are listed in Table 1.

As seen in Table 2, the mean NS of the supine group was statistically significantly higher than that of the lateral group (p=0.001) and there was no statistically significant difference between the other groups (p>0.05). In Table 2, statistical differences among three groups are seen. According to the Pearson correlation test results, seen in Table 3, no statistically significant correlation was found between age values and BMI, time, dose mGy, DAP and NS values (p>0.05). There was also no statistically significant correlation between BMI values and FT values (r=0.144, p=0.125).

However, a statistically significant positive correlation was found between BMI values and dose mGy values (r=0.242, p=0.009). Similarly, a statistically significant positive correlation was found between BMI values and DAP values (r=0.243, p=0.009). A statistically significant positive correlation was also observed between BMI values and NS (r=0.212, p=0.024).

Table 1. Comparison of patient characteristics and fluoroscopy parameters among lateral, supine, and traction groups

		Lateral		Supine		Traction		p-value
Age	Mean±SD	77.73±12.37		78.91±8.85		82.12±8.05		0.331†
Gender	Male	18	(34.62%)	11	(24.44%)	9	(52.94%)	0.101+
	Female	34	(65.38%)	34	(75.56%)	8	(47.06%)	
Height (cm)	Mean ± SD	164.73±8.35		163.51±8.15		167.18±8.39		0.299†
Weight (gr)	Mean ± SD	74.56±13.97		74.27±11.11		71.29±12.21		0.639†
BMI (w/h²)	Mean ± SD	27.39±4.59		27.83±3.98		25.51±4.33		0.171†
FT (seconds)	Mean ± SD	36.52±20.7		47.5±26.95		44.38±33.64		0.062‡
	Median (IQR)	31.1 (22.41-44.66)		41.88 (26.66-64.76)		35.88 (26.44-45.06)		
Dose (mGy)	Mean ± SD	16.68±12.46		19.76±15.25		22.23±26.45		0.515‡
	Median (IQR)	12.37 (8.57-20.84)		17.02 (8.77-24.52)		15.98 (8.39-23.76)		
DAP (Gy-cm²)	Mean ± SD	3.12±2.36		3.69±2.87		4.18±5.03		0.507‡
	Median (IQR)	2.28 (1.6-3.9)		3.14 (1.64-4.55)		3 (1.55-4.44)		
FS	Mean ± SD	56.94±22.75		77.44±35.17		69.53±32.87		0.003‡
	Median (IQR)	54 (43-62)		72 (52-104)		63 (42.5-91)		

†One-way analysis of variance (ANOVA), ‡Kruskal-Wallis test +chi-square test, BMI: Body mass index, FT: Fluoroscopy time, DAP: Dose-area product, FS: Fluoroscopy shot number, IQR: Interquartile range, SD: Standard deviation

Table 2. Statistical differences of mean number of shots in between lateral, supine and traction groups

	p*
Lateral / supine	0.001
Lateral / traction	0.119
Supine / traction	0.372

*Dunn's multiple comparison test

Statistically significant positive correlations were found between time, dose (mGy), DAP and NS. Strong correlations were found particularly between time and dose (r=0.891), time and DAP (r=0.888), time and NS (r=0.749), dose and DAP (r=0.999), dose and NS (r=0.564), and DAP and NS (r=0.561) (p=0.0001).

DISCUSSION

This study is the first to evaluate the use of fluoroscopy and ionizing radiation in the same research for three different patient positions-traction, supine and lateral for PFN procedures in hip fractures. In terms of ionizing radiation levels, no significant difference was found in FT, dose and DAP values in the three different patient positions. No statistically significant difference was found between the groups in terms of demographic characteristics such as age, gender, height, weight, and BMI; therefore, the groups were equalized. In the comparison between supine and lateral positions on the radiolucent table, the NS was significantly lower in the lateral position, while no difference was found in the surgeries performed on the traction table.

With the aging of the world population, hip fractures are more common in the community and among healthcare workers[22,24]. This study shows that the lateral position should be preferred in these cases to reduce surgical time and lower the NS. Considering the preparation time and complications of the traction table, it is emphasized that the lateral decubitus position is important in terms of low NS[26]. In our study, a significant positive correlation was found between time, DAP and dose and the NS.

Numerous studies have compared and evaluated the use of fluoroscopy in PFN applications by comparing only the NS[27-30]. However, issues such as radiation exposure and especially tissue damage should also be addressed, and such data can be expressed in Gy or Sv[11]. For this reason, it may be appropriate to evaluate parameters such as DAP, FT, and dose in studies such as ours, since it should be evaluated with a single parameter as stated by Bilekli et al.[31].

In the study by Bilekli et al.[31] a comparison of FT in hip fracture surgery according to supine and traction table positions was made and the mean time was found as 55.95 seconds for supine position and 48.29 seconds for traction table. In our study, these times were 47.5 seconds and 44.38 seconds, respectively, and the supine FT was found to be similarly high.

In a study by Zehir et al.[32], the mean duration of PFNA fluoroscopy in the supine position was reported to be 2.0 minutes, which is significantly different from 47.5 seconds in our study. Buxbaum et al.[33] reported the lowest FT as 76.45 seconds in hip fractures. Duramaz and İlter[34] reported the mean and median FT as 34 seconds for both, with the same

Table 3. Correlations between patient characteristics and fluoroscopy parameters*

		Age	BMI	FT	Dose	DAP	FS
Age	r		-0.096	-0.063	-0.094	-0.096	-0.053
	p		0.309	0.505	0.317	0.310	0.578
BMI	r	-0.096		0.144	0.242	0.243	0.212
	p	0.309		0.125	**0.009**	**0.009**	**0.024**
FT	r	-0.063	0.144		0.891	0.888	0.749
	p	0.505	0.125		0.0001	0.0001	0.0001
Dose	r	-0.094	0.242	0.891		0.999	0.564
	p	0.317	**0.009**	0.0001		0.0001	0.0001
DAP	r	-0.096	0.243	0.888	0.999		0.561
	p	0.310	**0.009**	0.0001	0.0001		0.0001
FS	r	-0.053	0.212	0.749	0.564	0.561	
	p	0.578	**0.024**	0.0001	0.0001	0.0001	

Pearson correlation tests, BMI: Body mass index, FT: Fluoroscopy time, DAP: Dose-area product, FS: Fluoroscopy shot number

surgical model. Patil[35] reported the mean FT as 72.6 seconds in PFN applications. In our study, the median was 34 seconds and the mean was 44 seconds on the traction table, which is significantly different from these two studies.

In a study by Kalem et al.[36], FT of PFNA application in the supine position with two different fluoroscopy devices (device A and B - these two fluoroscopy devices of the same brand and software, but with different image intensifier sizes) was reported to be 58.1 seconds and 98.9 seconds, respectively. In our study, this time was found to be 47.5 seconds with the same device model device B. In addition, while the mean DAP value in the supine position was reported as 7.3 in the same study, it was found to be 3.69 in this position in our study.

In the study of Bilekli et al.[31], the mean DAP was 2.84 in the traction position and 2.26 in the supine position, whereas in our study, these values were 4.18 and 3.69, respectively. Unlike our study, this study did not focus on dose values. In addition, it was thought that the differences between BMI values in the same study could explain the differences in DAP values. While the mean BMI values were 23.4 and 22 in Bilekli et al.[31] study, they were 27.8 and 25.5 in our study. In the literature, increased FT was associated with higher BMI and increased DAP value was also associated with higher BMI[37]. In our study, high BMI was positively correlated with dose mGy and DAP values except for time.

In the study by Rashid et al.[38], the mean FT for short PFN procedure was reported as 49 seconds and the median DAP was 1.40 Gy-cm^2. In our study, the median DAP value obtained in the lowest lateral position was 2.28 Gy-cm^2 and the median FT was 31 seconds. In terms of the NS, the mean number of fluoroscopy images in Rashid et al.[38] study was 109, whereas in our study, 54 shots were found in the laterel position. Despite the differences in FT and NS, the DAP mismatch remains unclear as more information on other details, such as patient position and operating table, was not provided.

In the study of Roukema et al.[39] on hip fractures, the reported dose value related to the use of fluoroscopy was 3.5 mGy, while in our study, this value was determined as the lowest 16.68 mGy.

In addition, while the mean fluoroscopy duration was 53 seconds in Roukema et al.[39] study, the lowest duration was 36.52 seconds in our study. The DAP value was reported as 0.0572 mGy-m^2 in Roukema et al.[39] study, whereas the lowest value was 3.12 Gy-cm^2 (0.312 mGy-m^2) in our study. The significant differences between these studies are due to factors such as different surgical techniques and materials used.

It is thought that the lower DAP values between the study of Bilekli et al.[31] and Roukema et al.[39] study may not be explained only by differences in BMI and surgical method. It is seen that only automatic mode was defined as the operating mode of fluoroscopy and the data of continuous or pulsed modes were not available in any study. Pulsed mode is known to reduce radiation exposure up to 64% compared to continuous mode[40]. It is thought that these factors may influence these differences. In our study, it was observed that all surgeons worked in the same fluoroscopy device with a continuous mode.

This study showed that patient position did not make a difference in terms of fluoroscopy use andionizing radiation in PFN applications in hip fractures. The lowest NS was observed in the lateral position and a positive correlation was found between BMI and dose and also BMI and DAP. These findings emphasize the necessity of preoperative BMI determination and exposure reduction measures in terms of patient and worker safety (exposure to ionizing radiation). The evaluation of BMI as a risk factor for high DAP exposure

may require consideration of measures to reduce risks. The widespread use of fluoroscopy devices in medical imaging and surgical procedures raises concerns about potential radiation exposure of staff and patients[6,7]. Therefore, ongoing collaboration and communication between operational staff and radiation professionals is necessary to ensure safe and effective use of the devices[10]. Radiation professionals play an important role in training personnel, promoting the correct use of protective equipment, and ensuring up-to-date safety protocols. This collaboration helps to minimize long-term health risks by reducing radiation exposure and improve the safety of medical practices[11,38].

Bundy et al.[1] stated that most of the cases exceeding the radiation threshold value determined in their study were performed by non-radiologists. This situation emphasizes the importance of training of radiation professionals and points to the errors of personnel who are not trained in radiation physics, biology, and dose reduction techniques.

Study Limitations

The limitations of our study include the fact that the duration of surgery was not evaluated, it was a single centered study, and different surgeons were involved. However, it is important that surgeons used their best technique in the study. Since the focus of our study was to show the effect of patient position on fluoroscopy dose, it is thought that whether the device operates in pulse or continuous mode has no effect on the data and conclusions obtained. There is a need for prospective randomized controlled studies to evaluate the effect of different modes of fluoroscopy in the future. In surgeries performed without a traction table, the fact that the radiation-producing part of the scopy device under the table provides less radiation to be released should not be overlooked, which is a handicap that this study did not evaluate.

CONCLUSION

The risk of exposure to high radiation doses increases significantly, especially in prolonged procedures. Therefore, it is important to improve safety measures and implement effective dose control methods to minimize radiation doses. It should be noted with this study that the NS is lower in the lateral decubitus position compared to other positions, and that BMI is related to ionizing radiation. Future research should be directed towards improving safety standards in this area.

Ethics

Ethics Committee Approval: Ethics committee approval for this retrospective study was obtained on with Kastamonu University Clinical Research Ethics Committee (decision no: 2024-KAEK-2 date: 17.01.2024).

Footnotes

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: F.U., M.A.S., Concept: F.U. M.A., A.E.Ş., Design: M.A., B.A., M.A.S., Data Collection or Processing: F.U., M.A.S., A.E.Ş., Analysis or Interpretation: M.A., B.A., Literature Search: M.A., B.A., Writing: F.U., M.A., B.A.

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

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Bundy JJ, McCracken IW, Shin DS, Monroe EJ, Johnson GE, Ingraham CR, et al. Fluoroscopically-guided interventions with radiation doses exceeding 5000 mGy reference point air kerma: a dosimetric analysis of 89,549 interventional radiology, neurointerventional radiology, vascular surgery, and neurosurgery encounters. CVIR Endovasc. 2020;3:69.
2. Wheeler JA, Weaver N, Balogh ZJ, Drobetz H, Kovendy A, Enninghorst N. Radiation exposure in patients with isolated limb trauma: acceptable or are we imaging too much? J Clin Med. 2020;9:3609.
3. Botchu R, Ravikumar K. Radiation exposure from fluoroscopy during fixation of hip fracture and fracture of ankle: Effect of surgical experience. Indian J Orthop. 2008;42:471-3.
4. Stecker MS, Balter S, Towbin RB, Miller DL, Vañó E, Bartal G, et al. Guidelines for patient radiation dose management. J Vasc Interv Radiol. 2009;20(7 Suppl):263-73.
5. Barry TP. Radiation exposure to an orthopedic surgeon. Clin Orthop Relat Res. 1984;182:160-4.
6. Yamashita K, Tamaki Y, Nakajima D, Omichi Y, Takahashi Y, Takai M, et al. A cadaveric simulation study of radiation exposure to the surgical team during fluoroscopic spinal surgery: how much are we exposed?. Spine Surg Relat Res. 2023;7:341-9.
7. Abas AA, Rahman RA, Yahya N, Kamaruzaman E, Zainuddin K, Manap NA. Occupational radiation exposure to anesthetists from fluoroscopic projections during orthopedic operative procedures. Clin Ter. 2014;165:253-7.
8. Ojodu I, Ogunsemoyin A, Hopp S, Pohlemann T, Ige O, Akinola O. C-arm fluoroscopy in orthopaedic surgical practice. Eur J Orthop Surg Traumatol. 2018;28:1563-8.
9. Kropelnicki A, Eaton R, Adamczyk A, Waterman J, Mohaghegh P. Establishing local diagnostic reference levels for common orthopaedic procedures using the mini C-arm fluoroscope. Br J Radiol. 2021;94:20190878.
10. Malik AT, Rai HH, Lakdawala RH, Noordin S. Does surgeon experience influence the amount of radiation exposure during orthopedic procedures? A systematic review. Orthop Rev (Pavia). 2019;11:7667.
11. Hayda RA, Hsu RY, DePasse JM, Gil JA. Radiation exposure and health risks for orthopaedic surgeons. J Am Acad Orthop Surg. 2018;26:268-77.
12. Mastrangelo G, Fedeli U, Fadda E, Giovanazzi A, Scoizzato L, Saia B. Increased cancer risk among surgeons in an orthopaedic hospital. Occup Med (Lond). 2005;55:498-500.
13. Vosbikian MM, Ilyas AM, Watson DD, Leinberry CF. Radiation exposure to hand surgeons' hands: a practical comparison of large and mini C-arm fluoroscopy. J Hand Surg Am. 2014;39:1805-9.
14. Pierce DA, Preston DL. Radiation-related cancer risks at low doses among atomic bomb survivors. Radiat Res. 2000;154:178-86.

15. Cho JH, Kim JY, Kang JE, Park PE, Kim JH, Lim JA, et al. A study to compare the radiation absorbed dose of the c-arm fluoroscopic modes. Korean J Pain. 2011;24:199-204.

16. De Silva T, Punnoose J, Uneri A, Goerres J, Jacobson M, Ketcha MD, et al. C-arm positioning using virtual fluoroscopy for image-guided surgery. Proc SPIE Int Soc Opt Eng. 2017;10135:101352K.

17. Baumgartner R, Libuit K, Ren D, Bakr O, Singh N, Kandemir U, et al. Reduction of radiation exposure from c-arm fluoroscopy during orthopaedic trauma operations with introduction of real-time dosimetry. J Orthop Trauma. 2016;30:53-8.

18. Jinnai Y, Baba T, Zhuang X, Tanabe H, Banno S, Watari T, et al. Does a fluoro-assisted direct anterior approach for total hip arthroplasty pose an excessive risk of radiation exposure to the surgeon? SICOT J. 2020;6:6.

19. Sonmez MM, Camur S, Erturer E, Ugurlar M, Kara A, Ozturk I. Strategies for proximal femoral nailing of unstable intertrochanteric fractures: lateral decubitus position or traction table. J Am Acad Orthop Surg. 2017;25:37-44.

20. Tucker MC, Schwappach JR, Leighton RK, Coupe K, Ricci WM. Results of femoral intramedullary nailing in patients who are obese versus those who are not obese: a prospective multicenter comparison study. J Orthop Trauma. 2007;21:523-9.

21. Vig KS, Adams C, Young JR, Perloff E, O'Connor CM, Czajka CM. Patient positioning for proximal femur fracture fixation: a review of best practices. Curr Rev Musculoskelet Med. 2021;14:272-81.

22. Simmermacher RK, Bosch AM, Van der Werken C. The AO/ASIF-proximal femoral nail (PFN): a new device for the treatment of unstable proximal femoral fractures. Injury. 1999;30:327-32.

23. Şahin E, Songür M, Kalem M, Zehir S, Aksekili MA, Keser S, et al. Traction table versus manual traction in the intramedullary nailing of unstable intertrochanteric fractures: A prospective randomized trial. Injury. 2016;47:1547-54.

24. Doğan N, Ertürk C, Gülabi D. Is proximal femoral nailing of unstable intertrochanteric fractures in the lateral decubitus position without a traction table as safe and effective as on a traction table? Injury. 2022;53:555-60.

25. Yamashita K, Higashino K, Hayashi H, Hayashi F, Fukui Y, Sairyo K. Pulsation and collimation during fluoroscopy to decrease radiation: a cadaver study. JB JS Open Access. 2017;2:e0039.

26. Flierl MA, Stahel PF, Hak DJ, Morgan SJ, Smith WR. Traction table-related complications in orthopaedic surgery. J Am Acad Orthop Surg. 2010;18:668-75.

27. Kashid MR, Gogia T, Prabhakara A, Jafri MA, Shaktawat DS, Shinde G. Comparative study between proximal femoral nail and proximal femoral nail antirotation in management of unstable trochanteric fractures. Int J Res Orthop. 2016;2:354-8.

28. Shah A, Badade K, Kadam R, Chhallani A, Sharma G, Pandey S. Clinical, functional and radiological outcomes of proximal femoral nail (PFN) with proximal femoral nail antirotation Asia (PFNA2) in the treatment of intertrochanteric and peritrochanteric femur fracture. Int J Orthop Sci. 2020;6:1156-60.

29. Mallya S, Kamath SU, Madegowda A, Krishnamurthy SL, Jain MK, Holla R. Comparison of radiological and functional outcome of unstable intertrochanteric femur fractures treated using PFN and PFNA-2 in patients with osteoporosis. Eur J Orthop Surg Traumatol. 2019;29:1035-42.

30. Rai B, Singh J, Singh V, Singh G, Pal B, Kumar D, et al. Evaluation of the outcomes of proximal femoral nail antirotation ii in the treatment of trochanteric fracture in elderly patients. Cureus. 2022;14:e24896.

31. Bilekli AB, Bahtiyar EE, Zeybek H, Neyişci Ç, Erdem Y, Çankaya D. Radiation exposure during proximal femoral nailing: Traction table versus conventional table. Jt Dis Relat Surg. 2022;33:338-44.

32. Zehir S, Şahin E, Zehir R. Comparison of clinical outcomes with three different intramedullary nailing devices in the treatment of unstable trochanteric fractures. Ulus Travma Acil Cerrahi Derg. 2015;21:469-76.

33. Buxbaum EJ, Ponzio DY, Griffiths S, Wu ES, Duque AF, Post ZD, et al. Impact of resident training level on radiation exposure during fixation of proximal femur fractures. J Orthop Trauma. 2020;34:170-5.

34. Duramaz A, İlter MH. The impact of proximal femoral nail type on clinical and radiological outcomes in the treatment of intertrochanteric femur fractures: a comparative study. Eur J Orthop Surg Traumatol. 2019;29:1441-9.

35. Patil SV. Management of intertrochanteric hip fractures by proximal femoral nail and dynamic hip screw fixation: a comparative study. Int J Orthop Sci. 2021;7:440-3.

36. Kalem M, Başarır K, Kocaoğlu H, Şahin E, Kınık H. The Effect of C-Arm mobility and field of vision on radiation exposure in the treatment of proximal femoral fractures: a randomized clinical trial. Biomed res int. 2018;2018:6768272.

37. Baratz MD, Hu YY, Zurakowski D, Appleton P, Rodriguez EK. The primary determinants of radiation use during fixation of proximal femur fractures. Injury. 2014;45:1614-9.

38. Rashid MS, Aziz S, Haydar S, Fleming SS, Datta A. Intra-operative fluoroscopic radiation exposure in orthopaedic trauma theatre. Eur J Orthop Surg Traumatol. 2018;28:9-14.

39. Roukema GR, De Jong L, Van Rijckevorsel VAJIM, Van Onkelen RS, Bekken JA, Van der Vlies CH, et al. Radiation exposure during direct versus indirect image acquisition during fluoroscopy-controlled internal fixation of a hip fracture: Results of a randomized controlled trial. Injury. 2019;50:2263-7.

40. Raza M, Houston J, Geleit R, Williams R, Trompeter A. The use of ionising radiation in orthopaedic surgery: principles, regulations and managing risk to surgeons and patients. Eur J Orthop Surg Traumatol. 2021;31:947-55.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.45822
Nam Kem Med J 2024;12(4):273-279

Health Service Utilization in Rural Areas of Edirne and Kırklareli

Edirne ve Kırklareli Kırsalında Sağlık Hizmeti Kullanımı

Gamze DEMİRAY[1], Mehmet GÜNEŞ[2], Burcu TOKUÇ[3], Muzaffer ESKiOCAK[4]

[1]*Efeler District Health Directorate, Aydın, Turkey*
[2]*Niğde Community Health Center, Niğde, Turkey*
[3]*Tekirdağ Namık Kemal University Faculty of Medicine, Department of Medical Education, Tekirdağ, Turkey*
[4]*Sanko University Faculty of Medicine, Department of Public Health, Gaziantep, Turkey*

ABSTRACT

Aim: This study aims to assess health service utilization and its correlation with socio-economic variables among rural residents of Edirne and Kırklareli provinces.

Materials and Methods: This cross-sectional study was conducted between May and October 2019 with a survey in 414 households in 50 villages in Edirne and Kırklareli provinces. Data were collected via a 42-question questionnaire.

Results: Of the visited villages, 36 (72%) lacked health institutions, while 5 (10%) had health centers and 9 (18%) had family health centers (FHC). During working hours, 50.2% preferred public hospitals, 37.2% favored FHC, and 9.2% chose private hospitals/practices. Notably, 64.5% of elderly participants with chronic conditions lacked regular follow-ups, along with 65.5% of women aged 15-49 years, while all children received regular care.

Conclusion: Although access to healthcare services appears to be sufficient in the rural areas of Edirne and Kırklareli, located in the Thrace region, it has been observed that there is a dependency on demand-based services. Notably, consistent primary care follow-ups, excluding childhood, appear lacking, highlighting a gap in providing qualified and reliable health services to the public.

Keywords: Thrace, rural area, health service

ÖZ

Amaç: Bu çalışma, Edirne ve Kırklareli illerinde kırsal kesimde yaşayanların sağlık hizmetlerinden yararlanma durumlarını ve bunun sosyo-ekonomik değişkenlerle ilişkisini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Mayıs ile Ekim 2019 tarihleri arasında yapılan bu kesitsel çalışma, Edirne ve Kırklareli illerine bağlı 50 köyde 414 hanede anket uygulamasıyla gerçekleştirilmiştir. Veriler, 42 sorudan oluşan bir anket ile toplanmıştır.

Bulgular: Ziyaret edilen köylerin 36'sında (%72) sağlık kurumu bulunmazken, 5'inde (%10) sağlık merkezi ve 9'unda (%18) aile sağlığı merkezi (ASM) bulunmaktadır. Çalışma saatleri içinde katılımcıların %50,2'si kamu hastanelerini tercih ederken, %37,2'si ASM'leri ve %9,2'si özel hastane ya da muayenehaneleri tercih etmiştir. Kronik hastalığı olan yaşlı katılımcıların %64,5'inin ve 15-49 yaş arası kadınların %65,5'inin düzenli takiplerinin yapılmadığı, ancak tüm çocukların düzenli bakım aldığı dikkat çekmiştir.

Sonuç: Trakya bölgesinde bulunan Edirne ve Kırklareli illeri kırsalında sağlık hizmetlerine erişim yeterli görünse de başvuru esaslı hizmetlere bağımlılık olduğu gözlenmiştir. Çocukluk dönemi haricinde düzenli birinci basamak sağlık hizmeti takiplerinin eksikliği, nitelikli ve güvenilir sağlık hizmetlerinin sunumunda bir boşluk olduğunu göstermektedir.

Anahtar Kelimeler: Trakya, kırsal, sağlık hizmeti

Address for Correspondence: Gamze DEMİRAY MD, Efeler District, Health Directorate, Aydın, Turkey
E-mail: gamzedemiray07@gmail.com **ORCID ID:** orcid.org/0000-0003-3728-2825
Received: 01.03.2024 **Accepted**: 23.08.2024

INTRODUCTION

Although globally rural areas are typically characterized as regions distant from urban centers, with low population density, predominantly elderly populations, and economies primarily reliant on agricultural activities, each country's definition of rural areas varies based on its own geographical structure, population density, economic, and social characteristics[1]. In Turkey, until March 2014, the Turkish Statistical Institute (TUIK) classified settlements with populations of 20,001 or more as urban and those with populations of 20,000 or fewer as rural, following the criteria established by the State Planning Organization in 1982 in its "Urban Threshold Survey: Urban Definition for Turkey." However, with the enactment of Law no. 6360 published in the Official Gazette in 2014, which granted metropolitan municipality status to 30 provinces, villages within the boundaries of these provinces were designated as neighborhoods, altering the rural-urban classification significantly within these metropolitan areas based on the 20,000 population threshold[2].

Numerous opportunities that enhance quality of life are less prevalent in rural areas compared to urban areas. Particularly in terms of education, healthcare services, employment opportunities, and technological infrastructure, cities hold significant advantages. Consequently, the younger population tends to prefer urban areas for residence, leading to an increase in the elderly population in rural areas.

According to the Address-Based Population Registration System 2023 data from the TUIK, 7% of Turkey's population resides in rural areas (towns and villages). The percentage of the population aged 65 years and over is 9.9% in urban areas and 30.1% in rural areas[3]. However, according to World Bank data published by the Ministry of Environment, Urbanization, and Climate Change, 23% of Turkey's population lives in rural areas[4].

We define healthcare services as planned activities aimed at preserving individual and community health, providing treatment when individuals are ill, enabling independent living in the event of disability, and improving public health[5]. In Turkey, preventive, curative, rehabilitative, and promotive healthcare services are provided by public and private healthcare institutions at the primary, secondary, and tertiary levels. Despite the tiered structure of healthcare service delivery, there is no mandatory referral system between tiers, and individuals can receive services from the institution of their choice. The choice of healthcare institution by individuals is influenced by various factors such as their economic status, the presence of social security coverage, proximity to healthcare facilities in their place of residence, educational background, previous experiences with healthcare institutions, technological infrastructure of healthcare institutions, as well as the socio-cultural structure of the community, and individual knowledge, attitudes, and beliefs[6,7].

In our country, primary health care services were provided through the "health centers" of socialization model until 2005. In the socialization model, primary services (preventive services for society and the environment) were provided through district-based health centers. In this model, health care services in rural areas were provided through the village type health centers and health posts that were staffed by midwives. The "family medicine" practice, which started as a pilot program in Düzce province in 2005, was expanded to cover the entire country in 2010. In family medicine model, healthcare services in rural areas are primarily provided through periodic visits by family physicians (FPs) to rural areas and in few villages that far from city centers by midwives and nurses stationed at health posts, who are affiliated with FPs located in the nearest urban areas[8].

Another unit that provides primary health care services is the community health centers (CHC) in this model. Unlike family health centers (FHC), which focus on individual-oriented activities, CHCs provide services aimed at the community. They aim to improve and protect the health of the community in their region. By conducting risk analyses related to community health, they identify existing problems and develop plans to address these issues[9]. They monitor, supervise, and coordinate family medicine units. Additionally, CHC are responsible for providing various primary health care services such as environmental health services, monitoring and intervention services for infectious and chronic diseases, forensic medicine services, school health services, worker and occupational safety services, health education services, and the licensing of private health institutions[10].

As a result of the change in the organizational chart of the Ministry of Health, following Decree Law no. 694 dated 15.08.2017, the responsibilities of CHCs are carried out by District Health Directorates in their respective districts, depending on the population and size of the region. However, there are still places where CHCs continue their activities[8].

The aim of this study is to determine the utilization of healthcare services by residents of rural areas in two provinces (Edirne and Kırklareli) in the Thrace region and to examine the relationship between individuals' healthcare service utilization and certain socio-economic variables.

MATERIALS AND METHODS

The study is cross-sectional research conducted in the rural areas of Edirne and Kırklareli provinces in the Thrace region between May and October 2019. Due to the lack of information regarding traditional urban and rural definitions in Law no. 6360, which connected the villages to the center and given

neighborhood status. Because of the ongoing unresolved issues in the urban/rural distinction since 2014, in this study, the status of settlements prior to Law no. 6360 was used, similar to the Turkey Demographic and Health Survey 2018[11].

The sample size was calculated as minimum 384 households, using tables prepared by the World Health Organization for "estimating a population proportion with a certain relative precision[12]." Approximately 10% of the 432 villages in the rural areas of Edirne and Kırklareli (50 villages; 29 villages from Edirne, 21 villages from Kırklareli, with different distances to district centers) were determined by simple random sampling method and 414 households were determined by weighting them according to the population of the villages. The households in the villages were selected using systematic sampling, with the mukhtar's house as the starting point, and data were collected through face-to-face interviews with one consenting individual per household. If there were infants or children in the household, interviews were conducted with their parents; if there were women aged 15-49 years, interviews were conducted with themselves; and if there were individuals aged 65 years or older, interviews were conducted with them separately. Individuals who agreed to participate in the study were informed about the research and verbal consent was obtained. In cases where no one was found at the selected household or if the household members refused to participate, interviews were conducted with one person from the neighboring household.

For data collection, a 42-item questionnaire was developed by researchers, based on relevant literature, to ascertain information regarding various socio-demographic characteristics, household income, social security status of household members, their health conditions, and healthcare utilization patterns (such as the healthcare facility visited within the last year, preferred healthcare facility in case of health issues, etc.). Additionally, healthcare utilization (including screenings and cancer screenings, etc.) for infants and children, women aged 15-49 years, and individuals aged 65 years and above were separately investigated if present in the household.

The distances of villages to the nearest state hospital (SH) were calculated using the Google Maps application for road transportation.

Ethical approval for the research was obtained from the Trakya University Scientific Research Ethics Committee (decision no: TÜTF-BAEK 2019/198, date: 13.05.2019).

Statistical Analysis

Data analysis was performed using IBM SPSS Ver 25.0 software, employing descriptive statistics along with the chi-square and Student's t-test. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Statistical significance level was accepted as $p<0.05$.

RESULTS

Within the scope of the study, a total of 414 households were reached, including 26 (52%) from Kırklareli and 24 (48%) from Edirne, representing 50 villages in total. At least one individual from each household was interviewed. Descriptive characteristics of the interviewees are summarized in Table 1.

The average number of individuals residing in the households was 3.2±1.6 (median: 3; min: 1; max: 14) people. Descriptive characteristics of the interviewed households are presented in Table 2.

In 36 of the visited villages (72%), there is no healthcare facility, while 5 villages (10%) have a health clinic and 9 villages (18%) have a primary healthcare center (PHC). It is noted that in villages without any healthcare facility and those with health clinics, mobile services are provided by their FP The average distance to the nearest SH from the villages is 16.5±8.5 km (min: 5.7-max: 60.3).

Table 1. Descriptive characteristics of the interviewees

Descriptive characteristics	No	%
Gender		
Female	192	46.4
Male	222	53.6
Age groups (year)		
18-25	31	7.7
26-35	39	9.9
36-45	61	15.9
46-55	79	20
56-65	99	26.6
65 and above	105	19.8
Marital status		
Married	328	79.2
Single	72	17.4
Widowed	11	2.7
Divorced	3	0.7
Education status		
Illiterate	8	1.9
Literate	4	1.0
Primary school graduate	4	63.5
Secondary school graduate	45	10.9
High school and above graduate	94	22.7
Source of income		
Officer	15	3.6
Worker	37	8.9
Farmer	109	26.3
Retired	117	28.3
Unemployed	95	22.9
Other	41	9.9
Total	414	100

The median number of healthcare service utilization in the past year among participants is 4.5 (mean: 5.4±4.7, min: 0-max: 19), and the median number of emergency department visits is 0 (mean: 1.0±1.7, min: 0-max: 10).

Table 2. Descriptive characteristics of households

Descriptive characteristics	n (%)
Number of individuals living in the household	
1 person	30 (7.2)
2-4 people	298 (72.0)
5 or more people	86 (20.8)
Number of income earners in the household	
1 person	251 (60.6)
2 people	131 (31.6)
3 or more people	32 (7.7)
Monthly income of the household*	
2020 TL and below	205 (49.5)
Above 2020 TL	209 (50.5)
Social security status of the household	
No social security	17 (4.1)
Presence of SGK premium debt in the household	
Having premium debt (Bağ-Kur insured)	40 (9.7)

*The minimum wage for the year 2019, when the study was conducted, is 2020 TL
SGK: Social security institution

The healthcare facilities where participants received services in the past year during office hours and their preferred healthcare facilities when facing a health problem are summarized in Table 3.

When participants were asked about the reasons for their choice of the initial place of application, 181 individuals (43.7%) indicated "proximity," 90 individuals (21.7%) stated "reliability," and 78 individuals (18.8%) mentioned "good technical facilities" as their reasons. Additionally, 32 individuals (7.7%) mentioned "affordability," and 21 individuals (5.1%) reported choosing based on knowing someone at the facility. The majority of those who preferred the PHCs (80.5%) stated that they chose it due to its proximity, while 30.7% of those who preferred a SH or university hospital mentioned better technical facilities, and 24.8% cited higher reliability as reasons. Among those who chose a SH, 13.9% mentioned affordability as the reason for their preference over other hospitals.

When examining the factors affecting the first choice of healthcare institution during working hours, it was determined that there was no significant difference based on the distance of the residence to the nearest SH, whether the household had any Social Security Institution (SSI) premium debt, or whether

Table 3. The healthcare facilities used in the past year and their primary choices for addressing health issues

Healthcare facilities	Receipt of healthcare services within the last year* n (%)	Their first-choice healthcare institution for health issues n (%)
Primary healthcare center	230 (55.6)	154 (37.2)
Mobile health service	52 (12.6)	0 (0)
State hospital	286 (69.1)	208 (50.2)
University hospital	54 (13.0)	13 (3.1)
Private hospital	81 (19.6)	28 (6.8)
Private clinic	10 (2.4)	10 (2.4)
Emergency service	169 (40.8)	1 (0.2)

*Since participants provided multiple responses, the total may exceed 100

Table 4. Factors influencing the choice of primary healthcare institution during office hours

		Preferers of primary care institutions n (%)	Preferers of non-primary care institutions n (%)	p value
Having outstanding premium debt despite having social security coverage	Yes	15 (37.5)	25 (62.5)	0.967*
	No	139 (37.2)	235 (62.8)	
Having a monthly household income below the minimum wage	Yes	65 (31.7)	140 (68.3)	0.022*
	No	89 (42.6)	120 (57.4)	
The presence of a primary health care center in their village	Yes	96 (41.4)	136 (58.6)	0.047*
	No	58 (31.9)	124 (68.1)	
The presence of children under 5 years of age in the household	Yes	16 (45.7)	19 (54.3)	0.276*
	No	138 (36.4)	241 (63.6)	
The presence of individuals over 65 years of age in the household	Yes	41 (39.0)	66 (61.0)	0.650*
	No	113 (36.6)	194 (63.4)	
Distance to the nearest state hospital		18.3±10.9 km	16.4±6.4 km	0.070**

Statistical significance level was accepted as p<0.05. *chi-square test, **Student's t-test

there were individuals over 65 years old or children under 5 years old in the household. However, differences were observed based on the household income and the presence of a FHC in the village of residence (Table 4). It was determined that households with income below the minimum wage tended to prefer non-primary care institutions more, while those living in areas where a PHC was available tended to prefer primary care institutions.

In the scope of the research, 105 individuals aged 65 years and over were interviewed, and out of these, 79 individuals (73.8%) reported having at least one diagnosed chronic disease. Among the 79 individuals with diagnosed chronic diseases, 51 (64.5%) stated that their FP did not conduct regular check-ups for their chronic conditions. Additionally, 94 individuals (87.8%) aged 65 years and over mentioned that their FP did not recommend any vaccine, while 13 individuals (12.1%) reported being recommended for vaccination. Out of the 13 individuals who were recommended for vaccination by their FP, 9 (69.3%) stated that they received the recommended vaccine(s), while 4 (30.7%) did not.

Within the households surveyed, 93 included female participants aged 15-49 years, and they were individually interviewed. Among these female participants, 61 (65.5%) reported that they did not receive regular check-ups by their FPs. Among the 19 women who had experienced pregnancy in the last 5 years, they preferred the following facilities for antenatal care: 84.2% preferred primary health centers, 73.6% preferred SH, and 31.5% preferred university hospitals (participants provided multiple responses). It was found that those who experienced pregnancy underwent antenatal care an average of 6±0.4 times at primary health centers, 6±1 times at SH, and 8±0.7 times at private hospitals (PHs). Out of the 19 women who experienced pregnancy, 11 (57.8%) had timely deliveries, 6 (31.5%) experienced preterm births, and 2 (10.5%) experienced induced abortions. One induced abortion was performed at a SH, and the other was performed at a PH. Among live births, 70.5% occurred at PHs, 23.5% at SH, and 5.8% at university hospitals.

In 35 households (8.5%), children under the age of 5 years were present. Among these households, 27 (77.1%) had one child under the age of 5 years, and 8 had two children. All children received infant and childhood check-ups by FPs. Besides the FP, children were taken for check-ups to SH (31.4%) and PHs (22.8%). All households with children under the age of 5 years (100%) reported that their children received all the vaccines recommended by the FP.

When asked, "Have you ever had cancer screening done?", 130 individuals (31.4%) reported having undergone screening. Out of 161 women aged 30 years and over, 72 (44.7%) had cervical cancer screening. Out of 141 women aged 40 years and over, 71 (50.4%) had mammography for breast cancer screening, and out of 243 individuals aged 50 years and over, 65 (26.7%) had colon cancer screening.

DISCUSSION

This study is a cross-sectional study that aimed at evaluating the utilization of health services and factors influencing health service usage among the rural population of Edirne and Kırklareli. A total of 414 households were surveyed. The average household size in our study (3.2 individuals) is similar to the average household size in Turkey in 2019 (3.35 individuals)[13].

Individuals residing in rural areas utilize health services less compared to those in urban areas[14]. One of the fundamental determinants of health service utilization is the distance traveled to obtain healthcare services, a fact well-established for a long time. A study conducted in Nigeria found that the utilization of health services decreased exponentially with increasing distance to healthcare facilities[15]. In our study, among the villages included, 36 (72%) had no healthcare facilities, 5 (10%) had health centers, and 9 (18%) had PHC . The average distance to the nearest SH from the villages was 16.5±8.5 km. A study conducted in Bursa reported similar findings, with rural neighborhoods being an average of 14.6 km away from primary health care centers and 16.57 km away from SH, comparable to our study[14].

Another significant factor affecting access to healthcare services is socio-economic status[16]. Among the 414 households surveyed, 49.5% had monthly incomes below the minimum wage, and 4.1% had no social security coverage, while 9.7% of households were insured under the Bağ-Kur system with premium debts. In 2019, general health insurance premiums of 9.1% of Turkish population were paid by governance and general health insurance premiums of 2.9% were paid by themselves[17]. According to Turkey Demographic and Health Survey 2018, 15% of women aged 15-49 years were in rural areas outside the scope of social security[11]. It is seen that the social security coverage in the villages where our study was conducted is better than in Turkey. A study conducted in Gebze in 2004 found the absence of social security coverage to be as high as 24.6%, while a study by Çakır[14] in Bursa reported that 46.8% of rural households had monthly incomes below the minimum wage, and the absence of social security coverage was approximately twice as high (8.2%) as in our study. These results suggest that social security coverage has expanded in our country over time[6].

Within the past year, excluding emergency situations, 69.1% of participants stated that they received services from SH, 55.6% from FHC, 19.6% from PH, and 12.6% from mobile health service when experiencing a health problem. Furthermore, when asked where they would prefer to receive services if they had a health issue, 50.2% indicated SH and 37.2% FHC. Despite living in rural areas and being an average of 16 km away, second-level healthcare facilities are the most utilized and preferred units for receiving healthcare services. Similarly, a study conducted in Eastern Anatolia in 2008 (67%) and in Bursa (44.5%) found that SH was the preferred initial point

of contact for healthcare services[14,18]. In a study conducted in Southern Ethiopia in 2019, participants preferred public primary healthcare institutions first, followed by educational and referral hospitals when they had a health problem[19]. In contrast to our findings, similar studies conducted in Turkey before and after the Health Transformation Program indicate that FHC were the primary choice for healthcare services[20-22]. These studies were mainly conducted in urban areas, and the primary reason for choosing FHC was their proximity. Similarly, in our study, the main reason for choosing FHC was its proximity. People living in rural areas generally travel to the nearest district centers to receive healthcare services and prefer SH due to the ability to directly access the desired level of care without a mandatory referral system between levels.

In our study, factors influencing the choice of the primary healthcare facility during working hours were examined. It was determined that whether the household had SSI premium debt, the presence of individuals aged 65 years and over or children under the age of 5 years did not affect the preference for first or second-level healthcare facilities. However, household income and the presence of FHC in the village of residence were found to influence this preference. Similarly, a study conducted in rural areas of Eskişehir found that those benefiting from mobile health services had significantly higher rates of referrals to second-level healthcare facilities[7]. The Ministry of Health transitioned to family medicine practice due to the inadequacy of the health center system established under Law no. 224 in meeting the healthcare needs of the population and the tendency of a large group of patients who could be treated at the primary care level to seek care from second and third-level healthcare facilities[23]. However, in our study and similar studies, it was observed that SH were the primary choice for healthcare services in rural areas, individuals receiving mobile health services preferred SH over FHC, and even those with poor socio-economic status preferred second-level healthcare facilities for receiving healthcare services. This suggests that family medicine practice may be inadequate in rural areas[7,14,18]. Similarly, in another study conducted in rural Indonesia, it was found that individuals with the poorest socio-economic status constituted the group that benefited the least from primary healthcare services[16].

In this study, 73.8% of the interviewed individuals over the age of 65 years had at least one diagnosed chronic illness. In Çakmur[24] study conducted in Kars province, this rate was 19% among individuals over 65 years old. In our study, 64.5% of individuals with a chronic illness stated that their FP did not conduct regular check-ups related to their chronic condition. This may suggest that the lack of chronic disease management by FPs and individuals' preference for being examined by specialists, indicating the influence of the perception of excessive specialization, contribute to the preference for SH as the first choice for healthcare services. Additionally, the fact that 87.8% of individuals aged 65 years and over reported that their FPs did not recommend any vaccines indicates that preventive services for the elderly are not effectively provided in the rural areas of these two provinces.

In this study, it was determined that the follow-up of women aged 15-49 years was not effectively conducted, although prenatal and child healthcare services were relatively better in terms of quantity in the rural areas of Edirne and Kırklareli. In our study, the rate of receiving prenatal care among pregnant women was found to be higher compared to Çakır[14] study conducted in Bursa and the Turkey Demographic and Health Survey 2018 data[11]. Despite the availability of follow-up services in SH and PHs, the effective provision of prenatal and child healthcare services may be influenced by the inclusion of these services in the performance criteria of FPs. In our study, 70% of the births in the last five years occurred in PHs, all of which took place in a healthcare facility.

Screenings conducted at the primary healthcare level are crucial for the early diagnosis of cancers. In our study, 31.4% of the participants had undergone at least one screening for breast, cervical, or colorectal cancer. This rate is similar to the cancer screening rates reported in Turkey and in the study conducted in Bursa[14,25]. However, it is lower compared to the screening rates in the European Union[26].

Study Limitations

The data obtained from this study only represent the provinces of Edirne and Kırklareli and cannot be generalized to the Thrace Region or Turkey. Other limitations include the fact that data on children were obtained from parents, which may introduce memory bias, and reliance on participants' self-reported healthcare usage.

CONCLUSION

Environmental and climatic conditions, socioeconomic factors, the quality and quantity of healthcare services provided, ethnic composition, cultural factors, and societal characteristics all influence health outcomes. While the environmental, climatic, and transportation conditions in Edirne and Kırklareli provinces do not pose significant barriers to accessing healthcare services, deficiencies in the delivery of primary healthcare services and the quality of care provided often direct people to secondary healthcare facilities. In our study, nearly half of the participants residing in rural or semi-rural areas reported receiving primary healthcare services through mobile units. Most participants stated that they would seek care at secondary healthcare facilities when faced with a health issue and would continue to do so. The lack of community-based family medicine practices, the absence of on-site healthcare delivery in rural areas, and the lack of home visits have limited primary healthcare services to those who seek them, leading to existing policies that encourage individuals to seek care primarily at hospitals.

According to the inverse care Law, the availability of quality healthcare tends to vary inversely with the need for healthcare

services in the population served, with studies indicating that this Law operates more strongly in areas where medical care is left to market forces and less so in areas dominated by public provision[27]. Hence, social policies play a crucial role as one of the most significant factors affecting health. It is imperative to provide healthcare services within the framework of equitable social policies. Rather than expecting the rural population to access healthcare services, a rights-based approach to health should involve bringing quality and reliable healthcare services to them, ensuring long-term access to healthcare, and reducing health inequalities between rural and urban areas.

Ethics Committee Approval: Ethical approval for the research was obtained from the Trakya University Scientific Research Ethics Committee (decision no: TÜTF-BAEK 2019/198, date: 13.05.2019).

Informed Consent: Individuals who agreed to participate in the study were informed about the research and verbal consent was obtained

Footnotes

Authorship Contributions

Konsept: B.T., M.E., Dizayn: B.T., M.E., Veri Toplama veya İşleme: G.D., Analiz veya Yorumlama: G.D., M.G., B.T., M.E., Literatür Arama: G.D., M.G., B.T., M.E., Yazan: G.D., M.G., B.T., M.E.

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

Financial Disclosure: The authors declared that this study received no financial support

REFERENCES

1. Hart LG, Larson EH, Lishner DM. Rural definitions for health policy and research. Am J Public Health. 2005;95:1149-55.
2. Çiftçi S, Aydınlı H. The changing rural-urban concepts and the legislation's effects on the nature in Turkey. Electronic Journal of Social Sciences. 2015;14:192-200.
3. TÜİK, Adrese Dayalı Nüfus Kayıt Sistemi Sonuçları 2023. https://data.tuik.gov.tr/Bulten/Index?p=Adrese-Dayali-Nufus-Kayit-Sistemi-Sonuclari-2023-49684..
4. T.C. Çevre, Şehircilik ve İklim Değişikliği Bakanlığı - Çevresel Göstergeler-Kentsel-Kırsal Nüfus Oranı. https://cevreselgostergeler.csb.gov.tr/kentsel---kirsal-nufus-orani-i-85670.
5. Öztek Z. Halk sağlığı: kuramlar ve uygulamalar. Ankara: Bireklam Arısı, 2020;37.
6. Ateş M, Erbaydar T, Demirkıran K, Özhan G, Cevahir E, İşçi E, et al. Utilization of health services and reasons for preferring health institutions by people living in Gebze: a survey. Hacettepe Journal of Health Administration. 2004;7:320-41.
7. Önsüz MF, Atalay Bİ, Işıklı B. Utilization of family medicine services in rural area of Eskisehir. ESTUDAM Journal of Public Health. 2016;1:19-27.
8. Akman E, Tarım M. Turkey and England health systems: comparison of primary health care. USAYSAD. 2020;6:303-16.
9. Tunç B. Birinci basamak sağlık hizmetlerinde kurum düzeyinde kişiye yönelik hizmet kapsayıcılığını değerlendirme ölçeği. (Tıpta Uzmanlık Tezi). Celal Bayar Üniversitesi Tıp Fakültesi. 2015; Manisa.
10. Saraçlı TS. Türkiye'de birinci basamak sağlık hizmetlerinde aile hekimliği modeli değerlendirmesi: İzmir ili pilot uygulaması. (Yüksek Lisans Tezi). Dokuz Eylül Üniversitesi Sosyal Bilimler Enstitüsü. 2010; İzmir.
11. Hacettepe University Institute of Population Studies. (2019). 2018 Turkey Demographic and Health Survey. Hacettepe University Institute of Population Studies, T.R. Presidency of Turkey Directorate of Strategy and Budget and TÜBİTAK, Ankara, Turkey. https://fs.hacettepe.edu.tr/hips/dosyalar/Ara%C5%9Ft%C4%B1rmalar%20-%20raporlar/2018%20TNSA/TDHS2018_mainReport_compressed.pdf.
12. Lwanga SK, Lemeshow S. Adequacy of sample size in health studies. Chichester: Wiley, 1990. Translated by: Hayran O. Istanbul: Marmara University Publications, 1991. https://digitallibrary.un.org/record/49698.
13. TUİK. İstatistiklerle Aile, 2019. https://data.tuik.gov.tr/.
14. Çakır R. Evaluation of primary health care services in rural areas: example of Bursa Province, Uludağ University faculty of medicine, Department of Public Health. Master thesis. 2017; Bursa.
15. Stock R. Distance and the utilization of health facilities in rural Nigeria. Soc Sci Med. 1983;17:563-70.
16. Suharmiati S, Laksono AD, Nantabah ZK, Kristiana L. Traditional health services utilization in rural Indonesia: does socioeconomic status matter? Rural Remote Health. 2023;23:7701.
17. SGK İstatistik Yıllığı – 2019. https://www.sgk.gov.tr/Istatistik/Yillik/fcd5e59b-6af9-4d90-a451-ee7500eb1cb4/ .
18. Üstü Y, Uğurlu M, Örnek M, Sanisoğlu SY. Evaluation of primary and secondary health care services in the Erzurum region between 2002-2008. Balkan Med J. 2011;28:55-61.
19. Bitew Workie S, Mekonen N, Michael MW, Molla G, Abrha S, Zema Z, et al. Modern health service utilization and associated factors among adults in southern ethiopia. J Environ Public Health. 2021;2021:8835780.
20. Özkan Bambal Ö, Lağarlı T, Eser E, Filibeli M, Bilecenoğlu T, Çivi G. et al. Assessment of the elements of the primary health care services for women, recorded in a family practice center in a suburban district of Manisa. Turk J Public Health. 2010;8:176-90.
21. İlhan MN, Tüzün H, Aycan S, Baran Aksakal FN, Özkan S. Birinci basamak sağlık kuruluşuna başvuranların sağlık hizmeti kullanma özellikleri ve bazı sosyoekonomik belirteçlerle değişimi: sağlık reformu öncesi son saptamalar. Toplum Hekimliği Bülteni. 2006;25:33-41.
22. Karakoç FY. Evaluation of the primary health care in Antalya (Kepez And Konyaalti District) in the second year of family medicine, Akdeniz University Faculty of Medicine, department of public health, master thesis. 2014; Antalya.
23. T.C.Sağlık Bakanlığı Aile Hekimliği Türkiye Modeli. Ankara: Sağlık Bakanlığı Yayınları. 2004;14-29.
24. Çakmur H. Frailty among elderly adults in a rural area of Turkey. Med Sci Monit. 2015;21:1232-42.
25. T.C. Sağlık Bakanlığı 2019 Faaliyet Raporu. http://www.sp.gov.tr/upload/xSPRapor/files/nmy6C+36626_tc-saglik-bakanligi-faaliyet-raporu-2019pdf.pdf .
26. OECD/EU: Health at a Glance: Europe 2019 – State of Health in the EU Cycle, Paris: OECD Publishing, 2019.
27. Hart JT. The inverse care law. Lancet. 1971;1:405-12.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.50490
Nam Kem Med J 2024;12(4):280-294

COVID-19 Vaccine Hesitancy: What Have We Learnt? - A Cross-Sectional Survey Among Adults in Tamil Nadu, India

COVİD-19 Aşı Tereddütü: Ne Öğrendik? - Hindistan, Tamil Nadu'daki Yetişkinler Arasında Kesitsel Bir Araştırma

Melvin GEORGE[1], Kaviya MANOHARAN[1], Juanna JINSON[1], Indiraa PRIYADHARSHINI[1], Chaarmila SHERIN C[1], Billy GRAHAM R[1], Ananda Keerthi ANAN D[1], Nirmal KUMAR D[1], Vedha Pal JAYAMANI S[2]

[1]SRM Medical College Hospital and Research Centre, Centre for Clinical Pharmacology, Tamil Nadu, India
[2]Jaya College of Paramedical Sciences Faculty of Pharmacy, Tamil Nadu, India

ABSTRACT

Aim: Today, vaccine hesitancy is one of the top 10 global health threats, which hinders adequate immunization coverage and herd immunity. The most recent global event that has led to a surge in vaccine hesitancy is the COVID-19 pandemic. COVID-19 vaccines have been studied extensively, but a sizable number of people continue to have misgivings towards COVID-19 vaccines.

Materials and Methods: We performed a cross-sectional survey among adults across Tamil Nadu, India, to measure the frequency of vaccine hesitancy and to understand the factors contributing to it.

Results: In our study population (n=1622), 49% were unwilling to get vaccinated. Hesitancy was higher among males when compared to females (54% vs. 41%) and among the older population when compared to the younger population (58% vs. 43%). The most preferred information sources regarding COVID-19 vaccines were television (38%), social media (25%), and newspapers (16%). Among the various social media platforms, WhatsApp was the most popular (33%), and Twitter was the least popular (2%). Half the population (52%) felt that herbal supplements were sufficient to provide immunity against COVID-19. The most common reason for hesitancy towards COVID-19 vaccination was the perception that the vaccine was not safe enough (52%).

Conclusion: Our study shows that even after sufficient time had passed since the start of the pandemic, vaccine hesitancy in a progressive state such as Tamil Nadu was disturbingly high. This warrants the need for more efforts to educate the public about the necessity of vaccines.

Keywords: COVID-19 vaccines, adults, willingness, source of information, hesitancy

ÖZ

Amaç: Aşı tereddüdü, günümüzde yeterli aşılama ve sürü bağışıklığını engelleyen en önemli 10 küresel sağlık tehdidinden biridir. Aşı tereddüdünde artışa yol açan en son küresel olay COVID-19 salgınıdır. COVID-19 aşılarının kapsamlı bir şekilde incelenmesine rağmen, önemli sayıda insan COVID-19 aşılarına karşı şüphe duymaya devam etmektedir.

Gereç ve Yöntem: Aşı tereddüdünün sıklığını ölçmek ve buna katkıda bulunan faktörleri anlamak için Hindistan'ın Tamil Nadu kentindeki yetişkinler arasında kesitsel bir anket gerçekleştirdik.

Bulgular: Çalışma popülasyonumuzda (n=1622), %49'u aşı yaptırmak istemiyordu. Aşı yaptırmaya karşı isteksizlik, erkeklerde kadınlara kıyasla (%54'e karşı %41) ve yaşlı popülasyonda genç popülasyona kıyasla (%58'e karşı %43) daha yüksekti. COVID-19 aşıları hakkında en çok tercih edilen bilgi kaynakları televizyon (%38), sosyal medya (%25) ve gazetelerdi (%16). Çeşitli sosyal medya platformları arasında WhatsApp en popüler (%33) ve Twitter ise en az popüler olanıydı (%2). Nüfusun yarısı (%52), bitkisel takviyelerin COVID-19'a karşı bağışıklık sağlamak için yeterli olduğunu düşünüyordu. COVID-19 aşısına karşı tereddüdün en yaygın nedeni, aşının yeterince güvenli olmadığı algısıydı (%52).

Sonuç: Çalışmamız, pandeminin başlangıcından bu yana yeterli zaman geçmesine rağmen, Tamil Nadu gibi ilerici bir eyalette aşı tereddüdünün rahatsız edici derecede yüksek olduğunu gösteriyor. Bu durum, halkı aşıların gerekliliği konusunda eğitmek için daha fazla çaba gösterilmesinin gerektiğini ortaya koymaktadır.

Anahtar Kelimeler: COVID-19 aşıları, yetişkinler, isteklilik, bilgi kaynağı, tereddüt

Address for Correspondence: Melvin GEORGE MD, SRM Medical College Hospital and Research Centre, Centre for Clinical Pharmacology, Tamil Nadu, India
E-mail: melving@srmist.edu.in **ORCID ID:** orcid.org/0000-0001-7101-8513
Received: 12.07.2024 **Accepted**: 12.09.2024

INTRODUCTION

India has one of the largest immunization programs in the world, with a total coverage of 76.1% (National Family Health Survey 2019-2020)[1]. The Universal Immunization Programme was implemented in the country in 1985. Under the aegis of the National Rural Health Mission, this program is a crucial, cost-effective public health intervention in the country. Immunization against 12 vaccine-preventable diseases is provided free of cost to the public, 11 at the national level (diphtheria, pertussis, tetanus, polio, measles, rubella, tuberculosis, hepatitis B, and meningitis or pneumonia caused by Haemophilus influenzae type b) and 3 at the sub-national level (rotavirus diarrhea, pneumococcal pneumonia, and Japanese encephalitis). These vaccines can be availed in any Indian state. The Government of India has also introduced strategies for capacity building and system strengthening through training programs, a National Cold Chain Management Information System, and an Electronic Vaccine Intelligence Network[2,3]. However, there still remain factions that remain hesitant to take vaccines.

Vaccine hesitancy refers to a delay in acceptance or refusal of vaccination despite the availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place, and vaccines. It is influenced by factors such as complacency, convenience, and confidence. A Vaccine Hesitancy Determinants Matrix was developed by the Strategic Advisory Group of Experts on Immunization Working Group enumerating the various factors influencing vaccine hesitancy. These factors were divided into three categories - contextual influences, individual and group influences, and vaccine/vaccination-specific issues[4]. This suggests the highly dynamic nature of vaccine hesitancy and the need for continuous research in this area.

Vaccine hesitancy is a phenomenon that has been reported ever since the discovery of the first vaccine[5] by Edward Jenner in 1796. There are also reports of skepticism towards vaccines against other highly contagious infections such as diphtheria, pertussis, tetanus[6], measles, mumps, rubella[7], the Human Papilloma Virus[8] and in recent times, COVID-19. Today, vaccine hesitancy is one of the top ten global health threats, as per the World Health Organization (WHO)[9].

Vaccines became, unarguably, our most formidable weapon against the coronavirus pandemic that began in 2019. Regulatory authorities like the United States Food and Drug Administration, European Medicines Agency, Medicines and Healthcare products Regulatory Agency, and Central Drugs Standard Control Organization approved several vaccines against the SARS-CoV-2 virus, such as Pfizer-Biotech, Moderna, Sputnik, and Astrazeneca[10]. In India, the two most widely used vaccines were Covishield and Covaxin, developed by Serum Institute of India and bharat biotech, respectively[11,12]. Since the beginning of vaccine rollout in mid-January 2021 until December 2021, approximately 1,32,93,84,230 doses were administered to the Indian public. The number rose to 2,20,67,82,117 in January 2024[13]. Overall, vaccine intake is steadily rising, but a sizable number of people remain hesitant to take vaccines.

Studies on COVID-19 vaccine acceptance and factors affecting it, performed in countries such as Ethiopia, Congo[14], Portugal[15], Ireland[16], Japan[17], UK[18], and US[19], have reported that vaccine hesitancy is a looming challenge today. Recent statistics show that 5% of the eligible population in India has received only a single dose, and 12% still remain unvaccinated against the coronavirus[20].

Tamil Nadu, a southern Indian state, has fared reasonably well with respect to social, economic, and health indicators in the last few decades. Yet a few studies report that COVID-19 vaccine hesitancy is a definite issue in this state, and it lags behind several others in COVID-19 vaccineuptake[21,22]. The emergence of Omicron and its variants reiterate the importance of protection conferred by vaccines.

The effectiveness of a vaccine is heavily dependent on its rate of acceptance by the public. We aimed to study the magnitude of vaccine hesitancy across the state of Tamil Nadu, India, and factors influencing it. Since misinformation about COVID-19 disease and vaccines was rampant at the time, our study also assessed levels of trust in various information sources, including social media platforms. The results of this study can play a crucial role in combating vaccine hesitancy during public health vaccination campaigns in future pandemics.

MATERIALS AND METHODS

This cross-sectional study was performed among adults in Tamil Nadu, India, during August and September 2021. The study was performed in compliance with the ethical principles of the Declaration of Helsinki. The study was SRM Medical College Hospital and Research Centre initiated after getting approval from the Ethics Committee of our institution (decision no: 2871/IEC/2021, date: 23.01.2021) and registration in the Clinical Trial Registry of India. Based on the availability of manpower and resources, a systematic random sampling strategy was employed so that the survey covered rural, semi-urban, and urban households in all the regions of Tamil Nadu (north, south, west, and central). Considering the 2021 population of Tamil Nadu as 72,147,030 (https://censusindia.gov.in/census.website/data/data-visualizations/PopulationSearch_PCA_Indicators), 95% confidence level, and 3% margin of error, the minimum sample size required was calculated as 1.070. After a proper explanation of the study purpose and the acquisition of written informed consent from the participants, information

was collected using an author-designed, internally validated questionnaire. The questionnaire consisted of 7 sections with 41 questions. Section 2 constituted the information sheet and informed consent, section 1 sought to determine sources of information used by the public, and section 3 assessed public perceptions regarding COVID-19 vaccines. Questions in sections 4, 5 and 6 were formulated in such a way so as to understand the degree of hesitancy and its contributing factors. Section 7 consisted of 8 questions that gathered demographic characteristics such as name, age, gender, educational status, occupation, and contact information (email/phone number, city, and district). The information was collected through a mixture of dichotomous and multiple-choice, close-ended questions. Two questions used the Likert-scale, and one open-ended question was added in section 6 to determine what was the most important information sought when a new vaccine is introduced or announced. Questions were prepared in English and Tamil languages. An online questionnaire was used as an additional method to achieve a wider reach. The public was encouraged to participate in the survey by explaining about the study. No financial incentives were given to the participants.

Statistical Analysis

Data were analyzed using SPSS version 16.0. Continuous variables were expressed as mean ± SD, and categorical variables were expressed as frequency with percentage. Comparison between various subgroups was done using the chi-square test. Multiple linear regression analyses were performed to determine the factors affecting vaccine hesitancy. A p-value less than 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the study population are described in Table 1. The mean age of participants was around 38±15 years. 60% of the respondents were males. 57% had only completed school-level education, and 90% were not associated with the healthcare profession. The proportion of healthcare professionals among those with degrees was 22.3%.

The most preferred information source regarding COVID-19 vaccines was television (38%) followed by social media (25%). Among the various social media platforms, WhatsApp (33%), Facebook (20%), and Instagram (11%) were the most popular. YouTube (8%) and Twitter (2%) were the least popular. A fourth of the respondents (26%) reported that they did not trust social media for vaccine information.

The most preferred vaccines were Covishield (62%), and Covaxin (24%), and a majority believed that both vaccines were of equal safety and efficacy. 79% of participants preferred to take vaccines in injection form than any other means.

It was noted that almost half the respondents believed herbal supplements to be sufficient for immunity against COVID-19. A little more than half reported that vaccine-associated negative publicity caused them to lose interest in getting vaccinated. 58%were against compulsory vaccination for all.

When asked about the various concerns about the vaccines, fever was reported as the most common (24%) (Figure 1). 64% of participants reported that information regarding safety was most important when a new vaccine came to market (Figure 2). Although 95% of participants conveyed that no one within their social circles had developed serious adverse reactions to these vaccines and 62% believed that the vaccines were adequately monitored for safety by the government, it was surprising to note that almost half the population (49%) was unwilling to get vaccinated. 76% were not vaccinated even with a single dose. Multiple linear regression analyses were performed to obtain the odds ratio (OR) and to determine the factors affecting vaccine hesitancy (Table 2). Being a healthcare professional [OR: 3.354; 95% confidence interval (CI): 1.972-5.705; p<0.001], the presence of a vaccine mandate (OR: 4.164; 95% CI: 3.158-5.490; p<0.001), societal pressure to get vaccinated (OR: 2.058; 95% CI: 1.546-2.738; p<0.001), the belief that COVID-19 vaccines have been adequately studied (OR: 1.829; 95% CI: 1.394-2.400; p<0.001) and are being monitored for safety by the government (OR: 1.437; 95% CI: 1.093-1.889; p=0.01), endorsement of these vaccines by celebrities (OR: 1.637; 95% CI: 1.259-2.129; p<0.001), and ambiguity regarding the time interval required between vaccine doses (OR: 1.734; 95% CI: 1.286-2.339; p<0.001) were found to decrease vaccine hesitancy. On the other hand, negative publicity about vaccines (OR: 0.615; 95% CI: 0.476-0.794; p<0.001), the influence of anti-vaccination groups (OR: 0.734; 95% CI: 0.565-0.953; p<0.001), the presence of a major illness (OR: 0.400; 95% CI: 0.307-0.521; p<0.001), and a past history of COVID-19 infection (OR: 0.268; 95% CI: 0.202-0.356; p<0.001) were found to increase vaccine hesitancy.

Subgroup analyses were performed based on age (Table 3 (a)), gender (Table 3 (b)), and education level (Table 3 (c)). For obtaining vaccine information, older adults relied mostly on television, whereas youngsters had equal preferences for television and social media. WhatsApp and Facebook had a similar degree of preference in both age groups (34% vs. 32%, 21% vs. 18%, p=0.0001). Older adults had greater preference for herbal supplements (59% vs. 47%, p=0.0001). Youngsters were more in favor of compulsory vaccination (49% vs. 33%, p=0.0001) and they were also under greater societal pressure to get themselves vaccinated (39% vs. 33%, p=0.018). The proportion of the unvaccinated population was higher in the older age group (79% vs. 73%, p=0.01032).

Table 1. Baseline characteristics

	Variable/characteristic	Frequency (%) or Mean ± SD (n=1622)
1.	Age (years)	37.88±15.38
2.	Gender	
	Male	977 (60.2)
	Female	645 (39.8)
3.	Occupation - Health care professional	
	Yes	161 (9.9)
	No	1461 (90.1)
4.	Education	
	School level education	926 (57.1)
	Completed undergraduate education	532 (32.8)
	Completed postgraduate education	164 (10.1)
5.	Sources used for information on COVID-19 vaccines	
	Television	631 (38.1)
	Social media	408 (25.2)
	Newspaper/magazines	269 (16.6)
	Healthcare professionals	242 (14.9)
	Journal articles	72 (4.4)
6.	Social media used for information on COVID-19 vaccines	
	WhatsApp	536 (33.0)
	Do not trust social media	427 (26.3)
	Facebook	319 (19.7)
	Instagram	178 (11.0)
	YouTube	132 (8.1)
	Twitter	29 (1.8)
7.	How was negative information related to COVID-19 vaccines clarified?	
	Ask a healthcare worker	629 (38.8)
	Ask a friend/family/relative	572 (35.3)
	Check authenticity on the internet	410 (25.3)
	Others	11 (0.7)
8.	Most trusted source for information on COVID-19 vaccines	
	Healthcare worker	907 (55.9)
	Friend/family	524 (32.3)
	Social media	168 (10.4)
	Other	23 (1.4)
9.	Least trusted source for information on COVID-19 vaccines	
	Social media	871 (53.7)
	Friend/family	573 (35.5)
	Healthcare worker	164 (10.1)
	Other	14 (0.9)
10.	Do you trust the companies manufacturing COVID-19 vaccines?	
	Yes	1202 (74.1)
	No	420 (25.9)
11.	Do you believe herbal supplements are sufficient for immunity against COVID-19 infection?	
	Yes	837 (51.6)
	No	785 (48.4)

Table 1. contiuned

	Variable/characteristic	Frequency (%) or Mean ± SD (n=1622)
12.	Do you believe COVID-19 vaccines strengthen the immune system?	
	Yes	1181 (72.8)
	No	441 (27.2)
13.	Most preferred COVID-19 vaccine	
	Covishield	1008 (62.1)
	Covaxin	385 (23.7)
	Sputnik	97 (6.0)
	Pfizer	94 (5.8)
	Moderna	20 (1.2)
	Others	18 (1.1)
14.	Attitude regarding Covishield and Covaxin	
	Covaxin and Covishield have equal safety and efficacy	973 (60.0)
	Covishield is safer and more effective than Covaxin	387 (23.9)
	Covaxin is safer and more effective than Covishield	214 (13.2)
	Both Covishield and Covaxin are harmful	48 (3.0)
15.	Preferred route of administration for COVID-19 vaccines	
	Injection	1284 (79.2)
	Oral (tablet/syrup)	168 (10.4)
	Nasal spray	151 (9.3)
	Others	18 (1.1)
16.	Does negative publicity influence your opinion about getting COVID-19 vaccines?	
	Yes	881 (54.3)
	No	740 (45.6)
17.	Do you believe that COVID-19 vaccination is a risk for your health?	
	Yes	550 (33.9)
	No	1072 (66.1)
18.	Do you think COVID-19 infection can occur even after vaccination?	
	Yes	319 (19.7)
	No	1303 (80.3)
19.	Should COVID-19 vaccine be made compulsory?	
	Yes	685 (42.2)
	No	937 (57.8)
20.	Do you feel social pressure to get COVID-19 vaccine?	
	Yes	588 (36.3)
	No	1034 (63.7)
21.	Are you concerned about side-effects of COVID-19 vaccines?	
	Yes	909 (56.0)
	No	713 (44.0)
22.	Serious adverse reactions to COVID-19 vaccines and percentage of participants who knew at least one person in their circle that developed said reaction	
	No	1548 (95.4)
	Death	30 (1.8)
	Hospitalization	17 (1.0)
	Fever with body pain	7 (0.4)
	Body pain	6 (0.4)
	Heart attack	5 (0.3)
	Fever	4 (0.2)
	Allergy	3 (0.2)
	Headache	2 (0.1)

Table 1. contiuned

	Variable/characteristic	Frequency (%) or Mean ± SD (n=1622)
23.	Do you believe that COVID-19 vaccines have been studied adequately? Yes No	 1024 (63.1) 598 (36.9)
24.	Do you believe that COVID-19 vaccines are being adequately monitored for safety by the Government of India? Yes No	 1000 (61.7) 622 (38.3)
25.	Do you believe that the vaccine should not be taken by persons with major illnesses such as cancer, heart disease, kidney disease etc.? Yes No	 1081 (66.6) 541 (33.4)
26.	Are you willing to get vaccinated against COVID-19? Yes No Already vaccinated	 663 (40.9) 796 (49.1) 163 (10.0)
27.	Have you been vaccinated against COVID-19? No Single Dose Double Dose	 1225 (75.6) 278 (17.1) 118 (7.3)
28.	Do you believe that the vaccine is not needed if the person has a history of COVID-19 infection in the past? No, it is still required. Yes, it is not required.	 1109 (68.4) 513 (31.6)
29.	Do you believe that celebrities can instill confidence in getting vaccinated against COVID-19 infection? Yes No	 682 (42.0) 940 (58.0)
30.	Have you lost interest in getting the COVID-19 vaccine due to the time interval between the two doses? Yes No	 418 (25.8) 1203 (74.2)

SD: Standard deviation

Older adults felt celebrities taking a COVID-19 vaccine made them more confident in doing the same when compared to younger adults (46% vs. 39%, p=0.009).

22% of males and 34% of females did not trust social media for information on vaccines (chi-square statistic 27.27; p=0.0001). There was no difference in preference towards social media platforms between genders. WhatsApp and Facebook were the most popular, and Twitter was the least popular information source. A greater proportion of male respondents reported that they felt greater social pressure to get vaccinated (52% vs. 39%, p=0.03) and that the vaccine should not be taken by persons with major illnesses (70% vs. 61%, p=0.0001). Most female respondents believed that vaccines ought to be made compulsory for all (51% vs. 36%, p=0.0001). They were also more willing to get vaccinated against COVID-19 (59% vs. 46%, p=0.0001). And as expected, a greater proportion of males were found to be unvaccinated compared to females (79% vs. 71%, p=0.0002).

When subgroup analysis was done with respect to education level, it was seen that television was the most preferred information source among school - educated participants (46%), whereas television and social media were equally preferred among college-educated participants (29% vs. 30%, p=0.0001). WhatsApp was the most popular social media platform in both groups. The school-level population preferred herbal supplements for immunity against COVID-19

infection (57% vs. 45%, p=0.0001) and was more influenced by negative publicity about vaccines (61% vs. 52%, p=0.0001). A greater proportion in the college educated group wanted the vaccine to be made compulsory (87% vs. 35% p=0.0001) and felt greater societal pressure to take vaccines (93% vs. 31%, p=0.0001). Unwillingness to get vaccinated was more prevalent among the school-completed population (58% vs. 38%, p=0.0001) and as expected, a greater proportion of these participants remained unvaccinated (82% vs. 67%, p=0.0001).

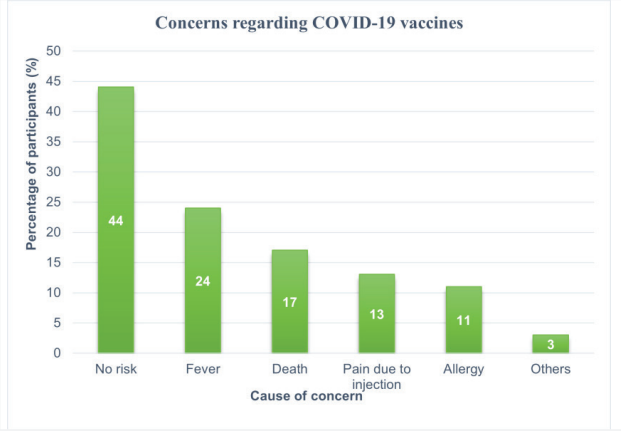


Figure 1. Concerns regarding the vaccine

In our study, 56% of the population were concerned about the risk that might occur after being vaccinated. Fever (24%) and death (17%) were the most common concerns. Injection and allergy were the least common concerns

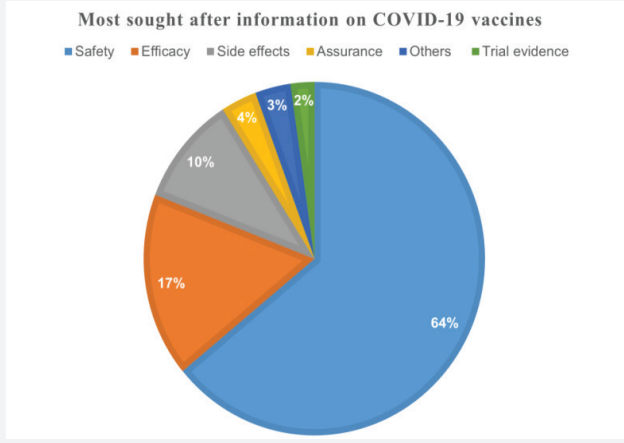


Figure 2. Most sought-after information about vaccines

Safety (64%) was the most important information sought when the new vaccines came to market. This was followed by the efficacy (17%) of and information (10%) about the vaccine

Table 2. Factors affecting COVID-19 vaccine hesitancy

Factor	Wald	Sig.	Exp (B)	95.0% CI for EXP (B)	
				Lower	Upper
Gender	1.647	0.199	0.847	0.657	1.092
Occupation - healthcare professional	19.931	0.000	3.354	1.972	5.705
Trust in vaccine manufacturing companies	2.562	0.109	1.281	0.946	1.734
Negative publicity about vaccines	13.843	0.000	0.615	0.476	0.794
Belief that vaccines are a risk to health	0.302	0.583	0.921	0.688	1.234
Belief that vaccination will give you COVID-19 infection	0.040	0.842	0.967	0.693	1.348
Vaccine mandate	102.155	0.000	4.164	3.158	5.490
Societal pressure	24.503	0.000	2.058	1.546	2.738
Influence of anti-vaccination groups	5.378	0.020	0.734	0.565	0.953
Concern regarding the risks of the vaccine	0.694	0.405	1.117	0.861	1.450
Belief that COVID-19 vaccines have been studied adequately	19.008	0.000	1.829	1.394	2.400
Belief that COVID-19 vaccines are being adequately monitored for safety by the Government of India	6.726	0.010	1.437	1.093	1.889
Need to get a booster dose	0.917	0.338	1.137	0.874	1.478
Presence of a major illness	45.986	0.000	0.400	0.307	0.521
History of COVID-19 infection in the past	83.088	0.000	0.268	0.202	0.356
Vaccine endorsement by celebrities	13.525	0.000	1.637	1.259	2.129
Ambiguity regarding time interval required between vaccine doses	13.007	0.000	1.734	1.286	2.339

CI: Confidence interval

Table 3 (a). Subgroup analysis – response of participants with respect to age				
	Variable/characteristic	n=1622		p-value
		Age <40 n=967	Age >40 n=655	
1.	Sources used for information on COVID-19 vaccines			0.0001
	Television	317 (32.8)	314 (47.9)	
	Social media	309 (31.9)	99 (15.1)	
	Newspaper/magazines	151 (15.6)	118 (18)	
	Healthcare professionals	144 (14.9)	98 (14.9)	
	Journal articles	46 (4.8)	26 (3.9)	
2.	Social media used to acquire COVID-19 vaccine information.			0.0001
	WhatsApp	325 (33.6)	211 (32.2)	
	Facebook	202 (20.9)	117 (17.9)	
	Did not trust social media	201 (20.8)	228 (34.8)	
	Instagram	165 (17)	12 (1.8)	
	YouTube	49 (5.1)	83 (12.7)	
	Twitter	25 (2.6)	4 (0.6)	
3.	How was negative information related to COVID-19 vaccines clarified?			0.0001
	Ask a healthcare worker	343 (35.5)	286 (43.7)	
	Check authenticity on the internet	309 (31.9)	101 (15.4)	
	Ask a friend/family/relative	308 (31.9)	264 (40.3)	
	Others	7 (0.7)	4 (0.6)	
4.	Most trusted source for information on COVID-19 vaccines			0.0001
	Healthcare worker	574 (59.4)	333 (50.8)	
	Friend/family	256 (26.5)	268 (40.9)	
	Social media	123 (12.7)	45 (6.9)	
	Other	14 (1.4)	9 (1.4)	
5.	Least trusted source for information on COVID-19 vaccines			0.011
	Social media	487 (50.4)	384 (58.6)	
	Friend/family	365 (37.7)	208 (31.8)	
	Healthcare worker	107 (11)	57 (8.7)	
	Other	8 (8.3)	6 (0.9)	
6.	Do you believe herbal supplements are sufficient for immunity against COVID-19 infection?			0.0001
	Yes	454 (46.9)	383 (58.5)	
	No	513 (53)	272 (41.5)	
7.	Most preferred COVID-19 vaccine			0.0001
	Covishield	550 (56.9)	458 (69.9)	
	Covaxin	244 (25.2)	141 (21.5)	
	Sputnik	80 (8.3)	17 (2.6)	
	Pfizer	64 (6.6)	30 (4.6)	
	Moderna	16 (1.7)	4 (0.6)	
	Other	13 (1.3)	5 (0.8)	
8.	Attitude regarding Covishield and Covaxin:			0.0001
	Covaxin and Covishield have equal safety and efficacy	529 (54.7)	444 (67.7)	
	Covishield is safer and more effective than Covaxin	254 (26.3)	133 (20.3)	
	Covaxin is safer and more effective than Covishield	153 (15.8)	61 (9.3)	
	Both Covishield and Covaxin are harmful	31 (3.2)	17 (2.6)	
9.	Should COVID-19 vaccine be made compulsory?			0.0001
	Yes	469 (48.5)	216 (32.9)	
	No	498 (51.5)	439 (67)	

Table 3 (a). continued

	Variable/characteristic	n=1622		p-value
		Age <40 n=967	Age >40 n=655	
10.	Do you feel social pressure to get COVID-19 vaccine? Yes No	 373 (38.6) 594 (61.4)	 215 (32.8) 440 (67.2)	0.018
11.	Do you believe that COVID-19 vaccination is a risk for your health? Yes No	 582 (60.2) 385 (39.8)	 327 (49.9) 328 (50)	0.0001
12.	Are you willing to get vaccinated against COVID-19? Yes No	 553 (57) 414 (42.8)	 273 (42) 382 (58.3)	0.0001
13.	Have you been vaccinated against COVID-19? Yes No	 258 (27) 709 (73.3)	 138 (21) 516 (78.8)	0.01032
14.	Do you believe that the vaccine is not needed if the person has a history of COVID-19 infection in the past? No, it is still required. Yes, it is not required.	 697 (72) 270 (27.9)	 412 (62.9) 243 (37)	0.0001
15.	Do you believe that celebrities can instill confidence in getting vaccinated against COVID-19 infection? Yes No	 381 (39.4) 586 (60.5)	 301(45.9) 354 (54)	0.009

DISCUSSION

Our study shows that 49% of study participants were unwilling to take vaccines. This finding resonates with an earlier study carried out across rural and urban groups in Tamil Nadu where 40.7% of participants were vaccine hesitant and 19.5% were vaccine deniers[21]. Similarly, a 2019-2020 study done in Maharashtra, India, showed that 37% of participants were either unwilling or unsure about receiving vaccines. Although WHO and Center for Disease Control (CDC) have declared that COVID-19 is no longer a public health emergency[23,24], herd immunity granted by vaccines still remains a formidable weapon against the disease at the community level, particularly in the face of new viral variants. Hence, it is essential that vaccine hesitancy be tackled effectively. At the time of data collection, more than ten months had passed since vaccine rollout, but the fact that half the study population was still unwilling to get vaccinated remains intriguing. One would expect that a greater degree of acceptance would have set in due to increasing knowledge gained about these vaccines.

Our study examined the various factors influencing vaccine hesitancy. Positive factors that reduced vaccine hesitancy included being a healthcare professional, the presence of a vaccine mandate, societal pressure to get vaccinated, the belief that COVID-19 vaccines have been adequately studied and are being monitored for safety by the government, endorsement of vaccines by celebrities, and ambiguity regarding the time interval required between vaccine doses. The higher acceptance of vaccines among healthcare professionals may be explained by their knowledge about the mechanisms underlying vaccination and its benefits, clinical experience, and the risk they face as frontline workers, especially during pandemics[25].On the other hand, they may also be reluctant to voice their hesitancy towards vaccines due to pressures from various organizations and their position as role models to the public. The introduction of a vaccine mandate appears to reduce vaccine hesitancy, possibly due to the fact that it is an authoritative decree that could impact several social activities, such as admission to schools and workplaces. It appears that the public perceives a vaccine mandate as a punitive strategy because 58% of our study population were against compulsory vaccination. They feel coercion is unwarranted as it forces them to take vaccines even when they are not personally convinced of their safety and efficacy. However, this is not the first instance of coercion for vaccination. For example, in the USA, children are expected to get vaccinated before attending school. Similarly, in Italy, fines are imposed if children do not take their regular vaccinations[26]. The third factor that appears to reduce vaccine hesitancy is societal pressure.

During the subgroup analysis, it was observed that unwillingness was more pronounced among males (54% vs. 41%; p<0.0001), probably due to greater social pressure from their employers to get vaccinated. However, few Indian studies report greater vaccine hesitancy among females[22]. 42% of our participants agreed that endorsement from notable personalities could be a favorable factor in influencing public opinion. The regression analysis also arrived at the same conclusion. The trust that COVID-19 vaccines have been adequately studied and are being monitored for safety by the government were other factors that reduced vaccine hesitancy. 38% of our study population felt that COVID-19 vaccines were inadequately studied. A similar proportion believed the Indian Government had not sufficiently evaluated vaccine safety.

Table 3 (b). Subgroup analysis – response of participants with respect to gender

	Variable/characteristic	n=1622		p-value
		Male n=977	Female n=645	
1.	Social media used for information on COVID-19 vaccines WhatsApp Facebook Do not trust social media Instagram YouTube Twitter	 348 (35.6) 226 (23.1) 213 (21.8) 93 (9.5) 77 (7.9) 20 (2)	 188 (29.1) 93 (14.4) 216 (33.5) 84 (13.0) 55 (8.5) 9 (1.4)	0.0001
2.	Preferred route of administration for COVID-19 vaccines Injection Nasal spray Oral (tablet/syrup) Others	 777 (79.5) 103 (10.5) 87 (8.9) 10 (1)	 507 (78.6) 48 (7.4) 81 (125) 8 (1.2)	0.026
3.	Does negative publicity influence your opinion about getting COVID-19 vaccines? Yes No	 565 (57.8) 412 (42.1)	 312 (48.3) 332 (51.4)	0.0001
4.	Should COVID-19 vaccine be made compulsory? Yes No	 355 (36.3) 622 (63.6)	 330 (51.1) 315 (48.8)	0.0001
5.	Do you feel social pressure to get COVID-19 vaccine? Yes No	 334 (51.8) 643 (65.8)	 254 (39.4) 391 (60.6)	0.033
6.	Are you concerned about side effects of COVID-19 vaccines? Yes No	 502 (51.4) 475 (48.6)	 407 (63.1) 238 (36.9)	0.0001
7.	Do you believe that the vaccine should not be taken by persons with major illnesses such as cancer, heart disease, kidney disease etc.? Yes No	 687 (70.3) 290 (29.7)	 394 (61.4) 251 (38.9)	0.0001
8.	Are you willing to get vaccinated against COVID-19? Yes No	 446 (46) 531 (54.3)	 380 (59) 265 (41)	0.0001
9.	Have you been vaccinated against COVID-19? Yes No	 207 (21) 769 (78.7)	 189 (29) 456 (70.7)	0.0002
10.	Do you believe that the vaccine is not needed if the person has a history of COVID-19 infection in the past? No, it is still required. Yes, is it not required.	 636 (65) 341 (34.9)	 473 (73.3) 172 (26.7)	0.0001

Table 3 (c). Subgroup analysis - Response of participants with respect to education level

	Variable/characteristic	n=1622		p-value
		School level n=926	College level n=696	
1.	Sources used for information on COVID-19 vaccines			0.0001
	Television	429 (46.3)	202 (29.0)	
	Social media	200 (21.6)	208 (29.9)	
	Newspaper/magazines	148 (15.9)	94 (13.5)	
	Healthcare professionals	129 (13.9)	140 (20.1)	
	Journal articles	20 (2.2)	52 (7.5)	
2.	Social media used for information on COVID-19 vaccines			0.0001
	WhatsApp	291 (31.4)	245 (35.2)	
	Do not trust social media	272 (29.4)	157 (22.5)	
	Facebook	181 (19.5)	138 (19.8)	
	YouTube	98 (10.6)	34 (4.8)	
	Instagram	76 (8.2)	101 (14.5)	
	Twitter	8 (0.9)	21 (3.0)	
3.	How was negative information related to COVID-19 vaccines clarified?			0.0001
	Ask a friend/family/relative	363 (39.2)	209 (30.0)	
	Ask a healthcare worker	352 (38.0)	277 (39.8)	
	Check its authenticity in the internet	206 (22.2)	204 (29.3)	
	Others	5 (0.5)	6 (0.8)	
4.	Do you trust the companies manufacturing COVID-19 vaccines?			0.003
	Yes	712 (76.8)	490 (70.4)	
	No	214 (23.1)	206 (29.5)	
5.	Do you believe herbal supplements are sufficient for immunity against COVID-19 infection?			0.0001
	Yes	525 (56.7)	312 (44.8)	
	No	401 (43.3)	384 (55.1)	
6.	Do you believe COVID-19 vaccines strengthen the immune system?			0.007
	Yes	698 (75.4)	483 (69.3)	
	No	228 (24.6)	213 (30.6)	
7.	Attitude regarding Covishield and Covaxin			0.0001
	Covaxin and Covishield have equal safety and efficacy	618 (66.7)	355 (51.0)	
	Covishield is safer and more effective than Covaxin	193 (20.8)	194 (27.9)	
	Covaxin is safer and more effective than Covishield	100 (10.8)	114 (20.7)	
	Both Covishield and Covaxin are equally harmful	15 (1.6)	33 (4.7)	
8.	Does negative publicity influence your opinion about getting COVID-19 vaccines?			0.0001
	Yes	566 (61.1)	360 (51.7)	
	No	360 (38.9)	384 (55.1)	
9.	Do you believe COVID-19 infection can occur even after vaccination?			0.0001
	Yes	148 (15.9)	171 (24.5)	
	No	778 (84.0)	525 (75.0)	
10.	Should COVID-19 vaccine be made compulsory?			0.0001
	Yes	323 (34.9)	603 (86.6)	
	No	603 (65.1)	334 (48.0)	
11.	Do you feel social pressure to get COVID-19 vaccine?			0.0001
	Yes	282 (30.5)	644 (92.5)	
	No	644 (69.5)	390 (56.0)	

Table 3 (c). continued

	Variable/characteristic	n=1622		p-value
		School level n=926	College level n=696	
12.	Are you concerned about side effects of COVID-19 vaccines? Yes No	 474 (51.2) 452 (48.8)	 452 (65.0) 261 (37.5)	0.0001
13.	Do you believe COVID-19 vaccines have been studied adequately? Yes No	 613 (66.2) 313 (33.8)	 313 (45.0) 285 (41.0)	0.003
14.	Do you believe that the vaccine should not be taken by persons with major illnesses such as cancer, heart disease, kidney disease etc.? Yes No	 636 (68.7) 290 (31.3)	 445 (64.0) 251 (36.1)	0.045
15.	Are you willing to be vaccinated against COVID-19? Yes No	 393 (42.0) 533 (57.6)	 433 (62.0) 263 (37.8)	0.0001
16.	Have you been vaccinated against COVID-19? Yes No	 162 (17.0) 761 (82.2)	 232 (33.0) 464 (66.6)	0.0001
17.	Do you believe that the vaccine is not needed if the person has a history of COVID-19 infection in the past? No, it is still required. Yes, it is not required.	 609 (65.8) 317 (34.2)	 500 (72.0) 196 (28.1)	0.009
18.	Do you believe that celebrities can instill confidence in getting vaccinated against COVID-19 infection? Yes No	 410 (44.2) 516 (55.7)	 272 (49.1) 424 (61)	0.036
19.	Do you think that people may lose interest in getting COVID-19 vaccine because of the time interval between the two doses? Yes No	 199 (21.5) 726 (78.4)	 219 (31.4) 477 (68.5)	0.0001

Some opined that more transparency was needed in sharing vaccine related information to the public. Although clinical trial results are available in the public domain, data from these trials are limited compared to the large vaccine roll-out database that the Indian Government has with respect to vaccine safety among recipients. Periodical disclosure of safety issues may elicit a greater degree of trust from the public. However, the authors are of the opinion that availability of more information could sometimes be counterproductive, if interpreted inappropriately.

Two of the factors that increased public vaccine hesitancy were negative publicity regarding vaccines and the influence of anti-vaccination groups. The presence of a major illness also made people hesitant to get vaccinated. Subgroup analysis revealed that older adults were more hesitant to get vaccinated, possibly due to greater fear with respect to safety issues and the presence of comorbidities. The majority of the participants also felt that taking vaccines in the presence of major illnesses such as cancer, heart or kidney disease was inappropriate, a perception shared among the various subgroups. An Indian survey among cancer patients revealed that 60% were vaccine hesitant, mainly for fear of the vaccine impacting cancer therapy, its side-effects, and lack of information[27]. These findings are consistent with studies done in the USA and other low- and middle-income countries[28]. A history of COVID-19 infection in the past was also a factor that contributed to increased vaccine hesitancy. Despite the government announcing that the vaccine can be taken 3 months after recovery from infection, 32% of the study population believed it was unnecessary for people who had a past history of COVID-19. This perception may have arisen from the knowledge that viral infections such as chickenpox and measles confer lifelong immunity to those infected once. However, experience has shown that naturally acquired immunity to COVID-19 is

short-lasting and several thousand individuals were infected during both the first and second waves[29]. The CDC states that vaccination can be delayed up to 3 post-infection months, but beyond that, booster doses with updated vaccines must be taken pr omptly[24]. This becomes crucial as the coronavirus continues to mutate and new variants emerge. This fact does not seem to have registered in people's minds, hence indicating the importance of communicating the need for vaccination even in those with a history of infection. Hesitancy was also higher among those with lesser education, a trend reported even in European and Canadian studies[30,31]. The major reasons for vaccine hesitancy among our participants were safety and availability (Figure 3).

Safety has been cited as a major concern even in earlier reports[32]. This is despite the fact that the prevalence of serious adverse events due to COVID-19 vaccines is extremely low. This could be attributed to fear mongering tactics by peddlers of misinformation who circulate fallacies and raise doubts about the vaccines' safety. In addition, it is a natural tendency for the human mind to succumb to 'negativity bias', i.e., it tends to remember the rare event of a serious adverse reaction occurring in one individual rather than the daily mundane news of millions taking the vaccine without any adverse reaction. Although the government undertook the herculean task of vaccinating the Indian population at a rapid pace, myths regarding vaccine safety still prevail. The CoWin platform, launched by the Indian government, was a welcome step that helped instill public faith in the government. This platform served as a digital backbone during the pandemic, helped increase transparency, and added credibility to the vaccination process. Collaborations between healthcare workers, activists, celebrities, and governmental and non-governmental organizations play key roles in this aspect.

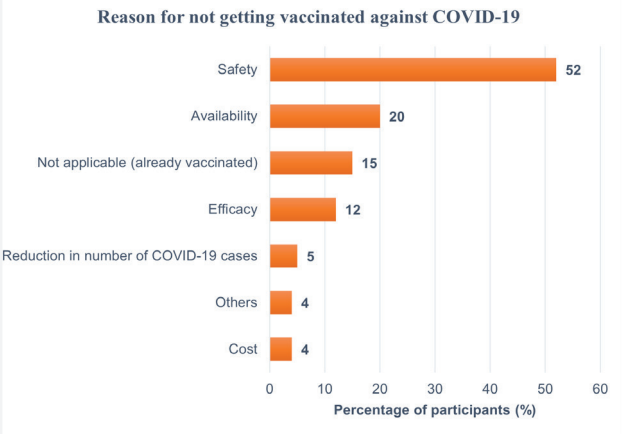


Figure 3. Most common reasons for vaccine hesitancy

The major reason for not getting vaccination was safety concerns (52%), followed by availability (20%) and efficacy (12%). Cost (5%) and reduced case load of COVID-19 (4%) were other reasons for not getting the vaccine

In our study, television was the most preferred source of information about vaccines (38%). This pattern was more common among the elderly and in those with school-level education. This trend was also observed in a survey carried out in Israel, where the majority of respondents reported getting COVID-19 vaccine information from local television[33]. The next important source of information was social media (25%), among which WhatsApp (33%) and Facebook (18%) were used by the majority. As anticipated, youngsters tended to use social media more when compared to the elderly (63% vs. 15%, p=0.0001). Similar results were seen in a health information national trends survey (2013, 2014, & 2017) in the USA, which reported significantly higher odds of the younger generation using social media for health communication[34]. Although social media provides abundant information, respondents in our study have agreed that its authenticity remains questionable, and hence it was the least trusted source (54%). Likewise, a cross-sectional study in Saudi Arabia showed that the majority of the participants did not trust information from social media, with WhatsApp being their least trusted source[35]. Participants placed reasonable trust in information obtained from healthcare workers (56%), but they reported that this was not easily accessible[36]. Scholarly articles that had the most precise and authentic information about vaccines were the least commonly used sources. Thus, it is imperative that accurate information regarding vaccines is disseminated aggressively by healthcare authorities through non-traditional methods like social media and television. Public engagement by the healthcare community through television may help address double-minded fence-sitters.

More than half the study participants (52%) believed that traditional herbal supplements like Kabasura Kudineer were sufficient for immunity against COVID-19. Although studies have shown that this formulation has beneficial effects in improving viral clearance[37-39], there are no studies to back its ability to prevent infection. Yet a good number of people do trust in its ability to prevent infection, thereby perpetrating a false sense of assurance.

Lessons learnt from COVID-19 vaccination may be extrapolated and used to tailor tactics that can improve vaccine acceptance rates during future pandemics. Efforts must be made early during the vaccine development period to understand the factors contributing to hesitancy. Infodemics are prevalent during any global crises, and the role played by the media is crucial during those times. As shown in our study, there is high information uptake from unreliable sources, making it imperative to ensure that data from infodemics are carefully filtered.

Study Limitations

Firstly, although the study attempted to gauge perception and behavioral practices towards COVID-19 vaccination among adults across Tamil Nadu, certain regions of the state were relatively underrepresented. However, care was taken to ensure that urban, semi-urban, and rural populations were included in the study. Secondly, the survey was done online for one-third of participants. Hence, the possibility of them not comprehending the questions cannot be ruled out. Thirdly, since vaccine hesitancy ebbs and flows as time progresses and more information becomes available, a follow-up study would have proven beneficial. But this was not included in the protocol for our study.

CONCLUSION

Age, gender, education level, and social media play major roles in formulating beliefs and thus determining the degree of public hesitancy toward vaccines. Our study showed that even after a year of the pandemic, vaccine hesitancy in a progressive state such as Tamil Nadu, India, was disturbingly high. This warrants increasing efforts to educate the public on the effectiveness and safety of vaccines. Greater engagement of healthcare workers through social media on the beneficial effects of vaccination is pivotal. Adequate measures must be ensured to convey accurate information and to increase public vaccine literacy through reliable sources.

Ethics

Ethics Committee Approval: The study was SRM Medical College Hospital and Research Centre initiated after getting approval from the Ethics Committee of our institution (approval number:2871/IEC/2021, date: 23.01.2021) and registration in the Clinical Trial Registry of India (CTRI/2021/08/035885).

Informed Consent: After a proper explanation of the study purpose and the acquisition of written informed consent from the participants, information was collected using an author-designed, internally validated questionnaire.

Footnotes

Authorship Contributions

Concept: M.G., Design: M.G., Data Collection or Processing: I.P., C.S.C., B.G.R., A.K.M., N.K.D., V.P.J.S., Analysis or Interpretation: M.G., K.M., I.P., V.P.J.S., Literature Search: K.M., J.J., C.S.C., Writing: M.G., K.M., J.J., C.S.C.

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

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Immunization and child health | UNICEF India [Internet]. [cited 2024 Aug 14]. https://www.unicef.org/india/what-we-do/immunization.
2. Immunization: national health mission [Internet]. [cited 2024 Aug 14]. https://nhm.gov.in/index1.php?lang=1&level=2&sublinkid=824&lid=220.
3. U-WIN [Internet]. [cited 2024 Aug 14]. https://uwin.mohfw.gov.in/home.
4. Vaccine hesitancy: Definition, scope and determinants - ClinicalKey [Internet]. [cited 2024 May 15]. https://www.clinicalkey.com/#!/content/play Content/ 1-s2.0-S0264410X15005009?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0264410X15005009%3Fshowall% 3Dtrue&referrer= https:%2F%2Fpubmed.ncbi.nlm.nih.gov%2F.
5. Martini M, Bifulco M, Orsini D. Smallpox vaccination and vaccine hesitancy in the kingdom of the two sicilies (1801) and the great modernity of Ferdinand IV of Bourbon: a glimpse of the past in the era of the SARS-COV-2 (COVID-19) pandemic. Public Health. 2022;213:47-53.
6. Nguyen KH, Srivastav A, Lindley MC, Fisher A, Kim D, Greby SM, et al. Parental vaccine hesitancy and association with childhood diphtheria, tetanus toxoid, and acellular pertussis; measles, mumps, and rubella; rotavirus; and combined 7-series vaccination. Am J Prev Med. 2022;62:367-76.
7. Novilla MLB, Goates MC, Redelfs AH, Quenzer M, Novilla LKB, Leffler T, et al. Why parents say no to having their children vaccinated against measles: a systematic review of the social determinants of parental perceptions on mmr vaccine hesitancy. Vaccines (Basel). 2023;11:926.
8. Beavis AL, Meek K, Moran MB, Fleszar L, Adler S, Rositch AF. Exploring HPV vaccine hesitant parents' perspectives on decision-making and motivators for vaccination. Vaccine X. 2022;12:100231.
9. Ten health issues WHO will tackle this year [Internet]. [cited 2024 Jan 12]. https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019.
10. COVID-19: Vaccines - UpToDate [Internet]. [cited 2024 Feb 21]. https://www.uptodate.com/contents/covid-19-vaccines.
11. COVAXIN - India's first indigenous Covid-19 vaccine | Bharat Biotech [Internet]. [cited 2024 Mar 2]. https://www.bharatbiotech.com/covaxin.html.
12. Kaur U, Ojha B, Pathak BK, Singh A, Giri KR, Singh A, et al. A prospective observational safety study on ChAdOx1 nCoV-19 corona virus vaccine (recombinant) use in healthcare workers- first results from India. EClinicalMedicine. 2021;38:101038.
13. MoHFW | Home [Internet]. [cited 2024 May 18]. https://www.mohfw.gov.in/
14. Majority of Africans would take a safe and effective COVID-19 vaccine [Internet]. Africa CDC. [cited 2024 May 17]. https://africacdc.org/news-item/majority-of-africans-would-take-a-safe-and-effective-covid-19-vaccine/.
15. Soares P, Rocha JV, Moniz M, Gama A, Laires PA, Pedro AR, et al. Factors associated with COVID-19 vaccine hesitancy. Vaccines. 2021;9:300.
16. Murphy J, Vallières F, Bentall RP, Shevlin M, McBride O, Hartman TK, et al. Psychological characteristics associated with COVID-19 vaccine hesitancy and resistance in Ireland and the United Kingdom. Nat Commun. 2021;12:29.
17. Yoda T, Katsuyama H. Willingness to Receive COVID-19 Vaccination in Japan. Vaccines (Basel). 2021;9:48.
18. Williams L, Flowers P, McLeod J, Young D, Rollins L; The catalyst project team. social patterning and stability of intention to accept a COVID-19 vaccine in scotland: will those most at risk accept a vaccine? Vaccines (Basel). 2021;9:17.
19. Fisher KA, Bloomstone SJ, Walder J, Crawford S, Fouayzi H, Mazor KM. Attitudes toward a potential SARS-CoV-2 Vaccine : A survey of U.S. adults. ann Intern Med. 2020;173:964-73.
20. Covid-19 vaccination in India - vaccinate India [Internet]. [cited 2024 Jan 23]. https://vaccinate-india.in/dashboard.

21. Danabal KGM, Magesh SS, Saravanan S, Gopichandran V. Attitude towards COVID 19 vaccines and vaccine hesitancy in urban and rural communities in Tamil Nadu, India - a community based survey. BMC Health Serv Res. 2021;21:994.

22. Umakanthan S, Patil S, Subramaniam N, Sharma R. COVID-19 Vaccine hesitancy and resistance in India Explored through a population-based longitudinal survey. Vaccines (Basel). 2021;9:1064.

23. WHO chief declares end to COVID-19 as a global health emergency | UN News [Internet]. 2023 [cited 2024 Jan 12]. https://news.un.org/en/story/2023/05/1136367.

24. CDC. Centers for disease control and prevention. 2020 [cited 2024 Mar 2]. COVID-19 and Your Health. https://www.cdc.gov/coronavirus/2019-ncov/your-health/end-of-phe.html.

25. Peterson CJ, Lee B, Nugent K. COVID-19 Vaccination hesitancy among healthcare workers-a review. Vaccines (Basel). 2022;10:948.

26. Savulescu J. Good reasons to vaccinate: mandatory or payment for risk? J Med Ethics. 2021;47:78-85.

27. Noronha V, Abraham G, Bondili S, Rajpurohit A, Menon R, Gattani S, et al. COVID-19 vaccine uptake and vaccine hesitancy in Indian patients with cancer: A questionnaire-based survey. Cancer Res Stat Treat. 2021;4:211-8.

28. Brandt EJ, Rosenberg J, Waselewski ME, Amaro X, Wasag J, Chang T. National Study of youth opinions on vaccination for COVID-19 in the U.S. J Adolesc Health. 2021;68:869-72.

29. Sarkar A, Chakrabarti AK, Dutta S. Covid-19 Infection in India: A comparative analysis of the second wave with the first wave. Pathogens. 2021;10:1222.

30. Syan SK, Gohari MR, Levitt EE, Belisario K, Gillard J, DeJesus J, et al. COVID-19 vaccine perceptions and differences by sex, age, and education in 1,367 community adults in ontario. Front Public Health. 2021;9:719665.

31. Humer E, Jesser A, Plener PL, Probst T, Pieh C. Education level and COVID-19 vaccination willingness in adolescents. Eur Child Adolesc Psychiatry. 2023;32:537-9.

32. Chandani S, Jani D, Sahu PK, Kataria U, Suryawanshi S, Khubchandani J, et al. COVID-19 vaccination hesitancy in India: State of the nation and priorities for research. Brain Behav Immun Health. 2021;18:100375.

33. Piltch-Loeb R, Savoia E, Goldberg B, Hughes B, Verhey T, Kayyem J, et al. Examining the effect of information channel on COVID-19 vaccine acceptance. PLos One. 2021;16:e0251095.

34. Huo J, Desai R, Hong YR, Turner K, Mainous AG 3rd, Bian J. Use of social media in health communication: findings from the health information national trends survey 2013, 2014, and 2017. Cancer Control. 2019;26:1073274819841442.

35. Alduraywish SA, Altamimi LA, Aldhuwayhi RA, AlZamil LR, Alzeghayer LY, Alsaleh FS, et al. Sources of health information and their impacts on medical knowledge perception among the saudi arabian population: cross-sectional study. J Med Internet Res. 2020;22:e14414.

36. Swoboda CM, Van Hulle JM, McAlearney AS, Huerta TR. Odds of talking to healthcare providers as the initial source of healthcare information: updated cross-sectional results from the Health Information National Trends Survey (HINTS). BMC Fam Pract. 2018;19:146.

37. Meenakumari R, Thangaraj K, Sundaram A, Sundaram MM, Shanmugapriya P, Mariappan A, et al. Clinical outcomes among COVID-19 patients managed with modern and traditional Siddha medicine - A retrospective cohort study. J Ayurveda Integr Med. 2022;13:100470.

38. Natarajan S, Anbarasi C, Sathiyarajeswaran P, Manickam P, Geetha S, Kathiravan R, et al. Kabasura Kudineer (KSK), a poly-herbal Siddha medicine, reduced SARS-CoV-2 viral load in asymptomatic COVID-19 individuals as compared to vitamin C and zinc supplementation: findings from a prospective, exploratory, open-labeled, comparative, randomized controlled trial, Tamil Nadu, India. Trials. 2021;22:623.

39. Srivastava A, Rengaraju M, Srivastava S, Narayanan V, Gupta V, Upadhayay R, et al. Efficacy of two siddha polyherbal decoctions, Nilavembu Kudineer and Kaba Sura Kudineer, along with standard allopathy treatment in the management of mild to moderate symptomatic COVID-19 patients-a double-blind, placebo-controlled, clinical trial. Trials. 2021;22:570.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.04809
Nam Kem Med J 2024;12(4):295-303

Opinions of NKU Faculty of Medicine Intern and Resident Doctors on Distance Medicine Education During the COVID-19 Pandemic Period

NKÜ Tıp Fakültesi Stajyer ve Intern Doktorların COVID-19 Pandemi Dönemindeki Uzaktan Tıp Eğitimine İlişkin Görüşleri

Eda ÇELİK GÜZEL[1], Büşra DURSUN[1], Aydan ÇEVİK VAROL[1], Gülsel AYAZ[2], Birol TOPÇU[3]

[1]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Family Medicine, Tekirdağ, Turkey
[2]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Medical Biology, Tekirdağ, Turkey
[3]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Biostatistics, Tekirdağ, Turkey

ABSTRACT

Aim: Throughout world history, people in the pandemic have not only been in danger of their physical health but also seriously affected their mental health. To prevent the spread of the virus during the COVID-19 pandemic, the Council of Higher Education of our country has closed schools and conducted education and training via online education. Therefore, the anxiety, uncertainty and closure of schools by the epidemic caused anxiety. The aim of our study; The effect of the COVID-19 pandemic on medical faculty student education is to evaluate the satisfaction of students from distance education applications.

Materials and Methods: Our study is a cross-sectional descriptive type and was conducted on 321 students studying in the 4th, 5th and 6th grades Tekirdağ Namık Kemal University Faculty of Medicine in the 2021-2022 academic year. A survey including students' sociodemographic characteristics and distance education perspective was applied to collect data. The data were evaluated with statistical analysis.

Results: Of the participating students, 85 were in 4th-grade, 157 were in 5th-grade, 79 were 6th-grade medical students. Answers to the question "If there was a second choice, would you choose the faculty of medicine?" 119 stated that they would choose the medical faculty again, 102 stated that they would not, and 100 stated that they were undecided. Answers to the question "What is your preferred education system option from today" 17 of the students preferred only the online education system, 127 only the face-to-face education system, and 177 preferred the system with online and face-to-face education have stated.

Conclusion: In terms of students' answers to the survey, it was seen that their level of perspective on distance education was undecided and it was determined that many factors affected distance education satisfaction. As a result, medical faculty students' anxiety increased during the pandemic period and they were less satisfied with the distance education system.

Keywords: Medicine, pandemic, online education, distance medicine education

ÖZ

Amaç: Dünya tarihinde pandemiler, kişileri yalnızca fiziksel sağlıkları yönünden tehlikeye atmakla kalmayıp aynı zamanda ruhsal sağlıklarınıda ciddi düzeyde etkilemişdir. COVID-19 pandemisinde virüsün yayılımını önlemek amacıyla Yükseköğretim Kurulu, okulların bir süreliğine kapatılarak eğitim-öğretimin uzaktan eğitimle yapılması yönünde karar almıştır. Dolayısıyla salgının kişilerde yarattığı endişe ve belirsizlik, ayrıca okulların kapanması öğrencilerin akademik geleceklerinde endişe ve kaygıya neden olmuştur. Çalışmamızın amacı; COVID-19 pandemisinin tıp fakültesi öğrenci eğitimi üzerine etkisi, öğrencilerin uzaktan eğitim uygulamalarından memnuniyet durumlarının değerlendirilmesidir.

Gereç ve Yöntem: Çalışmamız kesitsel tanımlayıcı tipte olup, 2021-2022 eğitim ve öğretim yılında Tekirdağ Namık Kemal Üniversitesi Tıp Fakültesi 4, 5 ve 6. sınıfta eğitim alan 321 öğrenci üzerinde yapılmıştır. Verilerin toplanmasında öğrencilerin sosyodemografik özelliklerini ve uzaktan eğitime bakış açısı içeren bir anket uygulanmıştır. Veriler, istatistiksel analizlerle değerlendirilmiştir.

Address for Correspondence: Eda ÇELİK GÜZEL MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Family Medicine, Tekirdağ, Turkey
E-mail: celikguzel@gmail.com **ORCID ID:** orcid.org/0000-0003-3022-4542
Received: 24.07.2024 **Accepted**: 23.09.2024

Bulgular: Katılımcı öğrencilerin 85'i 4. sınıf, 157'si 5. sınıf ve 79'u 6. sınıf tıp öğrencileriydi. Öğrencilerin "İkinci bir tercih şansı olsa tıp fakültesini seçer miydiniz?" sorusuna; 119'u tekrar tıp fakültesini seçeceğini, 102'si seçmeyeceğini, 100'ü ise kararsız olduğunu belirtmişlerdir. "Bugünden itibaren tercih ettiğiniz eğitim sistemi seçeneği nedir?" sorusuna öğrencilerin 17'si sadece çevrimiçi eğitim sistemini, 127'si sadece yüz yüze eğitim sistemini, 177'si ise çevrimiçi ve yüz yüze eğitimin beraber olduğu sistemi tercih ettiğini belirtmişlerdir.

Sonuç: Öğrencilerin ankete vermiş oldukları cevaplar açısından, uzaktan eğitime bakış düzeylerinin kararsız olduğu görülmüştür ve uzaktan eğitim memnuniyetini pek çok faktörün etkilendiği saptanmıştır. Sonuç olarak tıp fakültesi öğrencilerinde pandemi döneminde endişe artmış olup uzaktan eğitim sisteminden daha az memnun kalmışlardır.

Anahtar Kelimeler: Tıp, pandemi, uzaktan eğitim, uzaktan tıp eğitimi

INTRODUCTION

The aim of medical education is to train physicians to maintain the healthy state of the whole society[1,2]. Education is an active process that is constantly developing and changing. All kinds of events affecting human beings affect education[3]. In our country, the face-to-face education system is at the forefront in medical education and the "National Core Education Program" is taken as a guide by faculties to establish basic standards[4].

One of the tools that can be utilized in medical education is distance education. The United States Distance Learning Association defines distance education as the delivery of education to distant people through electronic means such as video, graphics, satellite, computer, multimedia technology[5].

The aim of distance education is to provide individuals with the opportunity to receive education and training through systems that keep pace with developing technology and contribute to education independently of time and space by eliminating time and geographical restrictions that may cause disruption of education[6]. The process that forms the basis of distance education started with the reproduction of written resources by printing them and thus making them suitable and easily accessible for distribution. It then took its current form with the integration of computer-aided systems, the use of multimedia tools and techniques, and fast and cost-effective access to content via the internet. Now, distance education is accepted as a support to formal education and as an education technique in its own right[7].

Although distance education has many benefits such as ensuring the sustainability of education and lifelong learning, reducing educational costs by having students and instructors in different places, it has some limitations in terms of method and timing[8]. In distance education, where communication and interaction are less compared to face-to-face education, it is necessary to plan, implement and evaluate the learning processes very well in cooperation with students and teachers in order to minimize the limitations and to ensure the successful completion of the education process[9].

Bringing students online brings to light deep inequalities in the education system (lack of device ownership, lack of secure internet connection, power and awareness of parents, etc.). In addition, many factors such as lack of infrastructure (software, hardware, etc.), economic factors, lack of technical staff, insufficient awareness of the society and especially students, regional differences in the use of information technologies constitute obstacles to e-learning and thus distance education[8]. In addition, for students who need family support in the educational environment, it is stated that parents' lack of digital literacy level to help their children transition to online learning or not having enough time to devote to home education also causes inequalities[10].

The COVID-19 virus has become a pandemic with its intercontinental spread and has exposed the whole world to political, social and economic devastation. In many countries, measures such as curfews, quarantines, self-isolation and social distancing, and the closure of places where there is a high probability of contact, schools and universities have come to the fore in order to break the rapid spread of the virus[11]. Education is undoubtedly one of the components most affected by the pandemic, and the pandemic has changed the way the whole world views and applies education[12,13].

Following the first COVID-19 case in Turkey, schools were suspended from March 16, 2020 until May 31, 2020, and open and distance online education was introduced for primary and secondary school students[12]. In addition, all higher education institutions suspended education in March 2020, the YÖK Courses Platform (Higher Education Institutions Courses) was opened to all students, and it was decided to continue the spring semester of the 2019-2020 academic year with open and distance education as of March 23, 2020[13].

Although the COVID-19 virus is thought to affect young people and children less in terms of health, these age groups have been one of the most affected segments of the pandemic due to this pause in their education. Students who have to receive education in these times of crisis are also challenged by the stress of the pandemic and the changing education process[14].

The COVID-19 pandemic has revealed the necessity of developing different ways of thinking and producing more modern and up-to-date solutions for the future of education globally in order to create an innovative educational environment[15]. Based on this awareness, our study aimed to investigate the impact of the COVID-19 pandemic and distance education on the education of 4th, 5th and 6th grade students of the Tekirdağ

Namık Kemal University Faculty of Medicine (FM), as well as the effects of the process on students.

MATERIAL AND METHODS

Our cross-sectional descriptive study was planned to be conducted on a total of 410 students (4th grade 175, 5th grade 117, 6th grade 118) studying in the 4th, 5th and 6th grades of Tekirdağ Namık Kemal University Faculty of Medicine in the 2021-2022 academic year. The study was initiated with the approval of the Tekirdağ Namık Kemal University University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: 2021.263.11.07, date: 30.11.2021).

The study included 321 volunteer students whose informed consents were obtained. As a data collection tool in this study, sociodemographic characteristics (53 questions) and Distance Education Perspective (UEBA) (26 questions) questionnaire prepared by the researchers were applied by face-to-face interview method. The positive items in the questionnaire, which consisted of 26 items in total and was prepared as a 5-point Likert scale, were scored as 5, 4, 3, 2, 1 from "strongly agree" to "strongly disagree", while the negative items were scored as 1, 2, 3, 4, 5 from "strongly agree" to "strongly disagree" in the opposite way. "Cronbach's alpha reliability coefficient" was used to determine the reliability of the questionnaire used to measure the characteristics.

Statistical Analysis

SPSS 23.0 for Windows program was used for statistical analysis. Normality assumptions of continuous variables were analyzed by the Kolmogorov-Smirnov test and homogeneity of variance was analyzed by the Levene's test. Mean and standard deviation were used for descriptive statistics of continuous variables and frequency (n) and percentage (%) values were used for categorical variables. In the comparison of two independent groups of variables, independent sample t-test was used if the data were normally distributed, and the Mann-Whitney U test was used if the data were not normally distributed. The Kruskal-Wallis-H test was used for independent three-group comparisons where the data were not normally distributed, and Anova was used when the data showed normal distribution. In subgroup comparisons, Tukey or Tamhane T2, post-hoc analyzes were used. Sperman's Rho correlation test was used for correlation analysis of continuous variables. In all analyses, $p<0.05$ was accepted as the significance level.

RESULTS

A total of 321 FM students participated in the study. Of all participants, 46.4% (n=149) were male and 53.6% (n=172) were female. Of the participating students, 26.5% (n=85) were 4th grade, 48.9% (n=157) were 5th grade and 24.6% (n=79) were 6th grade medical students (Table 1).

When the preferences of the students were analyzed, 283 students had chosen the medical school as their first choice in the university exam. When we looked at the answers given to the question "Would you choose FM if you had a second choice?", 37.1% (n=119) stated that they would choose FM again, 31.8% (n=102) stated that they would not choose FM and 31.2% (n=100) were undecided.

During the pandemic period, 69.8% (n=224) of the students were residing in the family house, 41.4% (n=133) in the

Table 1. Sociodemographic data of the participants

	n	%
Gender		
Male	149	46.4
Female	172	53.6
Mother's educational level		
Illiterate	13	4
Primary school	106	33.0
High school	71	22.5
Undergraduate	108	33.6
Graduate	22	6.9
Father's educational level		
Illiterate	1	0.3
Primary school	85	26.5
High school	64	20
Undergraduate	130	40.7
Graduate	40	12.5
Mother's occupation		
Officer	105	33.7
Worker	11	3.4
Self-employed	17	5.3
Retired	24	7.3
Housewife	155	50.3
Father's occupation		
Officer	143	44.5
Worker	31	9.7
Self-employed	79	24.6
Retired	53	16.5
Unemployed	2	0.6
The presence of a healthcare staff in the family		
No	95	29.5
Yes	223	70.5
Monthly income		
0-2500 TL	21	6.7
2501-5000 TL	57	18
5001-7500 TL	72	22.4
7501-10000 TL	63	19.6
10001 TL and above	97	30.2
Missing data are not included in the calculation		

student house, and 5.0% (n=16) in the dormitory. During this period, 27.7% (n=89) used the zoom video communication program and 69.5% (n=223) continued their distance education using the institutional education management and planning system (Keyps), the platform officially used by their university for distance education programs. 83.8% (n=269) of the participants attended distance education programs with their own computer, 26.8% (n=86) with their own phone, 4.0% (n=13) with their own tablet, and 6.5% (n=21) with someone else's computer. 2.5% (n=8) students had a monthly internet quota of less than 5 gb, 7.5% (n=24) had a monthly internet quota of 5-10 gb, 22.1% (n=71) had a monthly internet quota of 10-50 gb, and 67.9% (n=218) had a monthly internet quota of over 50 gb. As sources of online education, 78.5% (n=252) used online live broadcast, 83.2% (n=267) used PDF, word, powerpoint, 57.3% (n=184) used lecture recordings, 38.6% (n=124) used offline video recordings, 42.7% (n=137) used their own notes and 18.1% (n=58) used other lecturers' notes. In this survey, the number of students who participated in the study seems to be different since students could mark more than one option in the same question or not mark at all, but the study was conducted on 321 students.

When we examined the distribution of the answers to the question "What is your preferred education system option as of today?", 5.3% (n=17) of the students stated that they preferred online education system, 39.6% (n=127) preferred face-to-face education system, and 55.1% (n=177) preferred both online and face-to-face education system.

UEBA questionnaire consisted of 26 questions and the reliability analysis (Cronbach's Alpha) value for the questionnaire was 0.75. Accordingly, it is possible to say that the value found is quite reliable[16]. The average score of the whole questionnaire was 1.88±0.44. In the comparison of the mean UEBA questionnaire and sociodemographic characteristics, the mean score of female students was 1.81±0.41 and the mean score of male students was 1.95±0.45 (Table 2). It was determined that the mean of UEBA showed a statistically significant difference according to gender (p=0.005).

The mean UEBA score of male students was higher than that of female students. The mean UEBA score was 1.79±0.35 for children of illiterate mothers, 1.79±0.38 for children of primary school graduates, 2.06±0.48 for children of high school graduates, 1.86±0.44 for children of bachelor's degree graduates, and 1.88±0.45 for children of mothers with postgraduate education. It was observed that the mean UEBA score showed a statistically significant difference according to the educational level of the students' mothers (p=0.001). The mean UEBA score of the children of mothers who were primary school graduates and undergraduate graduates was statistically significantly lower than those who were high school graduates (Table 2).

Table 2. Comparison of average distance education perspective questionnaire value with sociodemographic characteristics

	Perspective on distance education		
	M ± SD	t or F	p-value
Gender			
Male	1.95±0.45	2.80	**0.005**[a]
Female	1.81±0.41		
Mother's educational level			
Illiterate	1.79±0.35	4.68	**0.001**[b]
Primary school	1.79±0.38		
High school	2.06±0.48		
Undergraduate	1.86±0.44		
Graduate	1.88±0.45		
Father's educational level			
Illiterate	2.46±0	1.34	0.256[b]
Primary school	1.80±0.41		
High school	1.91±0.45		
Undergraduate	1.89±0.44		
Graduate	1.92±0.45		
Mother's occupation			
Officer	1.91±0.41	0.70	0.593[b]
Worker	1.87±0.53		
Self-employed	1.88±0.38		
Retired	2.01±0.52		
Housewife	1.86±0.44		
Father's occupation			
Officer	1.90±0.45	0.80	0.529[b]
Worker	1.92±0.33		
Self-employed	1.90±0.45		
Retired	1.86±0.42		
Unemployed	1.38±0.22		
The presence of a healthcare staff in the family			
No	1.87±0.42	0.03	0.856[a]
Yes	1.88±0.48		
Monthly income			
0-2500 TL	1.75±0.36	0.676	0.609[b]
2501-5000 TL	1.85±0.50		
5001-7500 TL	1.92±0.43		
7501-10000 TL	1.90±0.39		
10001 TL and over	1.88±0.46		
		r	p
Age		0.047	0.401[c]
Number of siblings		-0.123	**0,030**[c]

[a]t-test, [b]ANOVA, [c]Spearman's rho correlation test, r: Correlation coefficient, M ± SD: Mean ± standard deviation

When the UEBA questionnaire scores were compared with the medical school grades and preferences of the students, the mean UEBA score of the 4th grade students was 1.83±0.45, of the 5th grade students was 1.96±0.41, and of the 6th grade students was 1.80±0.45. The mean UEBA score of 5th grade medical students was statistically significantly higher than the other grades (p=0.007).

In the comparison of the average UEBA questionnaire value with the content of distance education during the pandemic period, it was observed that there was no statistically significant relationship between the UEBA score and the residence status and device status of the students during the pandemic period. The average of the instructors who used online live broadcasting as an online education source was statistically significantly higher than those who did not (p=0.003) (Table 3). The mean UEBA score of the students who used the Zoom program, which is a video conferencing platform in distance education, was found to be 1.79±0.46, and the mean UEBA score of the students who used the institutional education management and planning system (Keyps) program, which is the platform officially used by the university for distance education program, was found to be 1.91±0.43. There was a statistically significant effect of the average UEBA score according to the programs used (p=0.038) (Table 3). Accordingly, it can be said that the UEBA averages of those who use Keyps program in distance education are higher than those who use Zoom program.

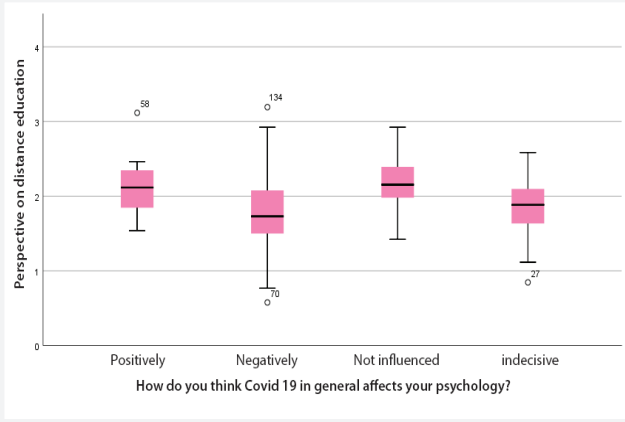


Figure 1. Distribution of perspective on distance education according to the psychological effects of COVİD-19 pandemic

Table 3. Comparison of the average distance education perspective survey and the content of distance education during the pandemic period

	Perspective on distance education		
	M ± SD	t or F	p-value
Residence status during the period			
Family house	1.89±0.42	-0.573	0.567
Student house	1.86±0.44	0.698	0.485
Dormitory	1.79±0.42	0.865	0.388
Program used in distance education			
Zoom	1.79±0.46	4.33	**0.038**[a]
Keyps	1.91±0.43		
Device status used in distance education			
Owned computer	1.87±0.43	1.16	0.249
Owned telephone	1.87±0.43	0.167	0.867
Owned tablet	1.88±0.44	1.46	0.146
Other's computer	1.83±0.52	0.499	0.618
Online education sources			
Online live performance	1.92±0.43	-2.98	**0.003**
PDF, Word, PowerPoint	1.88±0.44	0.01	0.991
Course records	1.90±0.46	-1.26	0.209
Offline video records	1.91±0.43	-1.01	0.314
Owned notes	1.92±0.45	-1.35	0.179
Notes of an instructor	1.88±0.40	-0.02	0.982

[a]t-test, M ± SD: Mean ± standard deviation

The students' response to the question "What were the effects of the COVID-19 pandemic on your psychology" is shown in Figure 1. In the comparison of the average UEBA value and the psychological effects of the COVID-19 pandemic; the average UEBA score of those who were affected by the COVID-19 pandemic on the psychology of the students in a good way was 2.11±0.38, those who were affected in a bad way were 1.80±0.45, those who were not affected were 2.15±0.35, and those who were undecided were 1.89±0.35. A significant difference was observed between the mean UEBA and the psychological effects of the COVID-19 pandemic on students (p<0.001). It was found that the mean of those whose psychology was affected in a good way was higher than those whose psychology was affected in a bad way; the mean of those whose psychology was not affected was higher than those whose psychology was affected in a bad way; and the mean of those whose psychology was not affected was higher than those who were undecided (Figure 1).

In the comparison of the average UEBA value with the preferred education systems, the average UEBA score of the students who would choose the online education system if they had the chance to choose it from now on was calculated as 2.23±0.60 points, the average of those who preferred the face-to-face education system was calculated as 1.64±0.39 points, and the average of those who chose the online and face-to-face education system was calculated as 2.02±0.36 points. There was a statistically significant difference between the mean UEBA score and the education system options preferred by the students as of today (p<0.001). It was determined that the mean of those who chose online education system was statistically significantly higher than those who chose face-to-face education system, and those who chose online and face-to-face education system were statistically significantly higher than those who chose face-to-face education system (Figure 2).

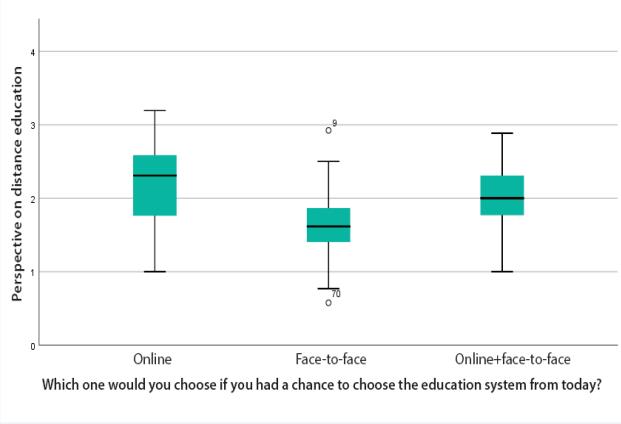


Figure 2. Distribution of perspective on distance education according to education system preference

When we examined the sub-factors of the UEBA questionnaire, 55.5% (n=81) of male students strongly disagreed, 24% (n=35) disagreed, 7.5% (n=11) strongly agreed with the statement "I think it is sufficient to give practice-based courses at a distance". For the same proposition, 54.1% (n=92) of the women strongly disagreed, 30% (n=51) disagreed, and no one strongly agreed. It was seen that the answers given to the statement "I think it is sufficient to give practice-based courses at a distance" showed a statistically significant difference according to gender (p=0.003).

In addition, in the comparisons of the statement "I would support the provision of university education completely online after the pandemic" and the grade level, 49 people who answered "strongly disagree" were in the 4th grade, 58 people were in the 5th grade, and 28 people were in the 6th grade; 22 people who answered "disagree" were in the 4th grade, 51 people were in the 5th grade, and 25 people were in the 6th grade.

CONCLUSION

Decisions made in line with global measures have led to new regulations in education systems, leading many educational institutions to adopt the distance education system and bringing about a major change in the academic lives of students. This change has made university students one of the groups most affected by the pandemic and put them in a psychosocially challenging period as well as physical risks[17]. In our study, we tried to determine the opinions of students who took distance education courses during the pandemic period on distance education and the impact of the pandemic.

In our study, a great majority of the students stated that they ranked the medical faculty first in their university preferences. In 1999, in another study conducted on Cerrahpaşa Medical Faculty students, this rate was 62.5%[18]. Considering the difference between the dates of the studies, it can be interpreted that medicine has become a more attractive profession in recent years.

An important detail that stood out in our study was that 31.8% of the students regretted their choice of medical school in response to the question "Would you choose medical school again if given a second choice?". Similarly, in other studies, the rates of regret were in parallel with our study[18,19]. The reasons for this may be listed as realizing that the profession of medicine is not suitable for them, their doubts about the future of medicine, and the concern that they will not be able to get the material and moral reward for their efforts during the challenging education process[19].

From this point of view, it can be concluded that students prefer MF with hope and enthusiasm, but a considerable number of

them regret their choice of medical school for reasons such as the problems they encounter during the education process and their doubts about the future of medicine.

When we examine the comparison of material satisfaction in distance education, it was observed that there was no significant relationship between the device status of the students used in distance education and whether it belonged to them or not and their attitudes towards distance education during the pandemic period. In another study conducted during the COVID-19 pandemic process, which is compatible with our study, no relationship was found between the technological device owned and attitudes[20].

However, there are other studies that found that students who had their own computers, tablets or smartphones had more positive attitudes towards distance education, which is inconsistent with our study[21]. An important point in terms of ensuring adequate participation in distance education is having sufficient internet quota to follow the lessons. A 20-minute video made instead of a 45-minute lecture in face-to-face education requires 500-600 mb internet quota if watched in high quality.

A 60-minute-high quality video requires an average quota of 1.5 gb. In other words, students need an average of 5 gb of internet per month in order to participate in the lessons[22]. 97.5% of the students who participated in our study stated that their internet quota was 5 gb or more, and according to this result, the internet quota of the students does not pose a problem in terms of participation in the lessons at a high rate.

According to our study results, having a higher level of internet quota than required to participate in trainings has a positive effect on people's psychology. On the other hand, we think that an insufficient internet quota will greatly affect people's satisfaction with distance education and their psychology through online-based activities.

While taking online courses, students face many technical problems in the university's distance education system, such as internet disconnections, audio and video problems, late or no uploading of the courses to the system[23]. In our study, half of the participants stated that they experienced technical problems in online education and that there was no unit they could reach for the technical problems they encountered. Considering that an effective technical service that students can access and get feedback to solve the problems they experience will affect their satisfaction with distance education, it is important to establish these units and to inform students about the existence of these units.

One of the most important criteria affecting the quality of distance education is the quantity and quality of teaching and learning resources and materials[24]. Adequate material support closely affects the effectiveness and satisfaction of distance education for both trainees and instructors[25]. In our study, the average of instructors who used live performance as an online education resource was statistically significantly higher than those who did not. In another similar study, it was observed that students preferred to receive education on online live performance[26].

Considering the students' perspectives on distance education; according to the findings of a study examining the attitudes of undergraduate and graduate students towards distance education, it was understood that students see distance education as a second option. This result is consistent with our study in which attitudes towards distance education during the pandemic period were found to be close to undecided, and we believe that social isolation has an effect on this situation[27].

In our study, it was determined that the mean UEBA score of the students showed a significant difference according to gender and the mean UEBA score of male students was higher than that of female students. In many studies in the literature, it has been found that distance education attitudes are higher in favor of males than females[27]. This may be because, according to a generally accepted view, male students tend to use technology more and more competently than female students. However, when the literature was examined, a study indicating that attitudes towards distance education did not differ according to gender was also found[28].

In our study, a significant difference was observed in the mean UEBA score according to the education level of the students' mothers (p=0.001). In another study compatible with our study, parents' distance education experiences were evaluated during the pandemic, and it was shown that family support and parental education level supported learning in students who had the opportunity to spend more time at home and also increased student motivation[29].

In addition, in line with the answers given, it was observed that the UEBA score decreased as the number of siblings increased. This relationship shows that students who resided in the family home with a rate of 69.8% during the pandemic period had problems accessing and focusing on online courses as the number of people living at home increased, which decreased their educational satisfaction.

In the comparison of the UEBA score by grades, the average UEBA score of 5th grade medical students was significantly higher than the other grades. Although there are studies showing that the grade level does not affect the attitude towards distance education, many different studies show that grade levels show differences in attitudes towards e-learning[30].

We think that it would be beneficial to organize the number and program of distance education courses according to the

grade level, especially in blended education applications. In our study, UEBA satisfaction of students receiving distance education during the pandemic process varies according to the education platform used. We think that educators and administrators comparing these differences and choosing the most efficient platform will increase student satisfaction[26,31].

When students were asked about the education system they would like to choose from now on, about half of the participants stated that they preferred a system in which online and face-to-face education were carried out together. In line with these opinions, it can be concluded that distance education can be an important alternative to traditional formal education and that blended education planned not only in emergency and compulsory situations but also in normal times will be satisfactory at both student and instructor levels.

In our study, a statistically significant difference was found between the average UEBA score of the participants who interpreted distance education in line with these factors and the education system options they preferred as of today. It was found that the UEBA average of those who chose online education or online + face-to-face system was statistically significantly higher than those who chose face-to-face education system.

The higher the level of satisfaction with distance education, the more favorable people are towards the inclusion of distance education in the education system.

The COVID-19 pandemic increases the level of stress in university students and decreases their social, physical and psychological well-being due to factors such as delays and uncertainties in educational activities, global effects of the pandemic, and difficulties in getting used to the process[17]. The two questions that were significantly associated in our study were how the pandemic affected their psychology and their average UEBA scores. Students who thought that the pandemic affected their psychology badly were less satisfied with distance education in our study.

Study Limitations

Our study has some limitations. The research conducted within the scope of the study is limited to 4th, 5th and 6th grade students of Tekirdağ Namık Kemal University Faculty of Medicine, and future studies can be conducted with all grades of FM and more general results can be obtained by comparing the results obtained with this study.

As a result, many factors such as gender, home environment, internet quota, technical problems, and the online platform used in education affect the satisfaction of students affected by extraordinary situations such as pandemics. We think that our study will contribute to the research on distance education satisfaction among FM students during the COVID-19 pandemic in Turkey and will also contribute to the research on how to plan distance education.

Ethics

Ethics Committee Approval: The study was initiated with the approval of the Tekirdağ Namık Kemal University University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: 2021.263.11.07, date: 30.11.2021).

Informed Consent: The study included 321 volunteer students whose informed consents were obtained.

Footnotes

Authorship Contributions

Concept: M.G., Design: M.G., Data Collection or Processing: I.P., C.S.C., B.G.R., A.K.M., N.K.D., V.P.J.S., Analysis or Interpretation: M.G., K.M., I.P., V.P.J.S., Literature Search: K.M., J.J., C.S.C., Writing: M.G., K.M., J.J., C.S.C.

Conflict of Interest: One author of this article, (Birol TOPÇU) is a member of the Editorial Board of the Namık Kemal Medical Journal. However, she did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Kahraman ME. The Effect of COVID-19 Epidemic on applied courses and the implementation of these courses by distance education: example of basic design course. İMÜ Sanat Tasarım ve Mimarlık Fakültesi Dergisi. 2020;6:44-56.
2. Aşkın R, Bozkurt Y, Zeybek Z. Covid-19 pandemisi: psikolojik etkileri ve terapötik müdahaleler. Sosyal Bilimler Dergisi. 2020;19:304-18.
3. Aktaş Reyhan F, Dağlı E. E-Learning perceptions of midwifery students in the Covid-19 Pandemic. J Midwifery and Health Sci. 2021;4:213-21.
4. Mezuniyet öncesi tıp eğitimi ulusal çekirdek eğitim programi 2020. (https://www.yok.gov.tr/Documents/Kurumsal/egitim_ogretim_dairesi/Ulusal-cekirdek-egitimi-programlari/mezuniyet-oncesi-tip-egitimi-cekirdek-egitimi-programi.pdf
5. Özbay Ö. The current status of distance education In The World and Turkey. The Journal of International Education Science. 2015;5:376-94.
6. Gürpınar E, Musal B. Tıp eğitiminin gelişim süreci. Toplum ve Hekim. 2003;18:446-51.
7. Vatansever K. History of Medical Education. Toplum ve Hekim. 2020;35:352-70.
8. Schmidt HG, Neufeld VR, Nooman ZM, Ogunbode T. Network of community-oriented educational institutions for the health sciences. Acad Med. 1991;66:259-63.
9. Odabaşı O, Sayek I, Kiper N. Undergraduate medical education in Turkey-2010. Turk Arch Pediatr. 2011;46:322-7.

10. UTEAK. Türkiye mezuniyet öncesi tıp eğitimi ulusal standartları. Hacettepe Üniversitesi hastaneleri basımevi, 2009 (Erişim tarihi:11.11.2022) https://cdn.istanbul.edu.tr/statics/istanbultip.istanbul.edu.tr/wp-content/uploads/attachments/021_uteak.2009.pdf

11. Bozkurt A. Koronavirüs (Covid-19) pandemi süreci ve pandemi sonrasi dünyada eğitime yönelik değerlendirmeler: yeni normal ve yeni eğitim paradigmasi. Açıköğretim Uygulamaları ve Araştırmaları Dergisi. 2020;6:112-42.

12. Başer A, Şahin H. Medical education from Atatürk to Present. Tıp Eğitimi Dünyası. 2017;16:70-83.

13. Ertuğ C. Coronavirüs (Covid-19) pandemisi ve pedagojik yansımaları: Türkiye'de açık ve uzaktan eğitim uygulamaları. Açıköğretim Uygulamaları ve Araştırmaları Dergisi. 2020;6:11-53.

14. Sümeyye K, Karaaziz M. The Effects of the Covid-19 Pandemic on the psychosocial area. Journal of Faculty of Architecture. 2021;3:81-91.

15. Bozkurt A, Sharma RC. Emergency remote teaching in a time of global crisis due to coronavirus pandemic. Asian Journal of Distance Education. 2020;15:1-6.

16. Yıldız D. A Comparison of reliability tests in field researches and an application on agricultural data. Uygulamalı Sosyal Bilimler Dergisi. 2018;1:1-28.

17. Kara B. The Psychological Impact of the COVID-19 pandemic on university students: a review of the current evidence. Sağlık ve Toplum. 2021;31:32-7.

18. Köksal S, Vehid S, Tunçkale A, Çerçel A, Erginöz E, Kaymaz A, ve ark. Cerrahpaşa Tıp fakültesi öğrencilerinin tıp eğitimi ve mezuniyet sonrası ile ilgili tutumları. Elektronik Cerrahpaşa Med J. 1999;30:251-8.

19. Açık Y, Oğuzöncül F, Polat SA, Güngör Y, Güngör L. Fırat Üniversitesi Tıp fakültesi öğrencilerinin tıp eğitimi ve mezuniyet sonrası hakkındaki düşünceleri. Toplum ve Hekim. 2002;17:195-201.

20. Yağan S. Attitudes and opinions of university students towards distance education carried out during the COVID-19 epidemic. Academic Platform Journal of Education and Change. 2021;4:147-74.

21. Kaban A, Science. University students' attitudes towards distance education. International Journal of Technology in Education and Science. 2021;5:311-22.

22. Tüzün F, Yörük Toraman N. Factors affecting distance education during pandemic. Ömer Halisdemir Üniversitesi İktisadi ve İdari Bilimler Fakültesi Dergisi. 2021;14:822-45.

23. Keskin M, Özer Kaya D. Evaluation of Students' Feedbacks on Web-Based Distance Education in the COVID-19 Process. İzmir Kâtip Çelebi Üniversitesi Sağlık Bilimleri Fakültesi Dergisi. 2020;5:59-67.

24. Chao T, Saj T, Tessier F. Establishing a quality review for online courses. Educause Quarterly. 2006;29:32-9.

25. Lloyd SA, Byrne MM, Mccoy TS. Faculty-perceived barriers of online education. MERLOT Journal of Online Learning and Teaching. 2012;8:1-10.

26. Serçemeli M, Kurnaz E. A research on students' perspectives to distance education and distance accounting education in the Covid-19 pandemia period. Journal of International Social Sciences Academic Researches. 2020;4:40-53.

27. Fidan M. Distance Education students' attitudes towards distance education and their epistemological beliefs. H. U. Journal of Education. 2016;31:536-50.

28. Ateş A, Altun E. Investigating preservice computer teachers' attitudes towards distance learning regarding various variables. Gazi Eğitim Fakültesi Dergisi. 2008;28:125-45.

29. Üstündağ A. Assessing of parents› distance learning experiences during pandemic. Ahi Evran Üniversitesi Sosyal Bilimler Enstitüsü Dergisi. 2021;7:572-89.

30. Çiftci S, Güneş E, Üstündağ MT. Attitudes of distance education students towards web based learning-a case study. Procedia Soc Behav Sci. 2010;2:2393-6.

31. Altuntaş-Yılmaz N. Investıgatıon of students' attitudes towards applied distance educatıon in the Covid-19 pandemic process in higher education institutions: example of physiotherapy and rehabilitation department. Necmettin Erbakan University Faculty of Health Sciences Journal. 2020;3:15-20.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.86570
Nam Kem Med J 2024;12(4):304-309

Complications and Management of Chemotherapy Port: Analysis of 322 Cases

Kemoterapi Port Uygulamasında Komplikasyonlar ve Yönetimi: 322 Olgunun Analizi

Melike ÜLKER

Tekirdağ Dr. İsmail Fehmi Cumalıoğlu City Hospital, Clinic of Thoracic Surgery, Tekirdağ, Turkey

ABSTRACT

Aim: Implantable central venous catheters are frequently preferred in malignancy patients in cases where drugs in the chemotherapy group that cause extravasation, drug group requiring continuous infusion and a single extremity as in breast carcinomas are used. In this study, it was aimed to present the complications that occur during chemotherapy port in the acute and chronic periods and the intervention method in malignancy patients.

Materials and Methods: Patients who underwent chemotherapy port application between January 2021 and June 2023 were examined retrospectively. They were evaluated by age, gender, malignancy types, acute and chronic complications, and surgical interventions for complications.

Results: A total of 322 patients were performed venous port catheter for chemotherapy. There were 201 (62.4%) males. The mean age was 58.9±11.4 (range: 20-82) years. The most common malignancy types were colorectal carcinoma in 116 patients (36%), gastric carcinoma in 70 patients (21.7%) and pancreatic carcinoma in 53 patients (16.5%). The most common port catheter application sites were the right jugular (n=267, 82.9%), left jugular (n=27, 8.4%) and right subclavian (n=22, 6.8%). Complications were observed in 19 (5.9%) cases in the series, including 8 (2.5%) venous thrombus, 7 (2.2%) wound infection, 2 (0.6%) pneumothorax, and 2 (0.6%) port dislocation.

Conclusion: In the patient group receiving chemotherapy, the use of chemotherapy ports has increased significantly in recent years due to its convenience. Although it is performed under local anesthesia, serious complications can be seen and the way to intervene in complications is important. I aimed to present complication and intervention methods with clinical experience.

Keywords: Chemotherapy, venous port catheter, ultrasonography

ÖZ

Amaç: İmplante edilebilen santral venöz kateterler; malignite hastalarında ekstravazasyona yol açan kemoterapi grubunda ilaç kullanılması, sürekli infüzyon gerektiren ilaç grubunun kullanılması ve meme karsinomlarında olduğu gibi tek ekstremite kullanımı gerektiren durumlarda sıklıkla tercih edilmektedir. Bu çalışmada, malignite hastalarında kemoterapi port uygulaması sırasında akut ve kronik dönemde gerçekleşen komplikasyonlar ve müdahale şeklinin sunulması amaçlandı.

Gereç ve Yöntem: Ocak 2021 ve Haziran 2023 tarihleri arasında kemoterapi port uygulaması yapılan hastalar restrospektif olarak incelendi. Hastalar yaş, cinsiyet, malignite tipleri, akut ve kronik komplikasyonları ve komplikasyonlara yönelik cerrahi müdahaleleri ile değerlendirildi.

Bulgular: Toplam 322 hastaya kemoterapi uygulanması amacı ile venöz port kateter takıldı. Olguların 201'i (%62,4) erkek idi. Yaş ortalaması 58,9±11,4 (aralık: 20-82) yıl idi. En sık görülen malignite tipinin kolorektal karsinom (n=116, %36), mide karsinomu (n=70, %21,7) ve pankreas karsinomu (53, %16,5) olduğu tespit edildi. En sık kullanılan port kateter uygulama yeri sırasıyla sağ juguler (n=267, %82,9), sol juguler (27, %8,4) ve sağ subklaviyen (22, %6,8) olarak bulundu. Seride 19 (%5,9) olguda komplikasyon görülmüş olup, sırasıyla 8 (%2,5) venöz trombüs, 7 (%2,2) yara yeri enfeksiyonu, 2 (%0,6) pnömotoraks ve 2 (%0,6) port dislokasyonu gözlendi.

Sonuç: Kemoterapi alan hasta grubunda, sağladığı kolaylıklardan dolayı kemoterapi port kullanımı son yıllarda ciddi olarak artmıştır. Lokal anestezi altında yapılmasına rağmen ciddi komplikasyonlar görülebilmekte ve komplikasyonlara müdahale etme şekli önem arz etmektedir. Klinik tecrübemle, komplikasyon ve müdahale şekillerini sunmayı hedefledim.

Anahtar Kelimeler: Kemoterapi, venöz port kateter, ultrasonografi

Address for Correspondence: Melike ÜLKER MD, Dr. İsmail Fehmi Cumalıoğlu City Hospital, Clinic of Thoracic Surgery, Tekirdağ, Turkey
E-mail: melike.ulker@hotmail.com **ORCID ID:** orcid.org/0000-0003-1739-8329
Received: 05.04.2024 **Accepted**: 04.10.2024

INTRODUCTION

Vascular access is important in patients planned for long-term chemotherapy. Implantable central venous port catheters are frequently used to avoid potential problems of the peripheral venous access, especially in cancer patients receiving long-term chemotherapy[1].

Partially implantable catheters were described by Broviac et al.[2] and Hickman et al.[3] in 1970 and the first vascular port catheter was realized in 1982 by Niederhuber et al.[4]. In malignancy patients receiving chemotherapy, the use of port catheters has increased in recent years due to frequent venous procedures, long duration of treatment, use of sclerosing agents in this treatment and excessive fluid replacement. They provide advantages over other central catheters due to their low infection rates, long duration of use and the fact that they do not restrict the daily activities of the patient[5].

Complications may occur during or after the insertion of port catheters. In the early period, pneumo-hemothorax, malposition, arrhythmia, cardiac perforation, hematoma in the port area, embolism, arteriovenous fistula, left thoracic duct lesion, phrenic or brachial plexus lesion may be observed. In the late period, skin necrosis, catheter breakage and embolism, infection, catheter occlusion and disconnection, extravasation of fluids and difficulty in blood aspiration may be observed[6,7].

In this study, it is aimed to present the complications that occur in the acute and chronic periods during the insertion of chemotherapy port in malignancy patients and the approach to these complications.

MATERIALS AND METHODS

Patients who underwent chemotherapy port insertion between January 2021 and June 2023 at Dr. İsmail Fehmi Cumalıoğlu City Hospital were examined retrospectively. The study permission was obtained from the Dr. İsmail Fehmi Cumalıoğlu City Hospital Clinical Research Ethics Committee (decision no.: 2022/10, date: 28.11.2022).

Patients were evaluated for complete blood count and bleeding time values before the insertion. The procedure was monitored and started under operating room conditions. The vascular area was determined by ultrasonography in the foreground, and ultrasonography was used again, if necessary, after the sterile field was provided. The relevant area was cleaned with povidone iodine and local anesthesia was performed with 20 cc prilocaine. With a 10 cc syringe, the vascular structure to be used was found and marked with a guidewire. A port area was created with a 3 cm incision on the midclavicular line above the pectoral muscle and the reservoir part was implanted with 2/0 vicryl. The reservoir and catheter were combined and passed under the skin to the vascular area entrance of the catheter. The tip of the catheter was advanced to the vena cava-right atrium junction with the help of a guidewire. The catheter length was determined by external visualization according to the patient's size (Figure 1).

The right jugular vein and then the right subclavian vein were used as the intervention site. Subclavian vein was preferred in the cachectic patient group. Patients who underwent unilateral mastectomy for breast cancer were treated from the opposite side. A chemotherapy port was inserted using the right femoral vein in a patient with a history of vena cava superior thrombus. All patients underwent chest radiography in the postoperative period (Figure 2). The localization of the catheter tip according to the cava-atrium junction was evaluated. The patients without complications were discharged at the 4th hour after the procedure.

Statistical Analysis

For statistical analysis, IBM SPSS Statistics version 26 was used. The descriptive results of the study are presented as frequencies with the corresponding percentages in the case of nominal or ordinal variables. Continuous variables are also presented as mean and standard deviation.

RESULTS

A total of 322 patients received venous port catheter for chemotherapy. There were 201 (62.4 %) males and 121 (37.6 %) females. The mean age was 58.9±11.4 (range: 20-82) years. The disease status of the patients at the time of the procedure was as follows: 201 (62.4%) had metastatic disease, 89 (27.6%) had undergone surgery for primary disease, and 32 (9.9%) had locally advanced disease. The malignancy types of the patients who underwent the procedure were as follows: 116 (36%) colorectal carcinoma, 70 (21.7%) gastric carcinoma, 53 (16.5%) pancreatic carcinoma, 27 (8.4%) breast carcinoma, and the others are shown in Table 1.

As side of port catheter insertion, 267 (82.9%) right jugular vein, 27 (8.4%) left jugular vein, 22 (6.8%) right subclavian vein, 5 (1.6%) left subclavian vein and 1 (0.3%) right femoral vein were used (Table 2).

Complications were observed in 19 (5.9%) cases in the series (Table 3). Pneumothorax developed in two cases (0.6%) during the procedure and was treated with tube thoracostomy. In two cases, the site of application was the subclavian vein. In the long term, eight (2.5%) venous thrombus cases were proven by ultrasonography and the port catheter was removed. After consultation with the oncology physician, a new port catheter from the opposite side was inserted in the same session in the patient group who continued to need a port. Local infection developed in seven cases (2.2%) where the subcutaneous port reservoir was present, and the port catheter was removed and the tissue was debrided if necessary (Figure 3).

In two cases (0.6%), the port catheter was detached from the reservoir and was found to be in the right ventricular area. The first case was a 52-year-old female patient who underwent surgery with a diagnosis of pancreatic carcinoma. Oncological treatment was planned and chemotherapy port was applied by us. Ten days after the procedure, a subcutaneous swelling was detected in the area of the port reservoir during chemotherapy treatment and the treatment was stopped. Intracardiac foreign body was removed from the femoral vein by angiography, which was found to be dislocated on radiographs (Figure 4A).

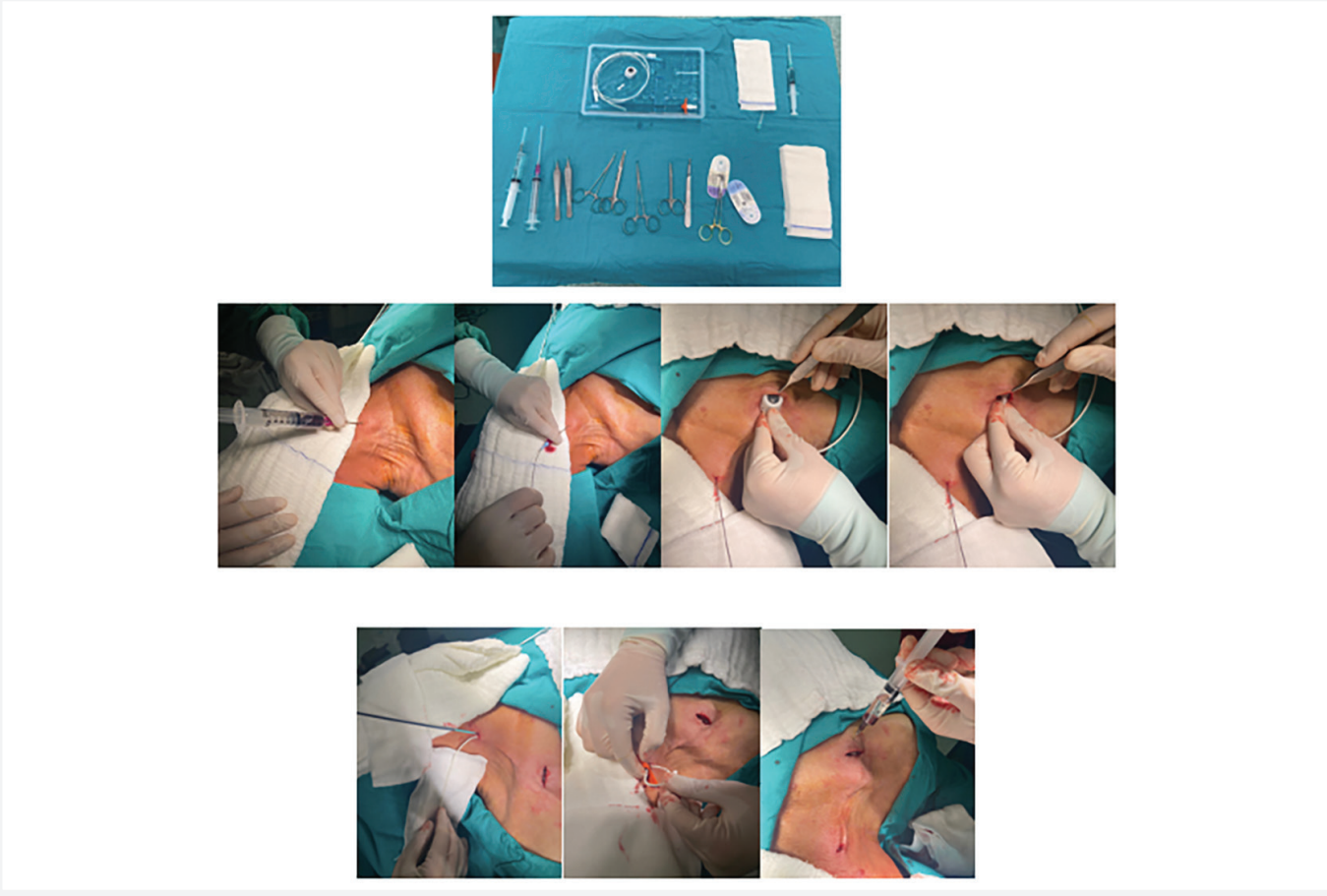


Figure 1. Surgical equipment to be used for port catheter insertion and images of the procedure

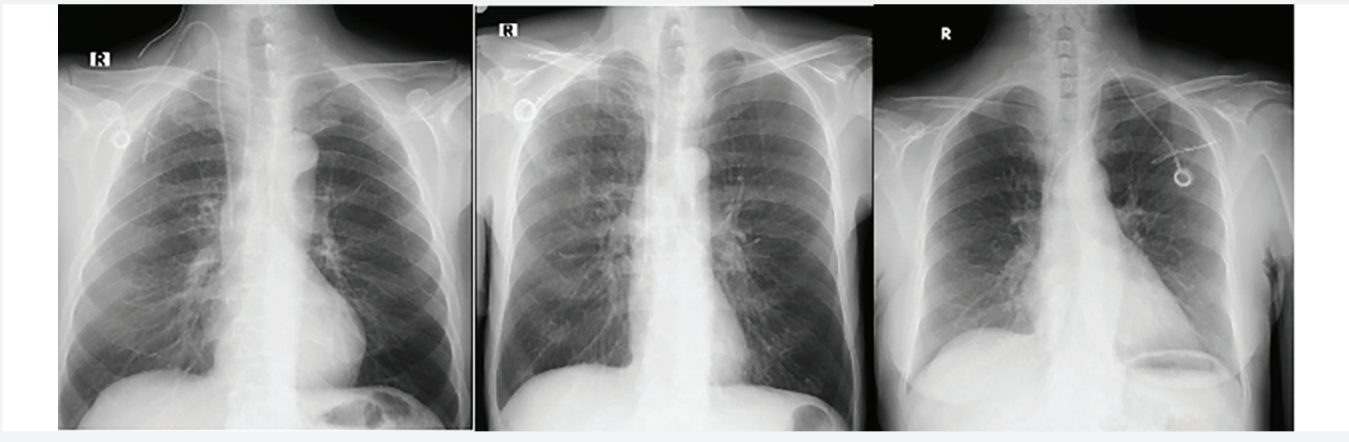


Figure 2. Chest radiography in the postoperative period; right jugular vein, right subclavien vein and left jugular vein, respectively

Table 1. Malignancy types of patients receiving chemotherapy port catheter

Types of malignancy	n	%
Colorectal	116	36
Gastric	70	21.7
Pancreas	53	16.5
Breast	27	8.4
Lung	14	4.3
Liver	10	3.1
Head-neck	10	3.1
Esophagus	9	2.8
Others*	13	4.1

*Cholangiocarcinoma, endometrial carcinoma, ovarian carcinoma, renal cell carcinoma, bladder carcinoma

Table 2. Location of chemotherapy ports

Anatomical location	n	%
Right jugular vein	267	82.9
Left jugular vein	27	8.4
Right subclavien vein	22	6.8
Left subclavien vein	5	1.6
Right femoral vein	1	0.3

Table 3. Complications and management

Complications	n	%	Management
Venous thrombus	8	2.5	Port catheter removal
Wound infection	7	2.2	Port catheter removal
Pneumothorax	2	0.6	Tube thoracostomy
Dislocated port catheter	2	0.6	Intracardiac foreign body removal with angiography

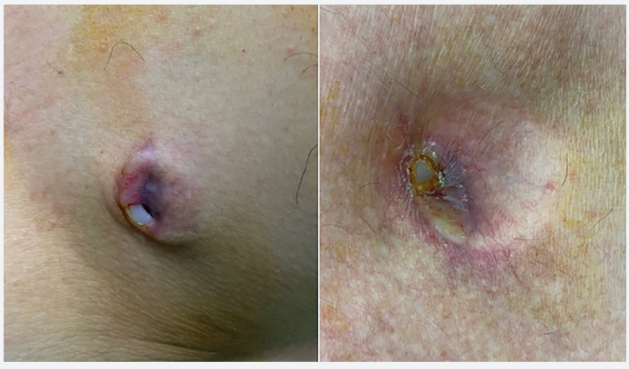


Figure 3. Images of wound infection

The other case was a 61-year-old female patient with a diagnosis of metastatic gastric carcinoma, who underwent chemotherapy port by us. She received the first chemotherapy treatment and there were no problems. During the second chemotherapy treatment, subcutaneous swelling was detected in the area of the port reservoir and the treatment was stopped. It was found that the catheter part was dislocated in the chest radiograph. An intracardiac foreign body was removed from the right femoral vein by angiography. Angiography images are shown in Figure 4B.

The procedure was performed in the angiography room. The femoral vein and artery were visualized with an incision applied to the femoral region and the vascular structure was taken under control with nylon tape due to hemorrhage that might develop during the procedure. The angiocatheter sent from the femoral vein was passed from the inferior vena cava to the intracardiac area. The angiocatheter was extended towards the superior vena cava and its lasso-shaped tip was extended from the superior-inferior line and the intracardiac dislocated catheter was held. After being fixed with the angiocatheter, it was removed from the femoral vein. No vascular injury was observed during the procedure.

DISCUSSION

Port catheters can be inserted through central veins such as subclavian and jugular veins. In practice, the subclavian vein may be preferred because of its proximity to the vena cava and right atrium. However, the possibility of development of pneumothorax is high (1-3.2%) in subclavian vein puncture with the Seldinger method[8,9]. In our study, jugular vein was used primarily and no pneumothorax was detected in this intervention line due to the routine use of ultrasonography. In the series, 2 (0.6%) pneumothorax complications were detected and occurred at the site of subclavian venous intervention in two cases.

Catheter lengths were calculated as 16-18 cm in right interventions and 20-22 cm in left interventions according to the Czepizak formula and according to the patient's height[10]. No arrhythmia was observed in any patient. After the insertion, the catheter was washed with heparin diluted with saline and found to be active. In some patients, when blood could not be punctured, stenosis was detected at the site of catheter entry into the vascular area, and the malfunctioning condition improved when the soft tissue area was freed. In the literature, the frequency of catheter malfunction has been reported as 0.8-5%. The most common cause of catheter malfunction is difficulty in blood puncture although there is no difficulty in infusion[11,12]. In our study, the catheter length was determined by external visualization according to the patient's size and no postoperative malfunction was observed.

Pain, erythema, tenderness at the port site indicates infection in this area. In cases of port infection, the port, which is the source of infection, should be removed immediately, the local wound site should be debrided, and oral antibiotics should be started. The incidence of port site infection has been reported to be 0.3-4.4%[13]. In our study, port infection was observed in 7

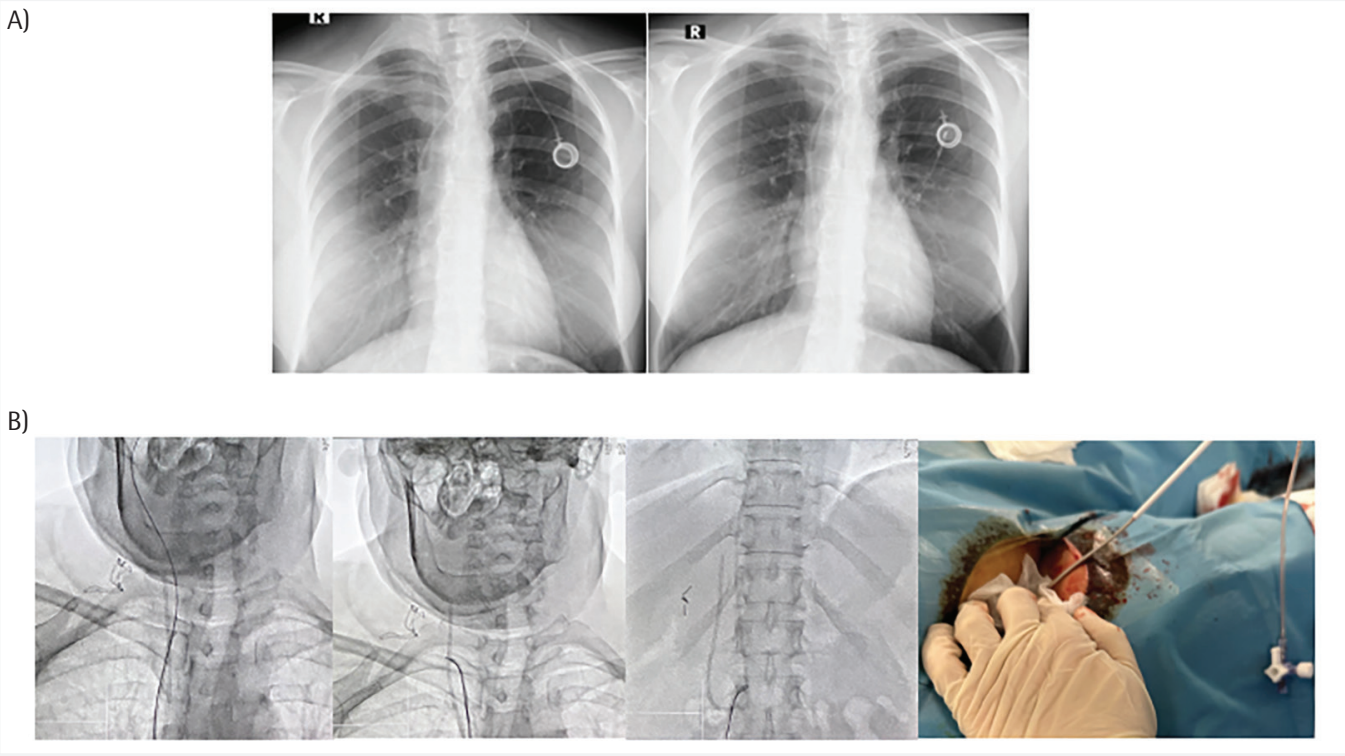


Figure 4. A) Dislocated port catheter at left jugular vein, **B)** Intracardiac foreign body removal with angiography

(2.2%) cases. It was observed that there were no port infections when the chemotherapy port reservoir was implanted as far away from the incision line as possible, by deepening from the incision line to create a port area towards the area where the soft tissue is thicker. We recommend the use of this technique.

The risk of pulmonary embolism due to venous thrombosis in patients with port insertion is between 5% and 40%. Although thrombosis may develop between 2 weeks and 2 years, 70% is observed in the first weeks[14]. Although pulmonary embolism was not observed in our study, catheter-induced venous thrombus was detected on Doppler ultrasonography performed in 8 (2.5%) patients due to catheter malfunction and the port catheter was removed and anticoagulant treatment was started.

The "pink off" complication, defined as a syndrome, occurs when the port catheter gets stuck between the clavicula and the first rib, resulting in rupture or fracture. In this case, infusion becomes difficult and pain or paresthesia may develop in the arm. The detached fragment should be removed as it may cause complications such as pulmonary embolism or cardiac arrhythmia. Lin et al.[15] reported that this syndrome developed in 73 cases in a study in which 3358 catheters were used. No "pink off" complication was observed in our study. In only two cases, dislocation of the catheter part into the right ventricle due to separation of the port catheter and the reservoir part was detected after the port catheter insertion. In the coronary angiography unit, the femoral vein was visualized through an incision made in the femoral region and the angiography catheter was inserted into the right ventricle and the catheter was removed from the femoral vein under radiographic visualization. These complications and treatments have not been reported in the literature and is recommended in early dislocated cases.

Study Limitations

Since the patients received treatment in different chemotherapy clinics, it could not be evaluated how long the patients could actively use the chemotherapy ports and whether there was a difference in usage according to the vascular structures.

CONCLUSION

Although port catheters inserted in the patient group using long-term chemotherapy increase the comfort of the patient and the physician, it should be kept in mind that the procedure is invasive and complications that may cause morbidity or mortality may develop. Experienced team, appropriate port determination, caution in the follow-up process and appropriate catheter care reduce the risks that may occur. In the clinical experience, using ultrasound during the procedure provides convenience for the physician.

Ethics

Ethics Committee Approval: The study permission was obtained from the Dr. İsmail Fehmi Cumalıoğlu City Hospital Clinical Research Ethics Committee (decision no.: 2022/10, date: 28.11.2022).

Informed Consent: Retrospective study.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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

REFERENCES

1. Stanislav GV, Fitzgibbons RJ Jr, Bailey RT Jr, Mailliard JA, Johnson PS, Feole JB. Reliability of implantable central venous access devices in patients with cancer. Arch Surg. 1987;122:1280-3.
2. Broviac JW, Cole JJ, Scribner BH. A silicone rubber atrial catheter for prolonged parenteral alimentation. Surg Gynecol Obstet. 1973;136:602-6.
3. Hickman RO, Buckner CD, Clift RA, Sanders JE, Stewart P, Thomas ED. A modified right atrial catheter for access to the venous system in marrow transplant recipients. Surg Gynecol Obstet. 1979;148:871-5.
4. Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. Surgery. 1982;92:706-12.
5. Carlo JT, Lamont JP, McCarty TM, Livingston S, Kuhn JA. A prospective randomized trial demonstrating valved implantable ports have fewer complications and lower overall cost than nonvalved implantable ports. Am J Surg. 2004;188:722-7.
6. Ballarini C, Intra M, Pisani Ceretti A, Cordovana A, Pagani M, Farina G, et al. Complications of subcutaneous infusion port in the general oncology population. Oncology. 1999;56:97-102.
7. Collier PE, Blocker SH, Graff DM, Doyle P. Cardiac tamponade from central venous catheters. Am J Surg. 1998;176:212-4.
8. Turcotte S, Dubé S, Beauchamp G. Peripherally inserted central venous catheters are not superior to central venous catheters in the acute care of surgical patients on the ward. World J Surg. 2006;30:1605-19.
9. Cowl CT, Weinstock JV, Al-Jurf A, Ephgrave K, Murray JA, Dillon K. Complications and cost associated with parenteral nutrition delivered to hospitalized patients through either subclavian or peripherally-inserted central catheters. Clin Nutr. 2000;19:237-43.
10. Czepizak CA, O'Callaghan JM, Venus B. Evaluation of formulas for optimal positioning of central venous catheters. Chest. 1995;107:1662-4.
11. Di Carlo I, Cordio S, La Greca G, Privitera G, Russello D, Puleo S, et al. Totally implantable venous access devices implanted surgically: a retrospective study on early and late complications. Arch Surg. 2001;136:1050-3.
12. Kurul S, Saip P, Aydin T. Totally implantable venous-access ports: local problems and extravasation injury. Lancet Oncol. 2002;3:684-93.
13. Gowda MR, Gowda RM, Khan IA, Punukollu G, Chand SP, Bixon R, et al. Positional ventricular tachycardia from a fractured mediport catheter with right ventricular migration--a case report. Angiology. 2004;55:557-60.
14. Gullo SM. Implanted ports. Technologic advances and nursing care issues. Nurs Clin North Am. 1993;28:859-71.
15. Lin CH, Wu HS, Chan DC, Hsieh CB, Huang MH, Yu JC. The mechanisms of failure of totally implantable central venous access system: analysis of 73 cases with fracture of catheter. Eur J Surg Oncol. 2010:36;100-3.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.25152
Nam Kem Med J 2024;12(4):310-317

A Single-Center Retrospective Evaluation of The Incidence and Survival of Invasive Fungal Infection in Allogeneic Stem Cell Transplant Patients

Allojeneik Kök Hücre Nakli Yapılan Hastalarda İnvazif Fungal Enfeksiyon Sıklığının, Risk Faktörlerinin ve Sağkalıma Etkisinin Retrospektif Değerlendirilmesi

Emre ODABAŞ[1], Ajda GÜNEŞ[2], Nur SOYER[2], Mahmut TOBU[2], Fahri ŞAHİN[2], Güray SAYDAM[2], BİLGİN ARDA[3], Filiz VURAL[2]

[1]İskenderun State Hospital, Clinic of Gastroenterology, Hatay, Turkey
[2]Ege University Medical Faculty Hospital, Department of Internal Medicine, Division of Hematology, İzmir, Turkey
[3]Ege University Medical Faculty Hospital, Department of Infectious Diseases and Clinical Microbiology, İzmir, Türkiye

ABSTRACT

Aim: The incidence of invasive fungal infection (IFI) is high in patients undergoing allogeneic hematopoietic stem cell transplantation. Despite new antifungal agents, IFI is still an important cause of mortality. Our study aimed to determine the risk factors of IFI and its effect on mortality.

Materials and Methods: One hundred and fifty-four patients who underwent allogeneic transplantation were included in the study. Demographic characteristics, underlying disease, transplantation characteristics, and IFI status of all patients were evaluated retrospectively. The study group was divided into two: 75 patients with definite, high probability and possible IFI (group 1) and 79 patients without IFI (group 2) according to the criteria of the international committee.

Results: Of 154 patients, 92 were male (59.7%) and 62 were female (40.3%) with a mean age of 41.87±14.04 years (range: 18-67 years). The most common transplant indication was acute myeloid leukemia in 58 patients (37.7%). In the analyzes performed on two groups, more IFI were observed in those who had acute graft-versus-host disease after transplantation (p= 0.035) and in those with CMV reactivation (p=0.002). The mean neutropenia duration was 30.89±20.40 in group 1 and 19.98±11.01 in group 2 (p=0.001). Underlying diseases, preparation regimen, donor compatibility, consanguineous marriage and IFI history were not found to be significant in terms of the development of IFI. The mortality rate due to IFI was found to be 24%. The mean duration of neutropenia was found to be longer in patients who died (p=0.02).

Conclusion: In our study, the frequency of IFI, risk factors and mortality rates were found to be similar to the literature. It would be appropriate for each center to evaluate the frequency of IFI and the risk factors that increase it and decide which treatment strategy is more beneficial for their patients.

Keywords: Allogeneic transplantation, invasive fungal infections, risk factors, mortality markers

ÖZ

Amaç: Allojeneik hematopoetik kök hücre nakli yapılan hastalarda invaziv fungal enfeksiyon (İFE) görülme sıklığı yüksektir. Yeni antifungal ajanlara rağmen İFE bu hastalarda halen önemli bir mortalite sebebidir. Çalışmamızda İFE gelişimini kolaylaştıran risk faktörlerinin ve mortaliteye etkisinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Allojeneik nakil yapılan 154 hasta çalışmaya dahil edildi. Tüm hastaların demografik özellikleri, altta yatan hastalığı, nakil özellikleri, İFE durumu retrospektif olarak değerlendirildi. Çalışma grubu uluslararası komitenin kriterleri kullanarak kesin, yüksek olası ve olası İFE olan 75 hasta (grup 1) ve İFE olmayan 79 hasta (grup 2) olarak ikiye ayrıldı.

Address for Correspondence: Emre ODABAŞ MD, İskenderun State Hospital, Clinic of Gastroenterology, Hatay, Turkey
E-mail: emre331odabas@hotmail.com **ORCID ID:** orcid.org/0000-0002-9982-0257
Received: 12.08.2024 **Accepted**: 05.10.2024

Bulgular: Yüz elli dört hastanın 92'si erkek (%59,7), 62'si kadın (%40,3) ve ortalama yaşı 41,87±14,04 (yaş aralığı: 18-67) idi. En sık nakil endikasyonu 58 hasta (%37,7) ile akut myeloid lösemi tanısıydı. İki grup üzerinden yapılan analizlerde nakil sonrası akut graft versus host hastalığı geçirenlerde (p=0,035) ve CMV reaktivasyonu görülenlerde (p=0,002) daha fazla İFE görüldü. Ayrıca grup 1'in nötropeni süresi ortalama 30,89±20,40 iken, grup 2'nin ortalama 19,98±11,01 idi (p=0,001). Hastalık tanısı, hazırlama rejimi, donör uyumu, akrabalık durumu ve İFE öyküsü ile İFE gelişimi açısından anlamlı farklılık bulunmadı. İFE nedeniyle mortalite oranı %24 saptandı. Exitus olan hastaların ortalama nötropeni süresi daha uzun bulundu (p=0,02).

Sonuç: Çalışmamızda literatürle benzer oranlarda İFE sıklığı, risk faktörleri ve mortalite oranı saptandı. Her merkezin İFE sıklığını, artıran risk faktörlerini değerlendirmesi ve hastaları için hangi tedavi stratejisinin daha yararlı olduğuna karar vermesi uygun bir seçenek olacaktır.

Anahtar Kelimeler: Allojeneik nakil, invaziv fungal enfeksiyonlar, risk faktörleri, mortalite belirteçleri

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a process that involves the infusion of stem cells from the patient (autologous HSCT) or from a human leukocyte antigen (HLA) compatible donor (allogeneic HSCT) following high-dose chemotherapy. It is a treatment method used in the treatment of many hematological, immunological and neoplastic diseases[1]. After allogeneic HSCT, immunosuppressive agents such as calcineurin inhibitors are taken for a long period of time for the prophylaxis or treatment of graft-versus-host reaction (GVHD)[2]. For this reason, patients who undergo HSCT are at high risk for serious life-threatening infections[3,4].

The incidence of invasive fungal infections (IFI) is high in patients undergoing allogeneic HSCT, and despite the recent use of new antifungal agents, IFI is an important cause of mortality in these patients. Factors such as the development of aplasia or GVHD after transplantation and the intensive use of immunosuppressive treatments also increase the risk of IFI[5,6]. In 2008, the European Organization for Research and Treatment of Invasive Fungal Infections Cooperative Group/ National Institute of Allergy and Infectious Diseases Mycosis Study Group (EORTC/MSG) Consensus group developed criteria for the classification of potential cases according to the probability of IFI, and these were revised in 2020[7,8]. As the frequency of antifungal prophylaxis increases, the importance of determining the patient group at risk for IFI increases[5,6]. Risk factors include the type of disease requiring allogeneic HSCT, type of preparatory regimen, history of previous IFI, presence of HLA compatibility, type and duration of prophylactic antifungal treatment, development and severity of acute or chronic GVHD after allogeneic transplantation, intensive treatment due to GVHD development, and cytomegalovirus (CMV) reaction[5,6,9-13].

Over the past 20 years, the epidemiology of IFI has changed with the prophylactic use of fluconazole against Candida albicans, and mold infections have become more common[14-17].

Changes in transplantation practices, including unrelated or haploidentical donor preferences, conditioning regimens, and strategies for diagnosing and treating IFI, likely influence the epidemiology and outcomes of IFI[16-19]. Although the frequency and response rates of IFI in allogeneic HSCT vary in the literature, the average frequency has been reported to be 10% to 26% and the mortality rate has been reported to be 40% to 90%, depending on the presence of risk factors[6,18,20,21,22].

The aim of this single-center and retrospective study was to evaluate the frequency, risk factors, clinical picture, treatment and survival of IFI in patients undergoing allogeneic stem cell transplantation.

MATERIALS AND METHODS

Patient Selection

All patients hospitalized in the adult hematology clinic of Ege University between 2011 and 2017, who underwent allogeneic stem cell transplantation regardless of indication, who were over 18 years of age and whose data were completely available, were included in the study. Exclusion criteria included transplantation for non-hematological malignancies or solid tumors. Patients who underwent multiple allogeneic HSCT during the study period were evaluated separately at the time of the second or third transplantation. Data were collected independently for each transplantation.

Study Design

A total of 154 patients who met our study criteria were included. All patients' data were retrospectively scanned from their medical files and the hospital's digital data system. Collected variables included the subject's demographic characteristics, underlying disease, transplant characteristics, IFI type, ad outcome.

Underlying disease and transplant characteristics included diagnosis of hematologic malignancy (according to the French-American-British criteria) or type and status of other underlying disease, donor type, HLA compatibility, regimen type (myeloablative, non-myeloablative), age at transplantation, and presence of previous IFI.

Features observed during follow-up of patients who underwent allogeneic transplantation were also recorded. Immunological risk factors (duration of neutropenia, duration of intensive care, presence of acute GVHD, GVHD treatment, CMV response)

and features related to IFI (primary and secondary prophylactic antifungal use status, type of antifungal used in prophylaxis, time of onset and duration) were recorded.

EORTC/MSG criteria were used to evaluate the presence of IFI, and blood galactomannan antigen positivity, high-resolution computed tomography findings, pathological evidence, and culture evidence were recorded. The patient group was divided into two. The first group consisted of 75 patients with definite, highly probable, and possible IFI using EORTC/MSG criteria. The definitions for IFI are summarized in Figure 1. Among these patients, there were patients who were started on antifungal treatment due to fever of unknown origin and were included in the probable IFI group. The other group consisted of 79 patients without IFI. All analyses were performed on these two groups. In patients who received IFI treatment, the type of IFI, the day of transplantation on which it developed, empirical treatment status, the type of antifungal drug used in treatment and any changes, the response to IFI after treatment, and the cause of death, if any, were recorded.

The study was carried out after obtaining the necessary permissions from the Clinical Research Ethics Committee of the Ege University Faculty of Medicine (decision no: 17-2/7, date: 13.03.2017).

Statistical Analysis

SPSS computer package program was used for statistical analyses. Data were given as number, percentage, mean and standard deviation. Frequency tables were used when evaluating study data. chi-square test and/or Fisher's exact test were used in statistical analyses. Wilcoxon W or Mann-Whitney U test was used for comparison of independent means. Significance level was taken as $p<0.05$.

RESULTS

General Patient Characteristics

A total of 154 patients who underwent allogeneic HSCT were included in the study. The mean age of the patients was 41.87±14.04 years (age range: 18-67), consisting of 92 males (59.7%) and 62 females (40.3%). The duration of hospitalization of the patients ranged from 25 to 195 days (median value: 47 days).

The most common allogeneic HSCT indication was acute myeloid leukemia diagnosis in 58 patients (37.7%). The graft source in all patients was granulocyte colony stimulation factor stimulated peripheral blood. Demographic data and transplantation-related characteristics of the patients (HLA compatibility, donor type, regimen type) are given in Table 1.

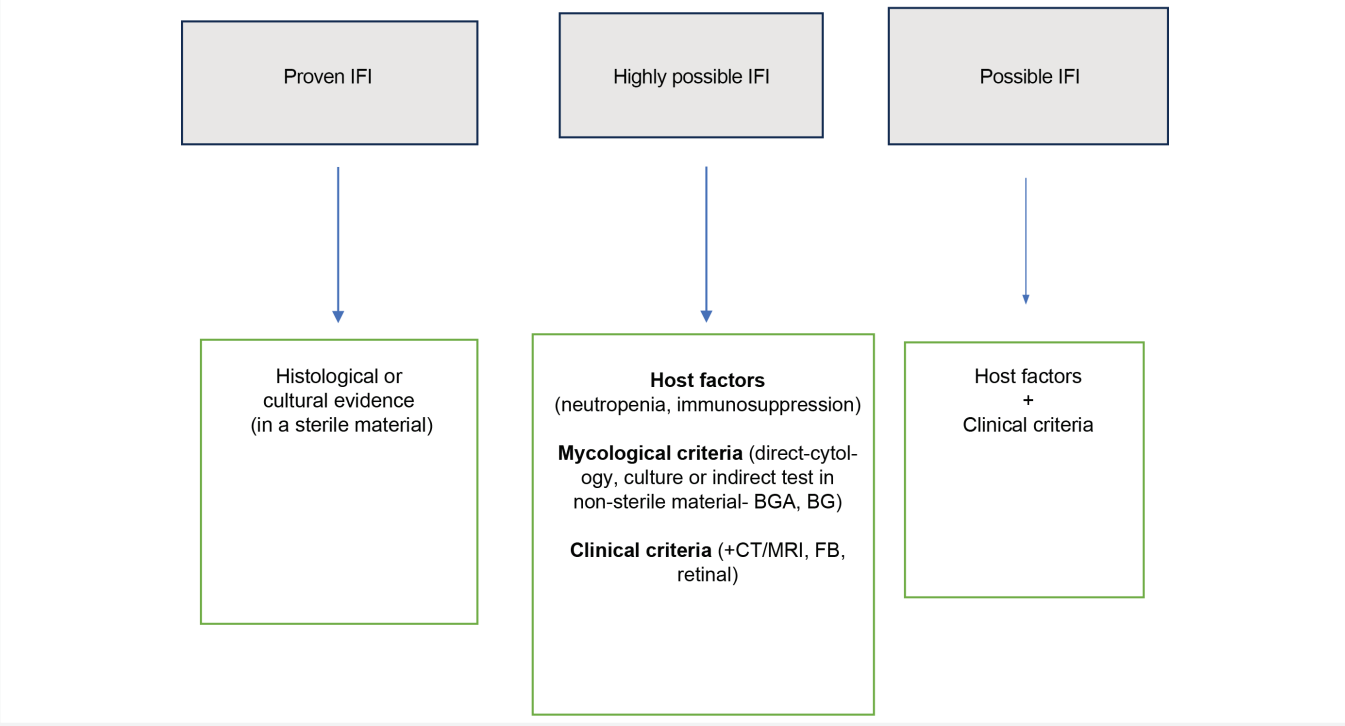


Figure 1. The main criteria of proven, highly possible and possible fungal infections

IFI: Invasive fungal infection, BGA: Galactannan antigen in the blood, BG: 1,3-β-d-glukan, CT: Computed tomography, FB: Flexible bronchoscopy, MRI: Magnetic resonance imaging

Thirty-four of the patients included in the study had acute GVHD. Twenty-nine of these 34 patients were treated with methylprednisolone. Five patients were given multiple treatments and photophoresis was applied after methylprednisolone. After transplantation, CMV-DNA elevation was observed in 46 of 154 patients. While antifungal treatment received due to IFI before transplantation was continued in five patients, 149 patients were given prophylactic antifungal treatment, 20 of which were for secondary prophylaxis (Table 2).

In 75 patients, according to EORTC/MSG criteria, 9 patients were diagnosed with proven IFI, 19 patients with high probability, and 47 patients with possible IFI (Group 1). No IFI findings developed in 79 patients and were included in the group that did not develop IFI (Group 2) (Table 2). In 7 of the 9 patients in the proven IFI group, the source of infection pathogen was isolated. The IFI characteristics of these 9 patients (patients' culture, pathology, CGA positivity, and CT findings and growth status) are summarized in Table 3.

Of the 75 patients who developed IFI, 26 out of 32 patients whose infection focus could be determined had IFI focus in the lungs, while 5 patients had other organ involvement. Nine of the patients who developed IFI received targeted therapy, 37 received preemptive therapy, and 29 received empirical therapy. The most preferred agent in first-line therapy was liposomal amphotericin-B (L-AmB) 43 (57.3%), followed by caspofungin with 32%. Voriconazole was not preferred in empirical therapy. L-AmB and caspofungin were preferred at approximately the same rates in empirical therapy. Antifungal

Table 1. Demographic characteristics of patients

Patient characteristics	Number (%) n=154 (100)
Age, year	
Mean ± SD	41.87±14.04
Median (min-max)	44 (18-67)
Male/Female (%)	92/62 (59.7/40.3)
Diagnoses (%)	
Acute myeloid leukemia	58 (37.7)
Acute lymphocytic leukemia	24 (15.6)
Myelodysplastic syndrome	19 (12.3)
Lymphomas	19 (12.3)
Myeloma	14 (9.1)
Aplastic anemia	8 (5.2)
Chronic leukemia	7 (4.5)
Myelofibrosis	5 (3.2)
Donor type	
Relative	136 (88.3)
HLA compatibility (A, B, DRB1, C and DQ pairs)	
10/10 (full)	126 (81.8)
9/10 (good)	18 (11.7)
5-8/10 (partial match, haploidentical transplantation)	10 (6.5)
Regime type	
Myeloablative	88 (57.1)
Duration of hospitalization (day)	
Mean ± SD	58.44±29.07
Median (min-max)	47 (25-195)
Acute GVHD	34 (22.1)
CMV response, present	46
Duration of hospitalization (day)	
Mean ± SD	25.29±17.12
Median (min-max)	20 (5-87)

SD: Standard deviation, HLA: Human leukocyte antigen, GVHD: Graft Versus Host Disease, CMV: Cytomegalovirus, SD: Standard deviation

Table 2. Fungal infection history and current status of patients with allogeneic HSCT

All patients n=154 (%)	
Those with history of IFI	65 (42.2)
Antifungal prophylaxis status	**n=154 (%)**
Primary prophylactic antifungal use, yes	129 (83.8)
Secondary prophylactic antifungal use, yes	20 (13)
Those getting active fungal infection therapy during allogeneic HSCT	5 (3.2)
Prophylactic antifungal type	**n=149 (%)**
Fluconazole	88 (59.1)
Posaconazole	44 (29.5)
Voriconazole	17 (11.4)
Fungal infection (according to EORTC/MSG criteria)	**n=154 (%)**
Proven	9 (5.9)
Highly possible	19 (12.3)
Possible	47 (30.5)
Impossible	79 (51.3)
Those with BGA positivity	26 (16.9)
Those with findings on CT	34 (22.1)
Fungal agent growth in culture, yes	7 (4.5)
Pathological finding	4 (2.6)
Those with invasive fungal infection n=75(%)	
Fungal infection type	**n=75(%)**
Pneumonia	26 (34.6)
Others	5 (9.4)
Non-focused	42 (56)
Treatment type (initial treatment)	**n=75 (%)**
L-AmB	43 (57.3)
Kaspofungin	24 (32.0)
Voriconazole	8 (10.7)
Those getting dual antifungal treatment	10 (13.3)

HSCT: Hemopoietic stem cell transplantation, IFI: Invasive fungal infection, EORTC/MSG: European Organization for Research and Treatment of Cancer/ Mycoses Study Group, BGA: Blood galactomannan antigen, CT: Computed tomography, L-AmB: Liposomal amphotericin-B

change was required in 30 patients (40%). The reason for antifungal change in the majority of patients was the lack of fever response. Of the patients who underwent antifungal drug change, 8 (26.6%) were exitus. Of the 10 patients who received dual antifungal therapy, 6 (60%) were exitus. 56 patients (76%) were evaluated as responding to IFI treatment. 18 patients were accepted as exitus due to IFI and related reasons.

Patients who developed and did not develop IFI were divided into Group 1 and Group 2, and possible risk factors and mortality analyses related to IFI development were performed on these two groups. Possible risk factors for IFI and significance rates for IFI development are shown in Table 4. IFI was significantly more common in those who had acute GVHD after transplantation (p=0.035) and in those who had CMV reactivation (p=0.002). In addition, the mean neutropenia duration in Group 1 (IFI development) was 30.89±20.40 (median value: 23.00), while in Group 2 (no IFI), it was 19.98±11.01 (median value: 17.00) (p=0.001).

Table 3. Factors and findings in proven IFI patients

Proven IFI patients	Growth in culture and its location	Pathology	BGA positivity	CT finding
1	Blood culture Candida crusei	No	No	No
2	No	Maxillary sinus Aspergillus spp.	No	Yes
3	Nasal tissue culture Aspergillus flavus	Nasal biopsy Mucormicosis	Yes	Yes
4	Blood culture Trichosporon spp.	No	Yes	Yes
5	DTA Aspergillus spp.	No	No	Yes
6	Maxillary sinus Pseudallescheriae boydii	Yes	Yes	Yes
7	No	Maksiller sinus Aspergillus spp.	No	Yes
8	Tissue biopsy Aspergillus spp.	yok	No	Yes
9	Blood culture Candida kefyr Saccharomyces cerevisiae	yok	yok	var

IFI: Invasive fungal infection, BGA: Blood galactomannan antigen, CT: Computed tomography, DTA: Deep tracheal aspiration

No significant difference was found between the two groups in terms of disease diagnosis, preparation regimen, donor compatibility, consanguinity status, previous IFI history and IFI development.

12% (n=20) of all patients died. While mortality due to IFI was 24% (n=18) in 75 patients with IFI, mortality was 3% (n=2) in 79 patients without IFI (p=0.001). The mean neutropenia duration of these 18 patients was 34.78±20.06 (median value: 35.00) days, while the duration of neutropenia in the 134 surviving patients was 23.76±16.20 (median value: 19.00) days and was found to be statistically significant (p=0.02).

Table 4. Factors affecting IFI development

	Group1 (those with IFI) n=75	Group 2 (those without IFI) n=79	p-value
Presence of acute GVHD			**0.035**
Yes	22	12	
CMV infection			**0.002**
Yes	31	15	
Duration of Neutropenia (day) Median (min-max)			**0.001**
	23.0 (8-87)	17.0 (5-71)	
Disease diagnosis			**0.67**
AML	27	31	
ALL	13	11	
MDS	11	8	
Lymphoma	11	8	
MM	4	10	
AA	4	4	
Chronic leukemia	4	**3**	
Myelofibrosis	1	**4**	
HLA compatibility (A, B, DRB1, C and DQ pairs)			**0.72**
10/10 (full)	61	65	
9/10 (good)	10	8	
5-8/10 (partial)	4	6	
Donor type			**0.26**
Relative	64	72	
Non-relative	11	7	
Preparation regime			**0.09**
Myeloablative	48	40	
Non-myeloablative	39	27	
History of previous IFI			**0.44**
Var	34	31	

IFI: Invasive fungal infection, GVHD: Graft versus host disease, CMV: Cytomegalovirus, AML: Acute myeloid leukemia, ALL: Acute lymphocytic leukemia, MDS: Myelodysplastic syndrome, MM: Multiple myeloma, AA: Aplastic anemia, HLA: Human leucocyte antigen

The prophylactic antifungal duration of these 18 patients was 23.00±17.58 (median value: 23.00). The prophylactic antifungal duration of the surviving 134 of these 152 patients was 31.07±14.52 (median value: 30.00). This was found to be statistically significant (p=0.017).

DISCUSSION

In our study evaluating the frequency, treatment and outcome of IFI developing after allogeneic HSCT, we found that the presence of acute GVHD, use of high-dose corticosteroids (CS) for GVHD, CMV infection and prolonged neutropenia were risk factors for the development of IFI. In addition, the duration of neutropenia was found to be associated with mortality after transplantation.

When we examine the distribution of IFI in our study, we see that the majority of the cases are possible IFI and the fever group of unknown cause. In many studies, only proven and high probability patients were accepted for IFI and the incidence of IFI was seen between 8.8% and 26%[6,13,18,20,23,24,25]. When we looked at the proven and high probability group among IFI patients in our study, the incidence was seen to be 18.2%, similar to other studies.

The gender distribution, mean age and allogeneic HSCT indication preparation regimens in our study were similar to the literature[6,23,24,26]. Similar to the literature, the most commonly used prophylactic antifungal was fluconazole[27] and the most common focus in the group developing IFI was the lungs[25,28]. The most preferred agent in the first-line treatment was L-AmB. In empirical treatment, L-AmB and caspofungin were preferred at approximately the same rates. These treatment options were consistent with the literature[29,30,31].

In our study, the most frequently isolated agent in patients with proven IFI was aspergillus. Mold species and non-albicans candida species were found to be higher. One of the reasons for this may be the decrease in candida species due to routine prophylaxis with fluconazole. The non-c.albicans increase in recent years is also seen in our center[9,15].

In our study, disease diagnosis, HLA compatibility, donor type, and regimen type were not found to be significant in terms of IFI development. While disease diagnosis and preparation regimen type were not found to be significant in terms of IFI development in studies, there are different results in terms of HLA compatibility and donor type and IFI development in studies[6,23,25,32].

A history of previous IFI was not found to be a significant risk factor for the development of IFI, which is inconsistent with the literature[6,23,24]. This may be due to the fact that antifungal treatments were started with a diagnosis of fever of unknown cause and possible IFIs were included in the study.

In an observational study conducted by Shi et al.[6], which examined 408 patients who underwent allogeneic HSCT, a history of IFI, HLA incompatibility, prolonged neutropenia duration, and grade 3 and 4 acute GVHD development were found to be associated with the development of IFI. In another study including 1248 patients who underwent allogeneic HSCT, proven and highly probable IFI developed in 163 patients, and HLA incompatibility, duration of neutropenia, and development of GVHD were found to be risk factors for IFI[10]. In a multicenter study conducted in China, independent risk factors for proven/probable IFI in patients undergoing allogeneic HSCT were identified as diabetes, HLA-matched unrelated donor, prolonged severe neutropenia, and immunosuppressive therapy[23]. In our study, similar to the literature, the presence of acute GVHD, use of high-dose CS for GVHD, and CMV infection were found to be significant risk factors for the development of IFI[6,10,11,20,23,24,28,33]. In addition, prolonged neutropenia was found to be the most important risk factor for the development of IFI in all patient groups.

In our study, it was found that IFI significantly increased transplantation treatment mortality (24% in the IFI group, 2% in the non-IFI group). In the literature, mortality rates related to IFI vary among studies. In a multicenter observational study conducted in China and evaluating 1401 patients who underwent allogeneic HSCT, the mortality rate in patients who developed IFI, similar to our study, was found to be 25%[24]. In many studies, mortality rates ranged from 40% to 90%[21,22]. It was thought that this difference was due to the longer follow-up period in studies with higher mortality rates.

Study Limitations

The limitations of our study were evaluated as its being retrospective, single-centered, the fact that patients were followed up only during hospitalization, and the low number of proven IFIs due to the lack of further examination due to the clinical response obtained after the initiation of empirical antifungal treatment.

CONCLUSION

In our study, the presence of acute GVHD, CMV infection and long duration of neutropenia were found to be risk factors for the development of IFI. In addition, the duration of neutropenia was found to be associated with mortality after allogeneic HSCT. In the prevention and treatment of IFIs, which seriously increase transplantation mortality, it would be appropriate for each center to evaluate the frequency of IFIs, take infection control measures, antifungal prophylaxis and identify patients at high risk of IFIs and decide which treatment strategy is more beneficial.

Ethics

Ethics Committee Approval: The study was carried out after obtaining the necessary permissions from the Clinical Research Ethics Committee of the Ege University Faculty of Medicine (decision no: 17-2/7, date: 13.03.2017).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.O., N.S., M.T., F.Ş., G.S., B.A., F.V., Design: B.A., F.V., Data Collection or Processing: E.O., Analysis or Interpretation: E.O., A.G., N.S., M.T., F.Ş., G.S., B.A., F.V., Literature Search: E.O., A.G., F.V., Writing: E.O.

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

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Goldman L, Schafer AI. Goldman's Cecil Medicine, 24th ed. Elsevier, 2012;1158-9.
2. Zeiser R, Blazar BR. Acute Graft-versus-host disease - biologic process, prevention, and therapy. N Engl J Med. 2017;377:2167-79.
3. Sahin U, Toprak SK, Atilla PA, Atilla E, Demirer T. An overview of infectious complications after allogeneic hematopoietic stem cell transplantation. J Infect Chemother. 2016;22:505-14.
4. Neofytos D. Antimicrobial prophylaxis and preemptive approaches for the prevention of infections in the stem cell transplant recipient, with analogies to the hematologic malignancy patient. Infect Dis Clin North Am. 2019;33:361-80.
5. Neofytos D, Horn D, Anaissie E, Steinbach W, Olyaei A, Fishman J, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis. 2009;48:265-73.
6. Shi JM, Pei XY, Luo Y, Tan YM, Tie RX, He JS, et al. Invasive fungal infection in allogeneic hematopoietic stem cell transplant recipients: single center experiences of 12 years. J Zhejiang Univ-Sci B. 2015;16:796-804
7. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46:1813-21.
8. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the european organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71:1367-76.
9. Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis. 2010;50:1091-100.
10. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. Clin Infect Dis. 2008;47:1041-50.
11. Fukuda T, Boeckh M, Carter RA, Sandmaier BM, Maris MB, Maloney DG, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood. 2003;102:827-33.
12. Thursky K, Byrnes G, Grigg A, Szer J, Slavin M. Risk factors for post-engraftment invasive aspergillosis in allogeneic stem cell transplantation. Bone Marrow Transplant. 2004;34:115-21.
13. Omer AK, Ziakas PD, Anagnostou T, Coughlin E, Kourkoumpetis T, McAfee SL, et al. Risk factors for invasive fungal disease after allogeneic hematopoietic stem cell transplantation: a single center experience. Biol Blood Marrow Transplant. 2013;19:1190-6.
14. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation--a prospective, randomized, double-blind study. J Infect Dis. 1995;171:1545-52.
15. Marr KA, Seidel K, Slavin MA, Bowden RA, Schoch HG, Flowers ME, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood. 2000;96:2055-61.
16. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood. 2002;100:4358-66.
17. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis. 2000;30:851-6.
18. Post MJ, Lass-Floerl C, Gastl G, Nachbaur D. Invasive fungal infections in allogeneic and autologous stem cell transplant recipients: a single-center study of 166 transplanted patients. Transpl Infect Dis. 2007;9:189-95.
19. Pagano L, Caira M, Nosari A, Van Lint MT, Candoni A, Offidani M, et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study--Sorveglianza epidemiologica infezioni fungine nelle emopatie maligne. Clin Infect Dis. 2007;45:1161-70.
20. Koldehoff M, Zakrzewski JL. Modern management of respiratory failure due to pulmonary mycoses following allogeneic hematopoietic stem-cell transplantation. Am J Hematol. 2005;79:158-63.
21. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis. 2001;32:358-66.
22. Dagenais TR, Keller NP. Pathogenesis of Aspergillus fumigatus in Invasive Aspergillosis. Clin Microbiol Rev. 2009;22:447-65.
23. Liu YC, Chien SH, Fan NW, Hu MH, Gau JP, Liu CJ, et al. Incidence and risk factors of probable and proven invasive fungal infection in adult patients receiving allogeneic hematopoietic stem cell transplantation. J Microbiol Immunol Infect. 2016;49:567-74.
24. Sun Y, Meng F, Han M, Zhang X, Yu L, Huang H, et al. Epidemiology, management, and outcome of invasive fungal disease in patients undergoing hematopoietic stem cell transplantation in China: a multicenter prospective observational study. Biol Blood Marrow Transplant. 2015;21:1117-26.
25. Harrison N, Mitterbauer M, Tobudic S, Kalhs P, Rabitsch W, Greinix H, et al. Incidence and characteristics of invasive fungal diseases in allogeneic hematopoietic stem cell transplant recipients: a retrospective cohort study. BMC Infect Dis. 2015;15:584.
26. Horowitz MM: Uses and Growth of Hematopoietic cell transplantation Thomas' Hematopoietic Cell Transplantation. In: Forman SJ, Negrin RS, Antin JH, Appelbaum FR, (eds). Stem Cell Transplantation 5th ed. 2015.
27. Maertens J, Marchetti O, Herbrecht R, Cornely OA, Flückiger U, Frêre P, et al. Third European Conference on Infections in Leukemia. European Conference on Infections in Leukemia. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3--2009 update. Bone Marrow Transplant. 2011;46:709-18.
28. Maziarz RT, Brazauskas R, Chen M, McLeod AA, Martino R, Wingard JR, et al. Pre-existing invasive fungal infection is not a contraindication for

allogeneic HSCT for patients with hematologic malignancies: a CIBMTR study. Bone Marrow Transplant. 2017;52:270-8.

29. Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med. 2004;351:1391-402.
30. Morrissey CO, Gilroy NM, Macesic N, Walker P, Ananda-Rajah M, May M, et al. Consensus guidelines for the use of empiric and diagnostic-driven antifungal treatment strategies in haematological malignancy, 2014. Intern Med J. 2014;44:1298-314.
31. Hebart H, Klingspor L, Klingebiel T, Loeffler J, Tollemar J, Ljungman P, et al. A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT. Bone Marrow Transplant. 2009;43:553-61.
32. Girmenia C, Raiola AM, Piciocchi A, Algarotti A, Stanzani M, Cudillo L, et al. Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Biol Blood Marrow Transplant. 2014;20:872-80.
33. Hovi L, Saarinen-Pihkala UM, Vettenranta K, Saxen H. Invasive fungal infections in pediatric bone marrow transplant recipients: single center experience of 10 years. Bone Marrow Transplant. 2000;26:999-1004.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.37233
Nam Kem Med J 2024;12(4):318-325

Disaster Affect Levels of Individuals Experienced by 2023 Kahramanmaraş Earthquake: A Case Study of Hatay

2023 Kahramanmaraş Depremini Yaşayanlarda Depremden Etkilenme Düzeyleri: Hatay Örneği

Berna Büşra ERGİN[1], Gamze DEMİRAY[2], Galip EKUKLU[1]

[1]Trakya University Faculty of Medicine, Department of Public Health, Edirne,Turkey
[2]Aydın Efeler Health Directorate, Aydın, Turkey

ABSTRACT

Aim: Earthquakes are significant natural disasters with profound medical, economic, and societal impacts. Unlike other disasters, they occur suddenly, causing extensive destruction, death, and injuries, which lead to numerous additional problems. This study aims to assess the levels of trauma and stress among individuals who experienced the earthquake in Hatay on February 6, 2023, and to identify potential influencing factors.

Materials and Methods: This descriptive study surveyed individuals residing in Hatay, who experienced the Kahramanmaraş earthquake. A convenience sampling method was used to select 200 participants. Data were collected using a questionnaire covering socio-demographic characteristics, earthquake experiences, and the Trauma Scale for Earthquake Survivors.

Results: 17% of the 200 participants stated that they were injured in the earthquake, 57% stated that they lost their loved ones and 78% stated that they suffered financial losses. Additionally, 46% reported their homes were "moderately/heavily damaged," and 68% indicated a need for financial support. The average trauma scale score was 65.8±17.3. Higher trauma scores were found among female participants, those who lost their relatives, suffered financial losses, had collapsed homes, or received/needed psychological support.

Conclusion: The study reveals that women, individuals with psychiatric illnesses, those who lost relatives, and those experiencing financial losses were significantly impacted by the earthquake. Key factors influencing trauma levels included gender, psychiatric illness, loss of relatives, financial support status, and income.

Keywords: Earthquakes, disasters, psychology, trauma

ÖZ

Amaç: Depremler, derin tıbbi, ekonomik ve toplumsal etkileri olan önemli doğal afetlerdir. Diğer afetlerden farklı olarak, aniden meydana gelirler ve geniş çapta yıkım, ölüm ve yaralanmalara yol açarak birçok ek probleme neden olurlar. Bu çalışma, 6 Şubat 2023'te Hatay'da depremi deneyimleyen bireyler arasındaki travma ve stres düzeylerini değerlendirmeyi ve bu düzeyleri etkileyen potansiyel faktörleri belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Bu tanımlayıcı çalışmada, Kahramanmaraş depremine tanık olan Hatay'da yaşayan bireyler araştırıldı. 200 katılımcı, kolayda örnekleme yöntemi kullanılarak seçildi. Veriler, sosyo-demografik özellikler, deprem deneyimleri ve Deprem Sonrası Travma Ölçeği'ni kapsayan bir anket kullanılarak toplandı.

Bulgular: 200 katılımcının %17'si depremde yaralandığını, %57'si sevdiklerini kaybettiğini ve %78'i maddi kayıp yaşadığını belirtti. Ayrıca, katılımcıların %46'sı evlerinin "orta/ağır hasarlı" olduğunu ve %68'i maddi destek ihtiyaç duyduklarını bildirdi. Ortalama travma ölçek puanı 65,8±17,3 idi. Kadın katılımcılar, yakınlarını kaybedenler, maddi kayıplar yaşayanlar, evleri yıkık olanlar veya psikolojik destek alan/almayı düşünenler daha yüksek travma puanlarına sahipti.

Sonuç: Çalışma, kadınların, psikiyatrik hastalığı olan bireylerin, yakınlarını kaybedenlerin ve maddi kayıplar yaşayanların depremden önemli ölçüde etkilendiğini ortaya koymaktadır. Travma düzeylerini etkileyen ana faktörler arasında cinsiyet, psikiyatrik hastalık, yakın kaybı, maddi destek alma durumu ve gelir durumu bulunmaktadır.

Anahtar Kelimeler: Deprem, afet, psikoloji, travma

Address for Correspondence: Berna Büşra ERGİN MD, Trakya University Faculty of Medicine, Department of Public Health, Edirne,Türkiye
E-mail: bernabusrah@gmail.com **ORCID ID:** orcid.org/0000-0002-8661-725X
Received: 13.08.2024 **Accepted**: 09.10.2024

INTRODUCTION

Natural disasters have historically resulted in a large number of casualties and suffering. Earthquakes are significant natural disasters with wide geographical impact affecting a large population, and they entail medical, economic, and societal consequences[1].

The World Health Organization defines health as "a state of complete physical, mental, and social well-being"[2]. Health is a holistic concept recognized and accepted legally, in addition to being acknowledged in theory and practice alongside medicine. While some survivors may sustain physical injuries during earthquakes, all individuals affected by the earthquake experience psychological impacts. The term "earthquake victim" in Turkish refers to all survivors and implies that all survivors are affected. Earthquakes, as a traumatic event within society, not only affect individuals but also lead to the loss of family members, relatives, individuals from their social circles, and material possessions, thus having lifelong consequences[3,4]. It is a well-known fact that disasters can have short- and long-term psychological effects, and they can become traumatic events for individuals[1,5,6]. Individual responses to trauma can vary. Not every traumatic event elicits similar responses in individuals, and even individuals experiencing the same traumatic event may respond differently[7]. Considering the effects of traumatic events on individuals, two periods can be identified: the acute phase and the post-traumatic period. Natural disasters are included in the definition of traumatic events in the DSM-V[8].

Earthquakes exhibit distinct characteristics from other traumatic events. They occur suddenly, leading to destruction, death, and injuries, thus giving rise to numerous additional problems. Moreover, due to aftershocks, they can also create chronic effects, making them particularly unique among natural disasters[9]. One of the variables closely associated with trauma is the concept of hopelessness. Hopelessness is generally defined as a feeling that a situation or problem cannot be resolved or corrected[10]. This feeling can lead individuals to lose their positive expectations about the future and their sense of hope[11].

A disaster like an earthquake can be the cause and initiator of psychological disorders in individuals. The emergence of psychological disorders disrupts individuals' work capacity, motivation, and mental focus. On the other hand, the loss of a spouse, child, parent, relative, friend, neighbor, and material possessions in an earthquake, as well as changes in living environment, can affect individuals' work capacity and productivity even without a disorder, through a natural psychological response called grief (mourning)[3,11-13].

In countries like Turkey, where major and destructive disasters occur frequently, it is essential to utilize appropriate measurement tools to assess individuals' experiences of disasters to improve the quality of preventive mental health services[3,14]. Early detection of post-traumatic stress and related symptoms is crucial for secondary preventive mental health services[5,6]. The aim of this study is to determine the levels of trauma and stress experienced by individuals who lived through the earthquake that occurred on February 6, 2023, in Hatay province, and to examine the influence of potential variables.

MATERIALS AND METHODS

The population of this descriptive study consists of individuals living in Hatay, who experienced the earthquake that occurred in Kahramanmaraş on 6 February 2023. The population of Hatay before the earthquake was 1.686.043. Since the current population data after the earthquake could not be reached, convenience sampling method was preferred in the sample selection process. Convenience sampling is a non-random sampling method in which the sample segment to be selected from the main mass is determined by the judgement of the researcher. In cases where it is not possible to determine the main mass (disaster, extraordinary situation, etc.), the researcher may have to resort to non-random sampling methods. In convenience sampling, data are collected from the main mass in the easiest, fastest and most economical way[15]. With 85% power, α=0.05 and 0.2 design effect, the sample size was calculated as 182; considering the possible data loss, 10% was added and the final sample size was determined as 200 people. The study was conducted between March 1 and June 30, 2023 by face-to-face interviews with individuals who were in the center of Antakya and who had experienced the earthquake, and by filling out the questionnaires through Google Forms. Our study is not a prospective study.

Data Collection Instruments

1. Survey Form: This form consists of 24 questions developed by the researchers based on literature findings. It includes questions about the sociodemographic characteristics of earthquake survivors (gender, marital status, age, parental status, education, income, etc.) and their experiences during the earthquake.

2. The Scale That Determines the Level of the Trauma after the Earthquake: This scale was developed by Fuat Tanhan and Murat Kayri in 2013[16]. It consists of a total of 20 items and 5 subscales: behavioral problems (4 items), emotional constriction (5 items), sensory constriction (4 items), cognitive constriction (4 items), and sleep problems (3 items). Permission to use the scale was obtained from Fuat Tanhan. In the Likert-type scale, questions numbered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13, 14, 15, 16, 17, 18, 19, and 20 are rated as "completely agree" with a score of 5 points, "strongly agree" with 4 points, "moderately agree" with

3 points, "slightly agree" with 2 points, and "not at all agree" with 1 point. Questions numbered 11 and 12 are reverse-scored. The lowest possible score from the scale is 20, and the highest is 100. An increase in scores indicates an increase in the level of individuals' earthquake impact. Reliability analyses of the scale resulted in Cronbach's alpha coefficients of 0.64 for the first subscale, 0.75 for the second subscale, 0.61 for the third subscale, 0.68 for the fourth subscale, and 0.70 for the fifth subscale. The Cronbach's alpha coefficient calculated for all items of the scale was found to be 0.87.

Data Collection: Data were collected through online (individuals also completed the online form in a face-to-face interview) and face-to-face interview methods. During the data collection process, participants were informed about the purpose of the research, and their consent was obtained. Each interview lasted an average of 25-30 minutes.

Data Analysis: Data were analyzed using IBM SPSS Statistics 21.0 software. Descriptive statistics, Student's t-test, Mann-Whitney U test, ANOVA test, and Tukey post-hoc, Games Howell post hoc tests were used in evaluating the findings. A significance level of $p<0.05$ was considered statistically significant in the results[17].

The study obtained approval from Trakya University Faculty of Medicine Deanship Non-invasive Scientific Research Ethics Committee (decision number: 10/06, date: 05.06.2023). Necessary permissions were obtained from Trakya University Dean's Office and the developers of the scale to conduct the research.

RESULTS

Of the 200 participants in the study, 123 (61.5%) were female and 121 (60.5%) were married. The mean age of the participants was 34.5±12.7 years. The descriptive characteristics of the participants are presented in Table 1. Thirty-four (17%) participants reported being injured in the earthquake centered in Kahramanmaraş on February 6, while 114 (57%) reported losing their loved ones in this earthquake. When asked if they experienced financial loss due to the earthquake, 156 people (78%) answered "yes." Regarding the condition of participants' homes after the earthquake, 17.5% were "collapsed," 46% were "moderately/heavily damaged," and 36.5% were "undamaged/slightly damaged." The number of participants who reported needing financial assistance due to the earthquake was 137 (68.5%), while 44 (22.0%) answered "yes" to the question "Are you currently receiving financial assistance?". While 54% of participants believed they needed psychological support, only 7.5% reported receiving psychological support. Some characteristics related to the earthquake experienced by the participants are presented in Table 2.

Table 1. Descriptive characteristics of participants

Descriptive Features	Number	Percentage (%)
Gender		
Female	123	61.5
Male	77	38.5
Marital Status		
Married	121	60.5
Single	79	39.5
Parental Status		
Yes	113	56.5
No	87	43.5
Number of children		
0	84	42.0
1-2	74	37.0
3-4	42	21.0
Education level		
Primary or middle school graduate	32	16.0
High school graduate	67	33.5
University graduate	101	50.5
Place of residence		
Container/tent/dormitory	40	20.0
With family/relatives	54	27.0
Rented house	68	34.0
Own house	38	19.0
Employment status before the earthquake		
Employed	129	64.5
Unemployed	71	35.5
Current employment status		
Employed	107	53.5
Unemployed	93	46.5
Chronic disease status		
Yes	51	25.5
No	149	74.5
Psychiatric disease status		
Yes	27	13.5
No	173	86.5
Tobacco use		
Yes	70	35.0
No/Quit	130	65.0
Income assessment		
Income exceeds expenses	33	16.5
Income equals expenses	58	29.0
Income falls short of expenses	109	54.5
Total	200	100.0

Table 2. Participants' earthquake experience

		Number	Percentage (%)
Earthquake injury status	Yes	34	17.0
	No	166	83.0
Previous experience of disaster	Evet	57	28.5
	Yes	57	28.5
Loss of relatives in the earthquake	No	143	71.5
	Yes	114	57.0
Financial loss due to the earthquake	Yes	156	78.0
	No	44	22.0
Damage status of the house due to the earthquake	Damaged/ slightly damaged	73	36.5
	Moderate/ severely damaged	92	46.0
	Collapsed	35	17.5
Had to receive financial support after the earthquake?	Yes	137	68.5
	No	63	31.5
Are you currently receiving financial support?	Yes	44	22.0
	No	156	78.0
Are you currently receiving psychological support?	Yes	15	7.5
	No	185	92.5
Do you think you need psychological support?	Yes	108	54.0
	No	92	46.0
Total		200	100.0

Of the participants, 57 (28.5%) stated that they had experienced a disaster before. When asked about the type of disaster experienced, the most frequently reported first three types of disasters were earthquake (61.4%), flood (26.3%), and COVID-19 pandemic (21.0%). The mean scale scores of the participants were 65.8±17.3.

The scores obtained from the scale by participants' socio-demographic characteristics are presented in Table 3.

It was found that female participants scored higher on the scale compared to male participants, and participants with psychiatric disorders scored higher on the scale compared to those without. When comparing the scores obtained from the scale with the situation of losing a loved one in the earthquake, it was found that the scores of those who lost their loved ones were higher. Participants who experienced financial loss after the earthquake scored higher on the scale compared to those who did not; similarly, those who had to receive financial assistance scored higher on the scale compared to those who did not receive assistance. In terms of income assessment among participants, those who indicated "my income is less than my expenses" scored higher on the scale compared to those who indicated "my income is equal to my expenses" and "my income is more than my expenses" (with respective p values of p=0.012 and p=0.005). When comparing the condition of the residence after the earthquake with the scores obtained from the scale, it was found that the scale score of participants whose residence was "collapsed" was higher compared to those whose residence was "undamaged/

Table 3. Participants' scores on the scale according to some sociodemographic characteristics

Variable		Scale score	p value
Mean ± standard deviation gender	Female	65.6±17.0	**0.005**
	Male	61.5±17.0	
Marital status	Married	66.5±15.5	0.498
	Single	64.8±19.7	
Childbearing status	Yes	66.6±15.1	0.505
	No	64.9±19.7	
Number of children*	0	64.5±19.6	0.480
	1-2	65.8±15.1	
	3-4	68.5±15.6	
Eğitim durumu*	Primary/secondary school graduate	70.0±14.5	0.307
	High school graduate	64.5±18.4	
	University graduate	65.4±17.1	
Chronic disease status	Yes	67.0±16.2	0.583
	No	65.5±17.6	
Psychiatric disease status**	Yes	74.0±14.2	**0.007**
	No	64.6±14.3	
Tobacco product use status	Yes	69.1±16.7	0.050
	No	64.1±17.3	

Table 3. Continued

Variable		Scale score	p value
Previous disaster experience	Yes	66.1±17.2	0.888
	No	65.7±17.3	
Earthquake injury status	Yes	67.2±20.7	0.601
	No	65.6±16.5	
Loss of relatives in the earthquake	Yes	69.3±16.2	**0.001**
	No	61.2±17.6	
Financial loss due to the earthquake	Yes	67.3±16.8	**0.018**
	No	60.4±17.9	
Monthly income assessment[1]	My income is less than my expenses	69.8±16.3	**0.001**
	My income is equal to my expenses	62.0±16.7	
	My income is more than my expenses	59.3±18.0	
House damage status due to the earthquake[2]	Undamaged/slightly damaged	61.2±18.4	**0.004**
	Moderate/severe	67.0±16.9	
	Collapsed	72.5±12.6	
Post-earthquake accommodation	Container/tent/dormitory	68.0±17.4	0.056
	Family/relative's place	67.7±16.4	
	Rented house	66.9±16.0	
	Own house	59.0±19.1	
Had to receive financial support after the earthquake?	Yes	69.3±15.5	**0.000**
	No	58.2±18.6	
Are you currently receiving financial support?	Yes	69.4±14.4	0.124
	No	64.8±17.9	
Are you currently receiving psychological support?[3]	Yes	75.8±15.4	**0.015**
	No	65.0±17.2	
Do you think you need psychological support?	Yes	72.6±14.6	**0.000**
	No	58.0±16.8	

[1]ANOVA, Tukey post hoc test, [2]ANOVA, Games Howell post hoc test, [3]Mann-Whitney U test

slightly damaged" (p=0.001). When comparing the situation of receiving psychological support after the earthquake with the scores obtained from the scale, it was found that the scores of those who received psychological support were higher. The scale scores of participants who believed they needed psychological support were higher compared to those who believed they did not need support.

A linear regression analysis was conducted to evaluate the main factors influencing the scale score by creating a model with independent variables that statistically affected the scale score. In the multiple linear regression analysis performed using backward stepwise method, it was found that gender, psychiatric illness status, loss of a loved one in the earthquake, receiving financial assistance due to the earthquake, and income status significantly influenced the scale score (p<0.05, Table 4).

DISCUSSION

In this study, the levels of impact of the earthquake centered in Kahramanmaraş on February 6, 2023, on individuals residing in Hatay, and the associated factors were presented. In a study conducted by Bilici et al.[18] on the level of impact of the Elazığ earthquake, it was found that women had significantly higher scores on the Beck Anxiety Scale compared to men, and the prevalence of moderate and severe anxiety was significantly higher among women. Similarly, in our study, the average scores obtained from the scale that determines the level of the trauma were found to be higher for female participants compared to male participants. Another study indicated that gender and earthquake experience were significant factors in the emotions felt after an earthquake. The reasons why women are more affected by earthquakes were highlighted in the study, including women's perception of their strong attachment to their families, higher levels of concern about their families compared to concerns about the earthquake

Table 4. Multiple linear regression model

Coefficient Table						
Model			**Regression coefficient**	**Standard error**	**Corrected regression coefficient**	**p value**
2*	**Intercept**		101.498	7.657		0.000
	Gender	**Female**	7.267	2.265	-0.205	0.002
		Male	Referans			
	Income status	**Less than expenses**	-11.068	3.060	0.320	0.000
		Equal to expenses	-6.025	3.414	0.158	0.079
		More than expenses	Referans			
	Psychiatric illness status	**Yes**	7.331	3.247	0.146	0.025
		No	Referans			
	Loss of a close relative due to the earthquake	**Yes**	5.598	2.359	0.240	0.019
		No	Referans			
	Receiving financial support due to the earthquake	Yes	8.903	3.414	0.240	0.000
		No	Referans			
*Model: F=10.0 p=0.000 R=0.487 R^2= 0.214						

itself, and the generally more emotional nature of women compared to men[19].

In the study by Bilici et al.[18], participants reported that the most common past disaster experiences were earthquakes/floods and similar natural disasters (27.8%). Similarly, in our study, the two most common past disasters experienced by participants were earthquakes (61.4%) and floods (26.3%). In a study examining the relationship between earthquake survivors' experience of property loss and their levels of depression in 2014, it was found that earthquake survivors who experienced a significant amount of property loss had higher levels of depression compared to those who did not experience significant property loss[20]. Consistent with this, our study also found that individuals who experienced financial loss due to the earthquake had higher levels of impact from the earthquake. Additionally, multiple linear regression analysis conducted using a backward stepwise method revealed that receiving financial assistance due to the earthquake and income status significantly influenced the scale score.

According to the results of the same study, there was a significant difference in the levels of depression among earthquake survivors based on the current condition of their homes. The depression levels of earthquake survivors whose homes remained intact were found to be higher compared to those whose homes were destroyed[20]. Similarly, in our study, a significant difference was found between the level of impact from the earthquake and the condition of the participants' homes.

In the same study, the location where earthquake survivors stayed after the earthquake was examined, and no significant difference was found in their levels of depression based on their current living situation[20]. Likewise, in our study, no significant difference was found between the level of impact from the earthquake and the location where participants stayed after the earthquake.

In another study, the experience of loss within the family during an earthquake was associated with a diagnosis of Post-Traumatic Stress Disorder[21]. Consistent with this finding, in our study, individuals who lost a family member during the earthquake had significantly higher scores on the scale.

Similarly, in a study conducted in 2023 using the scale that determines the level of the trauma after the Earthquake, it was found that individuals who received psychosocial support after an earthquake had significantly higher scale scores compared to those who did not receive psychosocial support post-earthquake[22]. In alignment with these results, our study also found that individuals who felt the need for psychological support after the earthquake and those who actually received psychological support had significantly higher scale scores.

Study Limitations

Our study has several limitations. Firstly, since this study was conducted on individuals affected by the earthquake in Hatay, the results may not be generalizable to all earthquake survivors in other regions. Additionally, due to the information that a portion of the Hatay population relocated from the city and some residential areas were destroyed after the earthquake, a non-probabilistic sampling method had to be employed. Finally, another limitation is the method of data collection, as the data were obtained through both online surveys and face-to-face interviews. This method may have led participants to provide biased or randomly filled responses to the questions.

CONCLUSION

The earthquake that occurred on February 6, 2023 in Kahramanmaraş affected a region where approximately 13.5 million people resided across 10 provinces, resulting in the loss of 50,096 lives[23]. This study investigates the levels of impact and associated factors of the February 6, 2023 earthquake centered in Kahramanmaraş among individuals residing in Hatay.

According to the findings of the study, one in every five participants was injured during the earthquake, with more than half losing a relative. Three-quarters of the participants reported experiencing financial losses due to the earthquake, while two-thirds stated that their homes became uninhabitable. Furthermore, over half of the participants expressed a need for psychological support, yet less than 10% reported currently receiving such support. Research results indicate that individuals affected by the earthquake, particularly women, those with psychiatric conditions, individuals who lost relatives, experienced financial losses, needed financial assistance post-earthquake, had lower income, resided in severely damaged homes, expressed a need for psychological support, and those currently receiving psychological support, exhibited higher levels of earthquake-induced distress according to the scale that determines the level of the trauma after the earthquake. Gender, psychiatric condition, loss of relatives, financial losses due to the earthquake, and income status were identified as factors contributing to increased scale scores, thereby exacerbating individuals' negative impacts from the earthquake.

To minimize the adverse effects of earthquakes, disaster awareness should be promoted in the community during pre-, during, and post-earthquake periods. Given that earthquakes can affect large populations, many individuals may experience various health issues and psychosocial disorders. Thus, proactive multidisciplinary approaches should be prioritized to expedite the rehabilitation processes of affected individuals. Considering that disadvantaged groups are more susceptible to the adverse effects of earthquakes, targeted interventions should be prioritized for these groups. The psychosocial support network should be structured to reach every individual both before and after earthquakes. Policies aimed at preparedness for disasters should be implemented to mitigate their impacts effectively.

Ethics

Ethics Committee Approval: The study obtained approval from Trakya University Faculty of Medicine Deanship Non-invasive Scientific Research Ethics Committee (decision number: 10/06 date: 05.06.2023). Necessary permissions were obtained from Dean's Office and the developers of the scale to conduct the research.

Informed Consent: During the data collection process, participants were informed about the purpose of the research, and their consent was obtained

Footnotes

Authorship Contributions

Concept: B.B.E., G.D., G.E., Design: B.B.E., G.D., G.E., Data Collection or Processing: B.B.E., G.D., Analysis or Interpretation: B.B.E., G.D., G.E., Literature Search: B.B.E., G.D., Writing: B.B.E., G.D., G.E.

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

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Noji EK. Public health issues in disasters. Crit Care Med. 2005;33:29-33.
2. WHO-Pan. American Health Organization. Mental health and psychosocial support in disaster situations in the caribbean. Health response to the earthquake in Haiti January 2010. 18.09.2024. https://iris.paho.org/handle/10665.2/3188
3. Ursano RJ, Fullerton CS, Weisaeth L, Raphael B. Individual and community responses to disasters. Textbook of disaster psychiatry. Cambridge University Press, 2007;3-28.
4. WHO-Pan. American Health Organization. Lessons to be learned fort he next massive sudden onset disaster 2012. 18.09.2024. https://iris.paho.org/bitstream/handle/10665.2/52841/9789275132524_eng.pdf?sequenc
5. López-Ibor JJ. Disasters and mental health: new challenges for the psychiatric profession. World J Biol Psychiatry. 2006;7:171-82.
6. Norwood AE, Ursano RJ, Fullerton CS. Disaster psychiatry: principles and practice. Psychiatr Q. 2000;71:207-26.
7. Özçetin A, Maraş A, Ataoğlu A, İçmeli C. The relationship between personality disorders and post-traumatic stress disorder developed after earthquake. Duzce Med J. 2008;10:8-18.
8. Amerikan Psikiyatri Birliği. DSM-V tanı ölçütleri el kitabı. Çev. E. Köroğlu. Ankara: Hekimler Yayın Birliği. 2013.
9. Hikichi H, Aida J, Tsuboya T, Kondo K, Kawachi I. Can community social cohesion prevent posttraumatic stress disorder in the aftermath of a disaster? a natural experiment from the 2011 tohoku earthquake and Tsunami. Am J Epidemiol. 2016;183:902-10.
10. Voelz ZR, Walker RL, Pettit JW, Joiner Jr TE, Wagner KD. Depressogenic attributional style: evidence of trait-like nature in youth psychiatric inpatients. Personality and Individual Differences. 2003;34:1129-40.
11. Shultz JM, Marcelin LH, Madanes SB, Espinel Z, Neria Y. The "Trauma Signature:" understanding the psychological consequences of the 2010 Haiti earthquake. Prehosp Disaster Med. 2011;26:353-66.
12. Aker AT, Hamzaoğlu O, Boşgelmez Ş. Validity of Kocaeli short screening scale for psychological Trauma (Kocaeli - SHORT). Dusunen Adam The Journal of Psychiatry and Neurological Sciences. 2007;20:172-8.
13. Kopala-Sibley DC, Kotov R, Bromet EJ, Carlson GA, Danzig AP, Black SR, et al. Personality diatheses and hurricane sandy: effects on post-disaster depression. Psychol Med. 2016;46:865-75.

14. Özdoğan S. Türkiye'nin deprem bölgeleri. Türkiye Coğrafyası Araştırma ve Uygulama Merkezi Dergisi. 1993;2:53-68.

15. Haşıloğlu SB, Baran T, Aydın O. A study on the potential problems in marketing research: convenience sampling and scale items with adverbs of frequency. Pamukkale University Journal of Business Research. 2015:19-28.

16. Tanhan F, Kayri M. The validity and reliability work of the scale that determines the level of the trauma after the earthquake. Educational Sciences Theory and Practice. 2013;13:1021-5.

17. George D. SPSS for windows step by step: a simple study guide and reference, 17.0 update, 10/e: Pearson Education India; 2011.

18. Bilici R, Tufan E, Turhan L, Uğurlu GK, Serap T, Kaşan T. Anxiety levels of individuals after an earthquake and factors affecting anxiety levels: An Elazığ-centered preliminary study. Firat Med J. 2013;18:15-9.

19. Yilmaz V, Cangur S, Çelik HE. Sex difference and earthquake experience effects on earthquake victims. Personality and individual differences. 2005;39:341-8.

20. Bedirli B. Deprem travmasının kronik psikolojik etkileri: düzce depremi'nden 14 yıl sonra travma sonrası stres ve depresyon belirtilerinin yaygınlığı ve ilişkili risk faktörleri, haliç üniversitesi sosyal bilimler Enstitüsü Psikoloji Ana Bilim Dalı. Yüksek Lisans Tezi. 2014;İstanbul.

21. Boztas MH, Aker AT, Munir K, Çelik F, Aydın A, Karasu U, et al. 2Post traumatic stress disorder among adults in the aftermath of 2011 Van-Ercis earthquake. Turkish J Clin Psy. 2019;22:380-8.

22. Tüccar E, Yavuz E. Psychosocial Investigation of the effects of Kahramanmaraş pazarcık earthquake (February 6, 2023) on individuals. Journal of Migration and Political Studies. 2023;1:54-77.

23. Anadolu Ajansı. Gündem Asrın Felaketi 2023 18.09.2024. https://www.aa.com.tr/tr/asrin-felaketi/kahramanmaras-merkezli-depremlerde-hayatini-kaybedenlerin-sayisi-50-bin-96-oldu/2850716#:~:text=Afet%20ve%20Acil%20Durum%20Y%C3%B6netimi,107%20bin%20204%20oldu%C4%9Funu%20bildirdi.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.35002
Nam Kem Med J 2024;12(4):326-331

Can Serum Albumin Level At Diagnosis Be A Guide for Clinical Features, Time to Treatment, and Response in Patients with Follicular Lymphoma?

Foliküler Lenfoma Hastalarında Tanı Anı Serum Albumin Düzeyi Klinik Özellikler, Tedaviye Kadar Geçen Süre ve Yanıt Hakkında Yol Gösterici Olabilir Mi?

Abdulkadir KARIŞMAZ[1], Burcu GÜLBAĞCI[2], Rafet EREN[3], Ceyda ASLAN[4], Elif SUYANI[5]

[1]*University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey*
[2]*Tekirdağ Provincial Health Directorate; Dr. İsmail Fehmi Cumalıoğlu City Hospital, Clinic of Medical Oncology, Tekirdağ, Turkey*
[3]*Biruni University Hospital; Biruni University Faculty Of Medicine, Department Of Hematology, İstanbul, Turkey*
[4]*Liv Hospital; İstinye University Faculty of Medicine, Department of Hematology, İstanbul, Turkey*
[5]*Adana City Training and Research Hospital, Clinic of Hemotology, Adana, Turkey*

ABSTRACT

Aim: The aim of the present study was to determine the association between serum albumin level and treatment demand, time to treatment and treatment response in patients with follicular lymphoma (FL).

Materials and Methods: We retrospectively evaluated the data of 25 FL patients. The data comprised gender, age, lactate dehydrogenase (LDH) level, number of nodal sites, presence of extranodal involvement, B symptoms and bulky mass, presence of bone marrow, liver and spleen involvement, Follicular Lymphoma International Prognostic Index score, Eastern Cooperative Oncology Group (ECOG) performance score, tumor grade, albumin level, globulin level, white blood cell count, platelet count and hemoglobin level at diagnosis; treatment demand, time to treatment, and response to treatment.

Results: The median age of the patients was 53 years. The patients were divided into 2 groups according to the median albumin level as >4.4 gr/dL and <4.4 gr/dL. While 13 (52%) patients had an albumin level of ≤4.4 gr/dL, 12 (48%) patients had an albumin level of >4.4 gr/dL. Two groups were comparable in terms of treatment demand, time to treatment and treatment response in patients who were applied treatment (p>0.05). No correlation was found between the level of serum albumin and the need for treatment in patients with FL.

Conclusion: FL, constituting approximately 20% of all non-hodgkin lymphomas, is the second most common lymphoma in adults. The age, LDH and hemoglobin levels, ECOG performance score, stage, extranodal, involvement, number of nodal sites involved, β2 microglobulin level, bone marrow involvement, presence of B symptoms and bulky mass are the conventional risk factors used to determine prognosis in FL. Although we found that treatment requirement was higher and time to treatment was shorter in patients with low serum albumin levels, they did not reach a statistical significance.

Keywords: Follicular lymphoma, albumin, treatment demand

ÖZ

Amaç: Bu çalışmanın amacı foliküler lenfoma (FL) tanılı hastalarda serum albumin düzeyi ile tedavi ihtiyacı, tedaviye kadar geçen süre ve tedaviye yanıt arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Mart 2011 ile Mayıs 2017 tarihleri arasında Sağlık Bilimleri Üniversitesi İstanbul Eğitim ve Araştırma Hastanesi Hematoloji Bölümünde FL tanısıyla takip edilen 25 FL hastasının verileri retrospektif olarak değerlendirildi. Histopatolojik olarak doğrulanmış FL hastalarının verileri hematoloji bölümünün tıbbi kayıtlarından incelendi. Veriler cinsiyet, yaş, laktat dehidrogenaz (LDH) düzeyi, nodal bölge sayısı, ekstranodal tutulum varlığı, B semptomları ve büyük kitle, kemik iliği, karaciğer ve dalak tutulumu varlığı, Foliküler Lenfoma Uluslararası Prognostik İndeksi

Address for Correspondence: Abdulkadir KARIŞMAZ MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey
E-mail: kkarismaz@hotmail.com **ORCID ID:** orcid.org/0000-0002-5556-7501
Received: 30.09.2024 **Accepted**: 25.10.2024

skoru, Doğu Kooperatif Onkoloji Grubu (ECOG) performans skoru, tümör derecesi, albumin düzeyi, globulin düzeyi, lökosit sayısı, beyaz kan hücresi, trombosit sayısı ve tanı anındaki hemoglobin düzeyini; tedavi gereksinimini, tedaviye kadar geçen süreyi ve tedaviye yanıtı içeriyordu.

Bulgular: Hastaların ortanca yaşı 53 (aralık 33-76) idi. 10 (%40) hasta kadın, 15 (%60) hasta erkekti. Hastalar albumin düzeyine göre >4,4 gr/dL ve <4,4 gr/dL olmak üzere 2 gruba ayrıldı. 13 (%52) hastanın albumin düzeyi ≤4,4 gr/dL iken, 12 (%48) hastanın albumin düzeyi >4,4 gr/dL idi. Tedavi uygulanan hastalarda tedavi gereksinimi, tedaviye kadar geçen süre ve tedaviye yanıt açısından iki grup benzerdi (p>0,05). FL'li hastalarda serum albumin düzeyi ile tedavi gereksinimi arasında bir korelasyon bulunmadı.

Sonuç: Tüm hodgkin dışı lenfomaların yaklaşık %20'sini oluşturan FL, yetişkinlerde en sık görülen ikinci lenfomadır. Yaş, LDH ve hemoglobin düzeyleri, ECOG performans skoru, evre, ekstranodal tutulum, tutulan nodal alan sayısı, β2 mikroglobulin düzeyi, kemik iliği tutulumu, B semptomlarının varlığı ve büyük kitle FL'de prognozu belirlemek için kullanılan risk faktörleridir. Serum albumin düzeyleri düşük olan hastalarda tedavi gereksiniminin daha yüksek ve tedaviye kadar geçen sürenin daha kısa olduğunu saptamamıza rağmen, bulgular istatistiksel olarak anlamlı değildi.

Anahtar Kelimeler: Foliküler lenfoma, albumin, tedavi gereksinimi

INTRODUCTION

Follicular lymphoma (FL) is an indolent type of lymphoma that develops from germinal center B cells. As the second most prevalent lymphoma in adults within Western nations, FL accounts for roughly 20% of all non-hodgkin lymphomas (NHL)[1,2]. Typically occurring around the age of 60 years, FL predominantly affects females. The most common initial presentation involves painless enlargement of peripheral lymph nodes at one or multiple sites. Furthermore, the bone marrow and spleen are commonly affected[2]. In the management of FL patients, determining the stage and assessing risk are crucial factors. Prognostic indicators commonly used for FL include the patient's age, levels of lactate dehydrogenase (LDH) and hemoglobin, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, involvement of extranodal sites, number of affected nodal areas, β2 microglobulin concentration, bone marrow infiltration, presence of B symptoms, and the existence of a bulky mass[1,3]. Researchers have examined the predictive value of serum albumin, a protein that decreases during inflammatory responses, in various solid tumor cancers. Studies have consistently demonstrated that higher albumin levels correlate with improved survival outcomes in these malignancies[4]. In the field of hematological malignancies, serum albumin levels have long been utilized as part of the International Staging System to assess prognosis in patients with multiple myeloma[5]. Furthermore, research has demonstrated that serum albumin levels serve as a prognostic indicator in various NHL, including diffuse large B cell lymphoma (DLBCL), localized aggressive NHL, and low-grade lymphomas[6,7,8]. This prognostic value extends to myelodysplastic syndrome as well[9]. In this study, we aimed to determine the association between serum albumin level and treatment demand, time to treatment and treatment response in patients with FL.

MATERIALS AND METHODS

We retrospectively evaluated the data of 25 FL patients, who were followed with the diagnosis of FL at University of Health Sciences, İstanbul Training and Research Hospital, Department of Hematology, between March 2011 and May 2017. The data of histopathologically verified FL patients were reviewed from the medical records of hematology department. The data comprised gender, age, LDH level, number of nodal sites, presence of extranodal involvement, B symptoms and bulky mass, presence of bone marrow, liver and spleen involvement, Follicular Lymphoma International Prognostic Index (FLIPI) score, ECOG score, tumor grade, albumin level, globulin level, white blood cell count (WBC), platelet count and hemoglobin level at diagnosis; treatment demand, time to treatment, and response to treatment. The patients were staged according to the Ann Arbor classification[10]. Staging procedure included physical examination, search for B symptoms, computed tomography (CT) scans or positron emission tomography-CT scans. The approval was obtained from the İstanbul Training and Research Hospital Ethics Committee of University of Health Sciences (decision no: 1085, date: 22.09.2017).

Statistical Analysis

Statistical evaluation was made by SPSS 24 program. Data were described as numbers and percentage or median and range, when appropriate. The x^2 Fisher's exact test was used for evaluating categorical values and the Mann-Whitney U test for continuous values in patient groups. All p values were 2-sided with statistical significance at 0.05 alpha levels.

RESULTS

The characteristics of 25 patients are summarized in Table 1. The median age of the patients was 53 years (range, 33-76). Ten (40%) patients were female and 15 (60%) were male. Four (16%) patients had hemoglobin level of <12 gr/dL and 21 (84%) patients had hemoglobin level of >12 gr/dL at the time of diagnosis. The median WBC was 8620/mm^3 (3930-16000/mm^3), platelet count was 246000/mm^3 (range, 32000-476000/mm^3), LDH was 198 IU/mL (range, 150-709), albumin was 4.4 gr/dL (range, 3.41-4.8) at the time of diagnosis. The number of nodal regions involved was median 5 (range, 1-9). Two (8%) patients had FLIPI score >4 and 23 (92%) patients had ≤4. Five (20%) patients were at stage I-II and 19 (76%) patients

Table 1. Patients' characteristics

Characteristic	n=25
Gender, n, (%)	
Female	10 (40%)
Male	15 (60 %)
Age, years, median (range)	53 (33-76)
Hemoglobin level, g/dL, n (%)	
<12	4 (16%)
>12	21 (84%)
WBC, $10^3/mm^3$, median (range)	8620 (3930-16000)
Platelet, $10^3/mm^3$, median (range)	246000 (32000-476000)
LDH level, U/dL, median (range)	198 (150-709)
Serum albumin level, g/dL, median (range)	4.4 (3.41- 4.8)
The number of nodal sites involved, median, (range)	5 (1-9)
FLIPI score, n (%)	
<=4	23 (92%)
>4	2 (8%)
Stage, n (%)	
Stage I-II	5 (20%)
Stage III-IV	19 (76%)
Unknown	1 (4%)
B symptom, n (%)	
Present	4 (16%)
Absent	11 (44%)
Unknown	10 (40%)
Bone marrow involvement, n (%)	
Present	11 (44%)
Absent	12 (48%)
Unknown	2 (8%)
Liver involvement, n (%)	
Present	0 (0%)
Absent	22 (88%)
Unknown	3 (12%)
Splenomegaly, n (%)	
Present	12 (48%)
Absent	13 (52%)
Unknown	
Bulky mass, n (%)	
Present	5 (20%)
Absent	19 (76%)
Unknown	1 (4%)
ECOG	0
Tumor grade, n (%)	
Grade 1-2	15 (60%)
Grade 3	10 (40%)
Time to treatment, months, median, (range)	2 (0-37)
Treatment demand, n, (%)	
Present	17 (68%)
Absent	8 (32%)
Response to treatment, n (%)	
Present	13 (76%)
Absent	2 (12%)
Unknown	2 (12%)

ECOG: Eastern Cooperative Oncology Group, FLIPI: Follicular Lymphoma International Prognostic Index, LDH: Lactate dehydrogenase, WBC: White blood cell count

at stage III-IV. Four (16%) patients had B symptoms, 11 (44%) patients had bone marrow involvement, 12 (48%) patients had splenomegaly and 5 (20%) patients had bulky mass. ECOG score of all patients included in the study was 0. Fifteen (60%) patients had histological grade 1 disease and 10 (40%) had grade 2. There were 17 (68%) patients who had treatment demand and 13 (76%) of them responded. The median duration between diagnosis and treatment was 2 (range: 0-37) months in patients requiring treatment.

The patients were divided into 2 groups according to the median albumin level as >4.4 gr/dL and <4.4 gr/dL. While 13 (52%) patients had an albumin level of ≤4.4 gr/dL, 12 (48%) patients had an albumin level of >4.4 gr/dL. Two groups were comparable in term of gender, age, hemoglobin level, WBC, platelet count, LDH level, FLIPI score stage, presence of B symptoms, bone marrow involvement, liver involvement and splenomegaly, and tumor grade at the time of diagnosis, treatment demand, time to treatment and treatment response in patients who were applied treatment (p>0.05) (Table 2). Bulky mass was present in 5 (42%) patients with albumin level <4.4 gr/dL and none of the patients had bulky mass with albumin >4.4 gr/dL (p=0.029) (Table 2).

DISCUSSION

At the time of diagnosis, most of FL patients do not exhibit noticeable symptoms related to the disease. For approximately 10-15% of FL patients diagnosed in early stages (I-II), there is a possibility of achieving a cure through radiotherapy treatment. For certain patients with early-stage disease, adopting a watch and wait strategy is considered an appropriate management approach[1,2,11,12]. For patients with advanced (stage III-IV) FL, different approaches are recommended based on their symptoms and tumor burden. Asymptomatic patients are advised to follow a watch and wait strategy. In cases where patients experience mild symptoms, rituximab monotherapy is the preferred treatment. However, for those with high tumor burden, combination therapy including rituximab is suggested[1,12,13]. The initiation of treatment for FL patients

Table 2. Comparison of patients with serum albumin ≤4.4 g/dL and serum albumin level >4.4 g/dL

Characteristic	Albumin ≤ 4.4 g/dL (n=13)	Albumin > 4.4 g/dL (n=12)	p value
Gender, n, (%)			
Female	6 (46%)	4 (33%)	0.688
Male	7 (54%)	8 (67%)	
Age, years, median (range)	56 (42-76)	46 (33-60)	0.238
Hemoglobin level, g/dL, n (%)			
<12	2 (17%)	2 (16%)	0.67
>12	10 (83%)	11 (84%)	
WBC, $10^3/mm^3$, median (range)	8370 (3930-15110)	8840 (4860-16000)	1
Platelet, $10^3/mm^3$, median (range)	235000 (32000-461000)	267000 (141000-476000)	0.434
LDH level, U/dL, median (range)	202 (150-289)	189 (152-709)	0.695
FLIPI score, n (%)			
<=4	12 (92%)	11 (92%)	1
>4	1 (8%)	1 (8%)	
Stage, n (%)			
Stage I-II	2 (15%)	3 (27%)	0.630
Stage III-IV	11 (85%)	8 (73%)	
B symptom, n (%)			
Present	3 (43%)	1 (12%)	0.282
Absent	4 (57%)	7 (88%)	
Bone marrow involvement, n (%)			
Present	6 (46%)	5 (50%)	1
Absent	7 (54%)	5 (50%)	
Liver involvement, n (%)			
Present	0	0	NA
Absent	11	11	
Splenomegaly, n (%)			
Present	6 (46%)	6 (50%)	1
Absent	7 (54%)	6 (50%)	
Unknown			
Bulky mass, n (%)			
Present	5 (42%)	0	0.029
Absent	7 (58%)	12 (100%)	
ECOG	0	0	NA
Tumor grade, n (%)			
Grade 1-2	8 (62%)	7 (58%)	1
Grade 3	5 (38%)	5 (42%)	
Time to treatment, months, median, (range)	2 (0-8)	5 (0-37)	0.101
Treatment demand, n, (%)			
Present	10 (77%)	7 (58%)	0.411
Absent	3 (23%)	5 (41%)	
Response to treatment, n (%)			
Present	8 (89%)	5 (83%)	1
Absent	1 (11%)	1 (17%)	

ECOG: Eastern Cooperative Oncology Group, FLIPI: Follicular Lymphoma International Prognostic Index, LDH: Lactate dehydrogenase, NA: Not applicable, WBC: White blood cell count

typically relies on the Groupe d'Etude des Lymphomes Folliculaires criteria. These guidelines consider several factors, including the presence of more than three nodal sites (each exceeding 3 cm in diameter), any nodal or extranodal tumor mass measuring 7 cm or larger, B symptoms, potential for local compressive symptoms that could compromise organ function, cytopenias (defined as leukocytes below 1.0 × 109/l and/or platelets under 100 × 109/l), leukemia (characterized by over 5.0 × 109/l malignant cells), enlarged spleen (exceeding 16 cm on CT scan), and the occurrence of pleural effusion or peritoneal ascites[1,13].

Despite those well-defined criteria, heterogeneous clinical course of the disease sometimes gives rise to uncertainty in terms of the initiation of treatment. Hence, any marker appraising about the treatment requirement might be beneficial in complex cases. In this instance albumin, being a readily available biochemical parameter, might be useful in treatment approach of FL patients. We aimed to evaluate the relationship of serum albumin levels with treatment demand, time to treatment and treatment response in FL patients. Although we found that treatment requirement was higher and time to treatment was shorter in patients with low serum albumin levels, they did not reach a statistical significance.

Previous studies have examined the significance of serum albumin levels in various blood cancers[6-9]. Research conducted by Bairey et al.[6] revealed that patients with DLBCL who had low albumin levels prior to treatment experienced poorer overall survival (OS) outcomes. In contrast to our research, the study mentioned used a threshold of 3.5 g/dL for albumin levels. In a related finding, Alici et al.[7] conducted research to identify prognostic factors specifically predicting survival in patients with localized aggressive NHL. Their results indicated that reduced serum albumin levels were associated with decreased survival rates. In addition to studying high-grade lymphomas, Bremnes et al.[8] examined the treatment outcomes and prognostic indicators in patients with low-grade NHL. Their research revealed that, unlike other types, FL patients with low pretreatment albumin levels were found to have reduced survival rates. Research on the predictive value of serum albumin levels extends beyond lymphoma patients to include myelodysplastic syndrome. A study by Sevindik et al.[9] demonstrated that serum albumin concentration serves as an autonomous indicator for both leukemia-free survival and OS. Unlike previous research, the slow-progressing nature of FL and the brief follow-up period prevented us from evaluating the connection between serum albumin levels and survival rates in FL patients. Nevertheless, this research is pioneering in its investigation of how serum albumin levels relate to treatment needs, the time before treatment initiation, and treatment efficacy in FL cases. The study's retrospective design and limited patient sample size may have hindered the ability to accurately determine the specific impact of serum albumin levels in FL.

Study Limitations

This study had some limitations that may have affected the results. Firstly, it included single center data and low number of patients. Additionally, since the data were collected retrospectively, not all data on FL may have been recorded.

CONCLUSION

We did not demonstrate an association between serum albumin level and treatment demand in FL patients. However, the precise contribution of serum albumin level to treatment decision has to be cleared with large number of FL patients before completely denial of its role.

Ethics

Ethics Committee Approval: The approval was obtained from the İstanbul Training and Research Hospital Ethics Committee of University of Health Sciences (decision no: 1085, date: 22.09.2017).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., C.A., E.S., Concept: A.K., B.G., E.S., Design: A.K., R.E., Data Collection or Processing: B.G., E.S., Analysis or Interpretation: R.E., C.A., Literature Search: R.E., C.A., Writing: C.A.

Conflict of Interest: One author of this article, (Abdulkadir KARIŞMAZ) is a member of the Editorial Board of the Namık Kemal Medical Journal. However, she did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest..

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Dreyling M, Ghielmini M, Rule S, Salles G, Ladetto M, Tonino SH, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32:298-308.
2. Gribben J.B., R.Hoffman, E.J.Benz Jr., et al. Clinical manifestations, staging and treatment of follicular lymphoma Hematology: Basic principles and practice. 6th Edition. Philadelphia, Elsevier, Saunders, 2012: 1215-1225.
3. Casulo C. Prognostic factors in follicular lymphoma: new tools to personalize risk. Hematology Am Soc Hematol Educ Program. 2016;2016:269-76.
4. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010;9:69.

5. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23:3412-20.

6. Bairey O, Shacham-Abulafia A, Shpilberg O, Gurion R. Serum albumin level at diagnosis of diffuse large B-cell lymphoma: an important simple prognostic factor. Hematol Oncol. 2016;34:184-92.

7. Alici S, Bavbek SE, Kaytan E, Eralp Y, Onat H. Prognostic factors in localized aggressive non-Hodgkin's lymphoma. Am J Clin Oncol. 2003;26:1-5.

8. Bremnes RM, Vik A, Helbekkmo N. Low-grade non-Hodgkin's lymphoma in northern Norway: treatment, outcome, and prognostic factors. Anticancer Res. 1998;18:1921-9.

9. Sevindik OG, Guc Z, Kahraman S, Medeni Solmaz S, Katgi A, Acar C, et al. Hypoalbuminemia is a surrogate biomarker of poor prognosis in myelodysplastic syndrome even when adjusting for comorbidities. Leuk Lymphoma. 2015;56:2552-5.

10. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989;7:1630-6.

11. Fowler N. Frontline strategy for follicular lymphoma: are we ready to abandon chemotherapy? Hematology Am Soc Hematol Educ Program. 2016;2016:277-83.

12. Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. Blood. 2016;127:2055-63.

13. Chen Q, Ayer T, Nastoupil LJ, Seward M, Zhang H, Sinha R, et al. Initial management strategies for follicular lymphoma. Int J Hematol Oncol. 2012;1:35-45.

ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.43925
Nam Kem Med J 2024;12(4):332-341

The Role of Layer-Specific Strain Echocardiography in The Diagnosis of Severe Coronary Artery Disease

Ciddi Koroner Arter Hastalığının Tanısında Katman Spesifik Strain Ekokardiyografinin Rolü

Çağlar KAYA[1], Mustafa YILMAZTEPE[3], Selçuk KORKMAZ[2], Hanefi Yekta GÜRLERTOP[1]

[1]*Trakya University Faculty of Medicine, Department of Cardiology, Edirne, Turkey*
[2]*Trakya University Faculty of Medicine, Department of Biostatistics, Edirne, Turkey*
[3]*University of Health Sciences, Bursa Faculty of Medicine, Department of Cardiology, Bursa, Turkey*

ABSTRACT

Aim: Several imaging techniques are in use for diagnosis and risk assessment in patients with suspected stable coronary artery disease (S-CAD). Measurement of global longitudinal strain (GLS) by two-dimensional speckle tracking (2D-STM) is a more accurate and reliable technique compared to transthoracic echocardiography. It provides a quantitative measure of left ventricular function. The aim of this prospective study was to determine the relationship between resting layer-specific longitudinal strain values and severe coronary lesions in patients with suspected S-CAD.

Materials and Methods: A total of 242 patients with suspected S-CAD were included in this study. They were scheduled for elective coronary angiograph. Patients were divided into two main groups: with (n=117) and without severe coronary artery disease (CAD) (n=125). Layer-specific GLS values were compared between groups as mid-myocardial, endocardial and epicardial layers, using 2D-STM.

Results: This study showed that GLS values of all layers were significantly lower in patients with severe CAD compared to controls (p<0.001). ROC curves were constructed to evaluate the diagnostic performance of GLS values and the area under the curve was 81-82% in three slices. The cut-off values were calculated to be -19.5 for the GLS mid-myocardium, -22.6 for the GLS endocardium, and -16.5 for the GLS epicardium.

Conclusion: As a result, GLS assessment by 2D-STM showed that GLS values were lower in all layers with severe CAD, suggesting that GLS assessment may be useful for detecting severe CAD. However, layer-specific strain analysis showed no incremental value over GLS analysis. These findings should be further investigated and improved in subgroups with a more homogeneous distribution. Further larger studies are needed.

Keywords: Strain echocardiography, coronary artery disease, speckle tracking

ÖZ

Amaç: Stabil kronik koroner arter hastalığı (S-KAH) şüphesi olan hastalarda tanı ve risk değerlendirmesi için çeşitli görüntüleme teknikleri kullanılmaktadır. İki boyutlu strain ekokardiyografi (2D-STM) ile global longitudinal strain (GLS) ölçümü, transtorasik ekokardiyografiye kıyasla daha doğru ve güvenilir bir tekniktir. Sol ventrikül fonksiyonunun kantitatif bir ölçümünü sağlar. Bu prospektif çalışmanın amacı, S-KAH şüphesi olan hastalarda istirahat katmanına özgü gerinim değerleri ile ciddi koroner lezyonlar arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: S-KAH şüphesi olan toplam 242 hasta bu çalışmaya dahil edildi. Bu hastalar elektif koroner anjiyografi için planlanmıştı. Hastalar iki ana gruba ayrıldı: ciddi koroner arter hastalığı (KAH) olan (n=117) ve olmayanlar (n=125). Katman spesifik GLS değerleri 2D-STM kullanılarak orta miyokardiyal, endokardiyal ve epikardiyal katmanlar olarak gruplar arasında karşılaştırıldı.

Bulgular: Bu çalışma, tüm katmanların GLS değerlerinin KAH olanlarda kontrollere kıyasla anlamlı derecede düşük olduğunu göstermiştir (p<0,001). GLS değerlerinin tanısal performansını değerlendirmek için ROC eğrileri oluşturulmuş ve eğri altındaki alan üç kesitte %81-82 olarak bulunmuştur. Kesim noktaları GLS orta miyokard için -19,5, GLS endokard için -22,6 ve GLS epikard için -16,5 olarak hesaplanmıştır.

Sonuç: Sonuç olarak, 2D-STM ile GLS değerlendirmesi, GLS değerlerinin KAH olanlarda tüm katmanlarda daha düşük olduğunu gösterdi ve GLS değerlendirmesinin KAH tespit etmek için yararlı olabileceğini düşündürdü. Bununla birlikte, katmana özgü gerinim analizi, GLS analizine göre artan bir değer göstermemiştir. Bu bulgular daha homojen dağılıma sahip alt gruplarda daha fazla araştırılmalı ve geliştirilmelidir. Daha büyük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Strain ekokardiyografi, koroner arter hastalığı, benek izleme

Address for Correspondence: Çağlar KAYA MD, Trakya University Faculty of Medicine, Department of Cardiology, Edirne, Turkey
E-mail: caglarkaya2626@gmail.com **ORCID ID:** orcid.org/0000-0002-2968-5352
Received: 22.09.2024 **Accepted**: 30.10.2024

INTRODUCTION

Coronary heart disease caused by atherosclerosis remains the leading cause of mortality and morbidity worldwide. Early diagnosis and effective treatment are of great importance in current practice. Non-invasive imaging techniques such as electrocardiography (ECG), transthoracic echocardiography (TTE), exercise testing (EST) and myocardial perfusion scintigraphy (MPS) are recommended for the diagnosis and risk assessment of patients with suspected coronary artery disease (CAD)[1]. The ECG is the basic test for assessing CAD. On the other hand, EST is a widely used technique that is easy to perform but has limited sensitivity and specificity. Although the diagnostic accuracy of MPS is high, it has important limitations such as radiation exposure and limited availability[2]. Resting TTE is one of the leading tests used to measure systolic and diastolic ventricular function in patients with stable CAD[3]. The echocardiographic examination assesses regional myocardial function using visual and numerical parameters such as wall thickness, wall motion, volumetric measurements, diastolic parameters, and tissue Doppler measurements[4]. However, many patients with stable CAD do not have echocardiographic pathology that is predictive of ischemia, such as wall motion abnormalities. Therefore, additional investigations are required to assess for ischemia. In addition, despite these detailed examinations, some studies have shown that many patients have non-critical coronary stenosis on elective coronary angiography (CAG), as opposed to emergency angiography[5]. Therefore, different methods need to be used to diagnose severe CAD. Two-dimensional echocardiography is used for global and layer-specific analysis of the left ventricle (LV). This method allows numerical measurement of regional myocardial functions by evaluating each myocardial segment separately[6]. Longitudinal analysis provides more accurate information for the early detection of endocardial ischemia and the prediction of myocardial dysfunction. This is because the endocardium is more sensitive to ischemia[7]. This study aimed to determine the relationship between resting strain echocardiographic measurements and severe CAD and to increase patient selectivity using the layer-specific strain technique in planning CAG.

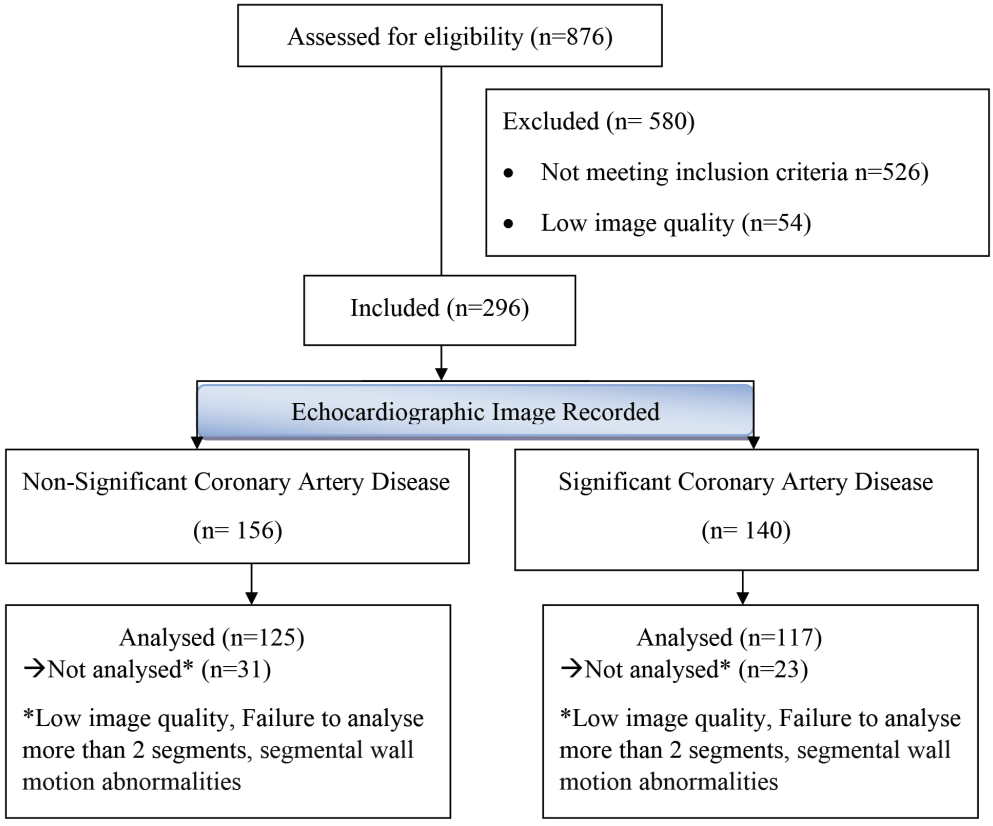
MATERIALS AND METHODS

Eight hundred and seventy-six patients with suspected stable CAD and a CAG decision were assessed for the study between 11/2018 and 07/2019. Patients were excluded if they had a history of acute coronary syndrome (ACS), myocardial infarction (MI), coronary artery bypass graft surgery or coronary intervention, heart failure, moderate or severe valvular disease, reduced ejection fraction, poor image quality, segmental wall motion abnormalities, malignancy, or atrial fibrillation. A detailed medical history was obtained and recorded, including diabetes mellitus, hypertension, and hyperlipidemia. Of these, 296 patients were selected according to the inclusion criteria. The echocardiographic images of 296 patients selected according to the exclusion/inclusion criteria were recorded and assessed for suitability by an experienced cardiologist. 242 images suitable for analysis were selected and included in the study. Patients were divided into two main groups, as significant and non-significant CAD, according to the results of CAG. The flowchart used to select patients for evaluation is shown in Table 1. The Trakya University Ethics Committee approved this study (decision no: 2018/384-18/26, date: 05.11.2018). Our study was conducted following the Declaration of Helsinki.

Echocardiography Assessment

All enrolled patients underwent 2D echocardiograms at rest by a cardiologist blinded to CAG results or patient clinical information. Echocardiographic images were acquired using Vivid S70 systems (Horton, Norway, GE Healthcare,). The images were transferred to the Echo-PAC workstation. Patients were not included if the image quality was insufficient for speckle tracking analysis. All patient measurements were performed according to echocardiography guidelines[8]. Apical 4-chamber, apical long-axis, and apical 2-chamber images were obtained from the recordings. LV M-mode measurements, pulsed-wave Doppler measurements (mitral inflow velocities; E, A), and tissue Doppler recordings (lateral-septal e') were also obtained. The Modified Simpson's method was used to calculate LV ejection fraction in two planes. In the parasternal long-axis view, we measured left atrial diameter (LAD), LV end-diastolic/systolic diameters, and wall thicknesses in M-mode. E/e values were averaged from septal and lateral E values. All images were transferred to the Echo-PAC workstation for 2D speckle tracking analysis. Three beats of 2D images (apical 2-chamber, apical long-axis, and 4-chamber view at 50-80 fps) were considered adequate for measurements. All measurements were calculated by an experienced two cardiologists blinded to the enrolment group. Current guidelines for measurement were used to calculate analyses[9,10]. Three points were measured, one each side of the mitral annulus and apex. The program automatically traced the myocardial boundaries and curves were generated (Figure 1A). Images were optimized for measurement through manual adjustments by the examiner. Images with poorly traced myocardial borders were excluded. Out of 296 patients, 54 were excluded due to poor image quality or more than 2 unanalyzed segments. After adjustments, the software automatically calculated the measurements. In apical long-axis images, the closure of the aortic valves was defined as the end of systole. After processing the images from three different axes, a 17-segment bull's eye model was generated (Figure 1B). Global longitudinal values were automatically calculated by the software as epicardial, endocardial, and

Table 1. Flow diagram of the study



myocardial (GLS-myo, GLS-endo, GLS-epi). The total regional longitudinal (RLS) was calculated by averaging the peak values of all segments based on the 17-segment models according to the perfusion regions of all three main coronary arteries[11]. Intra- and inter-observer reliability was assessed by randomly recalculating the images of 20 patients. The same operator assessed intra-observer variability 45 days after the initial analysis. Inter-observer reliability was assessed by comparison of images from 20 patients randomly selected by a different operator.

Coronary Angiography Assessment

An experienced cardiologist blinded to the patient's clinical information assessed the angiograms. The degree of stenosis was based on the projection where the stenosis was most visible. The patients were split into two groups. Patients were considered to have significant CAD if they had 70% or more stenosis. The non-significant CAD group (control group) included patients with normal coronary arteries, atherosclerotic arteries, or less than 50% stenosis. The SYNTAX scoring system was used to guide treatment decisions in patients with multiple CAD and major coronary lesions. The SYNTAX score (SS) was calculated by two different experienced observers using the online calculator version 2.28 (http://www.syntaxscore.com)[12]. In the scoring system, 32 and above were grouped as a high SS, below 22 as a low SS, and between 22 and 32 as a medium SS[13].

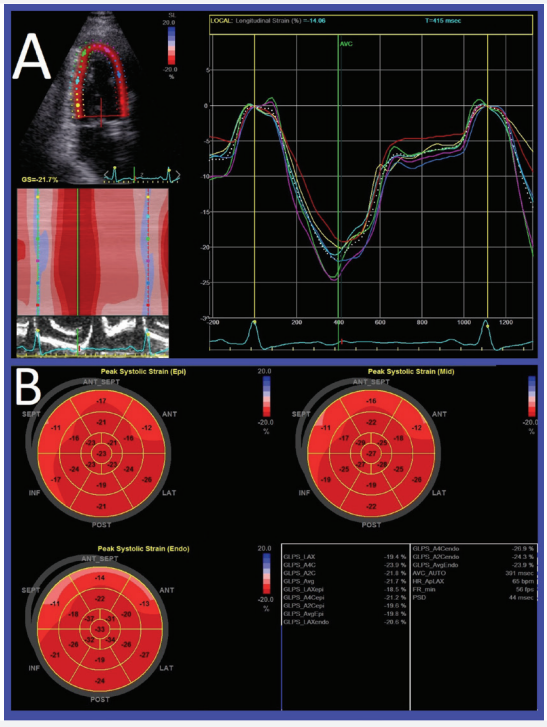


Figure 1. A) Final curves were calculated automatically after tracking the endo-myocardial border, B) "Bullseye" graphics were obtained from measurements of three apical images

Statistical Analysis

Normal distribution was tested using the Shapiro-Wilk test. The Student's t test is used for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. In examining relationships between quantitative variables, the Pearson correlation was calculated for normally distributed variables and the Spearman's correlation was calculated for non-normally distributed variables. The Pearson chi-square test was used to assess relationships between qualitative variables. Cut-off point values were obtained using ROC analysis. Risk factors for coronary heart disease were determined by logistic regression analysis. Bland-Altman plots were generated to determine interobserver and intraobserver agreement. Mean and standard deviation were used as descriptive statistics for variables that followed a normal distribution, and median and interquartile range for variables that did not follow a normal distribution. Frequencies and percentages were used for qualitative variables. The significance level for all statistical analyses was set at 0.05. TURCOSA statistical software (Turcosa Analytics Ltd Co, Turkey, www.turcosa.com.tr) was used for all statistical analyses.

RESULTS

A total of 242 patients were enrolled. According to the results of CAG, all patients were divided into two main groups. 117 (48.3%) patients were in the significant CAD group. One hundred twenty-five (51.7%) patients with normal or atherosclerotic coronary arteries were classified as having non-significant CAD. The non-significant CAD group was defined as the control group. Indications for CAG were evaluated in 3 groups: 66 (27.3%) typical angina, 66 (27.3%) positive exercise and 110 (45.5%) positive MPS. The control group had a higher proportion of female patients. Predictably, CAD was found to be significantly higher in patients with advanced age, male sex, diabetes mellitus, and hyperlipidemia (HL) ($p<0.005$). Table 2 shows all clinical characteristics and angiographic results. There were 48 (41.0%) single-vessel disease, 26 (22.2%) two-vessel disease, and 43 (36.8%) three-vessel disease. LAD lesions (76.0%) were most common in the significant CAD group. The conventional echocardiographic parameters and the values of global longitudinal are shown in Table 3. Wall thicknesses were significantly higher in the significant CAD group. The high number of hypertensive patients in the CAD group (79.50%) may explain this. There was no difference in ejection fraction (EF) between the two groups. The significant CAD group had higher left ventricular mass index and LAD. There was no

Table 2. The Clinical characteristics of patients

	Non-significant CAD (n=125)	Significant CAD (n=117)	p-value
Age	56.65±9.57	61.75±9.45	<0.001
Male n (%)	48 (38.4%)	78 (66.7%)	<0.001
BMI kg/m^2	29.01±4.28	29.35±4.76	0.560
Systolic BP mm Hg	129.44±15.85	132.26±17.62	0.192
Diastolic BP mm Hg	78.08±9.00	78.67±9.97	0.626
Heart rate bpm	72.40±8.60	71.44±7.36	0.355
DM n (%)	26 (20.80%)	50 (42.7%)	<0.001
HT n (%)	88 (70.40%)	93 (79.50)	0.104
Smoker n (%)	58 (46.40%)	70 (59.80%)	0.036
Family History n (%)	42 (33.60%)	30 (25.60%)	0.176
HL n (%)	44 (35.20%)	71 (60.70%)	<0.001
B-Blocker n (%)	7 (5.60%)	6 (5.10%)	0.871
CCB n (%)	24 (19.20%)	24 (20.50%)	0.798
1 vessel disease	-	48 (41.0%)	-
2 vessel disease	-	26 (22.2%)	-
3 vessel disease	-	43 (36.8%)	-
LMCA	-	6 (5.1%)	-
LAD	-	90 (76.9%)	-
CX	-	70 (59.8%)	-
RCA	-	70 (59.8%)	-

BMI: Body-mass index, CAD: Coronary artery disease, Cx: Circumflex artery, DM: Diabetes mellitus, HL: Hyperlipidemia, HT: Hypertension, LAD: Left anterior descending artery, LMCA: Left main coronary artery, RCA: Right coronary artery, CCB: Calcium chanel blocker, BP: Blood pressure

Table 3. Conventional echocardiographic parameters and longitudinal values

	Non-significant CAD (n=125)	Significant CAD (n=117)	p-value
Echocardiographic parameters			
LV EF (%)	65.78±4.43	64.92±4.97	0.156
LV EDD (mm)	46.05±3.98	45.86±4.21	0.726
LV ESD (mm)	29.35±3.38	29.63±4.13	0.563
Interventricular thickness (mm)	10.94±1.24	11.77±1.52	<0.001
Posterior wall thickness (mm)	10.45±1.20	10.86±1.33	0.011
LV mass index (gr/m^2)	93.01±17.09	98.12±20.44	0.036
LAD (mm)	34.52±3.80	35.91±4.02	0.006
LA volume index (mL/m^2)	21.64±4.58	21.83±5.33	0.761
E (m/s)	0.77±0.16	0.79±0.18	0.415
A (m/s)	0.80±0.21	0.85±0.22	0.067
E/A ratio	1.01±0.29	1.05±0.95	0.681
E' (m/s)	0.10±0.03	0.09±0.02	0.081
E/e'	9.11±7.91	9.10±2.96	0.994
Dt. (ms)	235.50±44.44	231.62±49.64	0.522
2D global longitudinal parameters			
GLS mid-myocardial %	-21.68±2.27	-18.25±2.92	<0.001
GLS endocardium %	-24.58±2.57	-20.78±3.31	<0.001
GLS epicardial %	-19.18±2.05	-16.07±2.72	<0.001
GLS endo-epi %	5.40±1.07	4.71±1.11	<0.001
GLS endo/epi ratio	1.28±0.057	1.30±0.076	0.10

CAD: Coronary artery disease, EDD: End-diastolic diameter, EF: Ejection fraction, ESD: End-systolic diameter, Dt: Deceleration time, LAD: Left atrial diameter, E: Pulsed wave trans-mitral early diastolic velocity, e' Early myocardial diastolic velocity, GLS: Global longitudinal, LA: Left atrium, LV: Left ventricle

significant difference in diastolic filling parameters (such as E, A, E ') between the two groups. The GLS values of all segments (endocardium, myocardium, and epicardium) were lower in the significant CAD group, as shown by layer-specific measurements. Comparison of the difference between GLS-endo and GLS-epi (GLS endo-epi) showed a smaller difference in the significant CAD group. No difference was observed at the GLS-endo / epi ratio. No correlation was found between GLS and syntax scoring. Syntax groups and GLS measurements were compared. The GLS values of all layers were measured to be significantly lower in Group 2 than in Group 1. The relationship between the GLS and the syntax groups is shown in Table 4. ROC curves were constructed for the evaluation of the diagnostic performance of the GLS values (Figure 2). The cut-off values were calculated to be -19.5 for the GLS mid-myocardium, -22.6 for the GLS endocardium and -16.5 for the GLS epicardium. There was a significant difference in all three of the slices. The area under the curve was 81-82% in all three slices. All RLS values of coronary territories were lower in all layers in patients with significant stenosis. The RLS values are shown in Table 5. There was no relationship between the RLS values of the vessel-specific myocardial regions and the lesions that were detected in the corresponding region. ROC curves for vessel specific RLS are shown in Figure 3. Analyses of GLS were compared for both sexes. There was no significant difference in the GLS measurements in either gender (GLS midmyocardial; -21.75 / -21,56 p: 0.658). Intra- and inter-observer variability was assessed by Bland-Altman analysis. (Figure 4). Intra-observer reliability was 96%, 95%, and 93% for the endocardium, myocardium, and epicardium, respectively. The inter-observer reliability was 86%, 86%, and 86% for the endocardium, myocardium, and epicardium, respectively. Independent predictors were assessed by multivariate regression analysis. Risk factors (age, hypertension, smoking, diabetes, HL, and family history) and GLS endocardial-mid-myocardial-epicardial measurements were included in the regression analyses. Age, sex, and diabetes were determined as independent variables [age odd ratio (OR): 1.08, confidence interval (CI): 0.098-3.05; male OR: 3.27 CI: 1.43-7.82; DM OR: 2.94 CI: 1.33-6.76].

DISCUSSION

The importance of non-invasive imaging for assessing CAD severity is growing. Routine TTE's ability to evaluate LV function is limited, and more accurate results require advanced quantitative techniques. While echocardiography is

Table 4. The relationship between Syntax scoring and GLS in the severe CAD group (n=117). Additionally, the relationship between Syntax scoring and GLS

	Correlation (r)		p-value	
GLS mid-myocardium	-0.1064		0.254	
GLS endocardium	-0.010		0.279	
GLS epicardium	-0.1252		0.179	
GLS endo-epi	0.006		0.950	
GLS endo/epi	0.0949		0.309	
	Syntax<22 (1. Group) (n=94)	**Syntax 22-32 (2. Group) (n= 19)**	**Syntax>32 (3. Group) (n=4)**	**p-value**
GLS mid-myocardium	-18.80 (16.63-20.28)	-15.80 (14.15-18.50)	-21.10 (19.13-21.25)	0.019
GLS endocardium	-21.45 (18.93-22.98)	-18.50 (15.75-21.25)	-23.60 (22.55-24.00)	0.009
GLS epicardium	-16.30 (14.80-18.20)	-14.10 (12.30-16.40)	-18.35 (16.70-19.08)	0.034
GLS endo-epi	4.70 (4.00-5.65)	4.20 (3.45-4.75)	5.35 (4.52-6.35	0.023
GLS endo/epi	1.29 (1.24-1.34)	1.28 (1.25-1.32)	1.34 (1.24-1.43)	0.486

GLS: Global longitudinal, CAD: Coronary artery disease, GLS: Global longitudinal

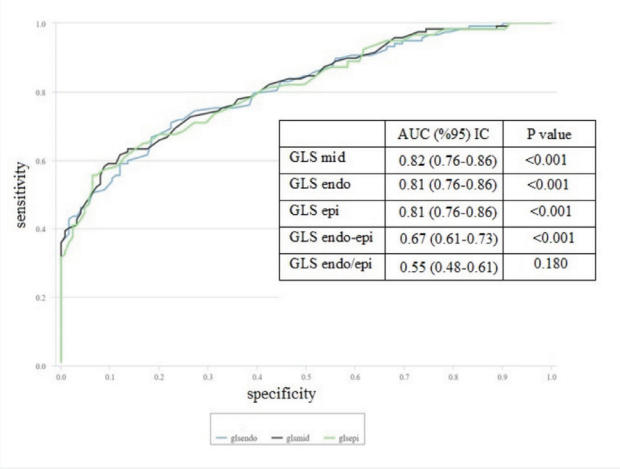


Figure 2. ROC curves demonstrate the value of layer-specific GLS for the diagnosis of CAD

GLS: Global longitudinal, CAD: Coronary artery disease, AUC: Area under the curve, IC: Confidence interval, ROC: Receiver operating characteristic

effective for assessing LV systolic dysfunction, routine 2D-TTE is inadequate for patients without prior MI or structural heart disease. Analysis may show early myocardial deterioration even in patients with normal EF. Some published studies have shown an association between CAD and strain testing. In the study by Anwar[14], peak systolic values were lower in patients with CAD. Our study also showed significantly reduced GLS values for all layers in CAD patients. Myocardial fibers in the longitudinal direction are more sensitive to ischemia[15]. Therefore, longitudinal assessment provides better results for the detection of CAD. Longitudinal measurements using 2D speckle tracking are critical for the diagnosis and follow-up of patients with ACS in several published studies[16]. Our study evaluated the success of strain echocardiography by using speckle tracking before CAG in patients with suspected CAD.

A recently published similar small study by Zhang et al.[17] found that longitudinal values measured by 2D speckle tracking were significantly reduced in patients with ACS. A retrospective study by Montgomery et al.[18] compared resting GLS values with strain echocardiographic wall motion index in patients undergoing CAG within 10 days of strain echocardiography. It was found that similar results were obtained. It was therefore suggested that strain assessment could replace strain echocardiography. In a study conducted by Yılmaztepe and Uçar[19], 79 patients were evaluated retrospectively, and a significant decrease in peak systolic GLS values was detected in all layers in the group with severe CAD like our study. In their studies, it was stated that transmural GLS was an independent predictor. However, GLS measurements were not found to be a significant predictor for all layers in the logistic regression analysis of our research. Likewise, in a more recent study designed by Hagemann et al.[20], it was found that mid-myocardial and epicardial GLS measurements might be independent predictors in the determination of severe CAD. However, unlike that study, our study did not measure circumferential. Looking at the results of three recent studies, we can see that the GLS measure alone

Table 5. Regional longitudinal values			
	Non-significant CAD (n=125)	Significant CAD (n=117)	p-value
LAD			
RLS mid-myocardium	-21.90±2.88	-18.98±3.89	<0.001
RLS endocardium	-26.01±3.48	-23.02±4.44	<0.001
RLS epicardium	-18.85±2.58	-16.19±3.29	<0.001
CX			
RLS mid-myocardium	-20.75±4.74	-17.56±3.27	<0.001
RLS endocardium	-22.91±3.32	-19.81±3.58	<0.001
RLS epicardium	-18.55±3.19	-15.82±3.12	<0.001
RCA			
RLS mid-myocardium	-21.65±3.18	-18.92±3.55	<0.001
RLS endocardium	-23.67±3.43	-20.66±3.93	<0.001
RLS epicardium	-20.01±3.00	-17.90±5.23	<0.001

RLS: Regional longitudinal, CAD: Coronary artery disease, CX: Circumflex artery, LAD: Left anterior descending artery, RCA: Right coronary artery

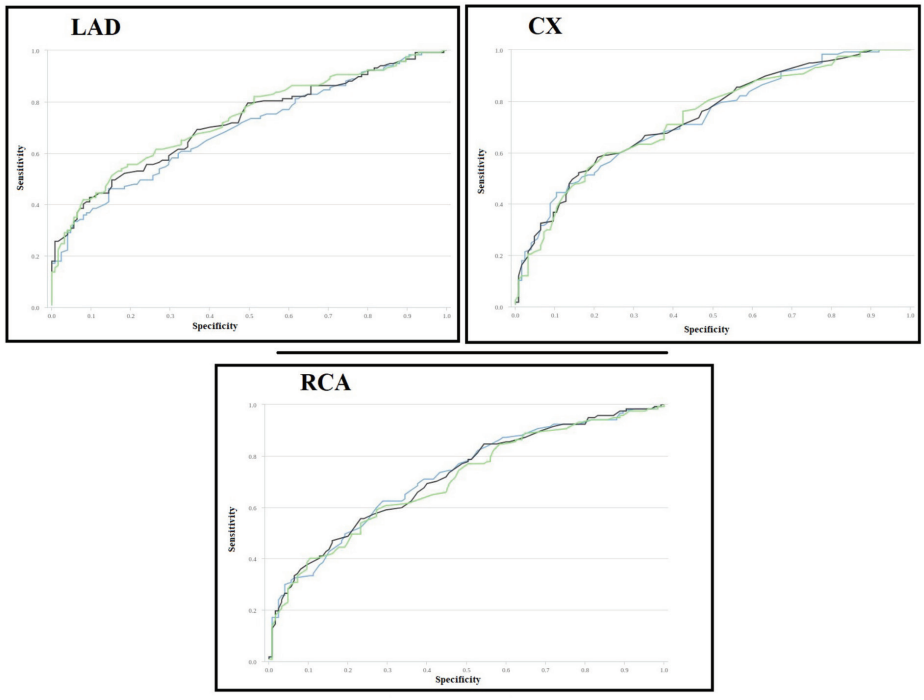


Figure 3. ROC analysis for diagnostic evaluation in regional analysis

LAD: Left anterior descending artery, CX: Circumflex artery, RCA: Right coronary artery, ROC: Receiver operating characteristic

may not be significant at any layer. The clinical significance of layer-specific assessment has not been fully demonstrated in recent studies in the literature. In another recent article, it has been stated that GLS measurements of the whole wall provide more accurate information than layer-specific measurements because of the adjacent layers. It has also been highlighted that current technology is not able to separate the deformation in all layers[10].

Strain echocardiography is more sensitive than EF in assessing LV function, but is influenced by age, sex, and hemodynamic factors such as preload, afterload, and mechanical desynchrony

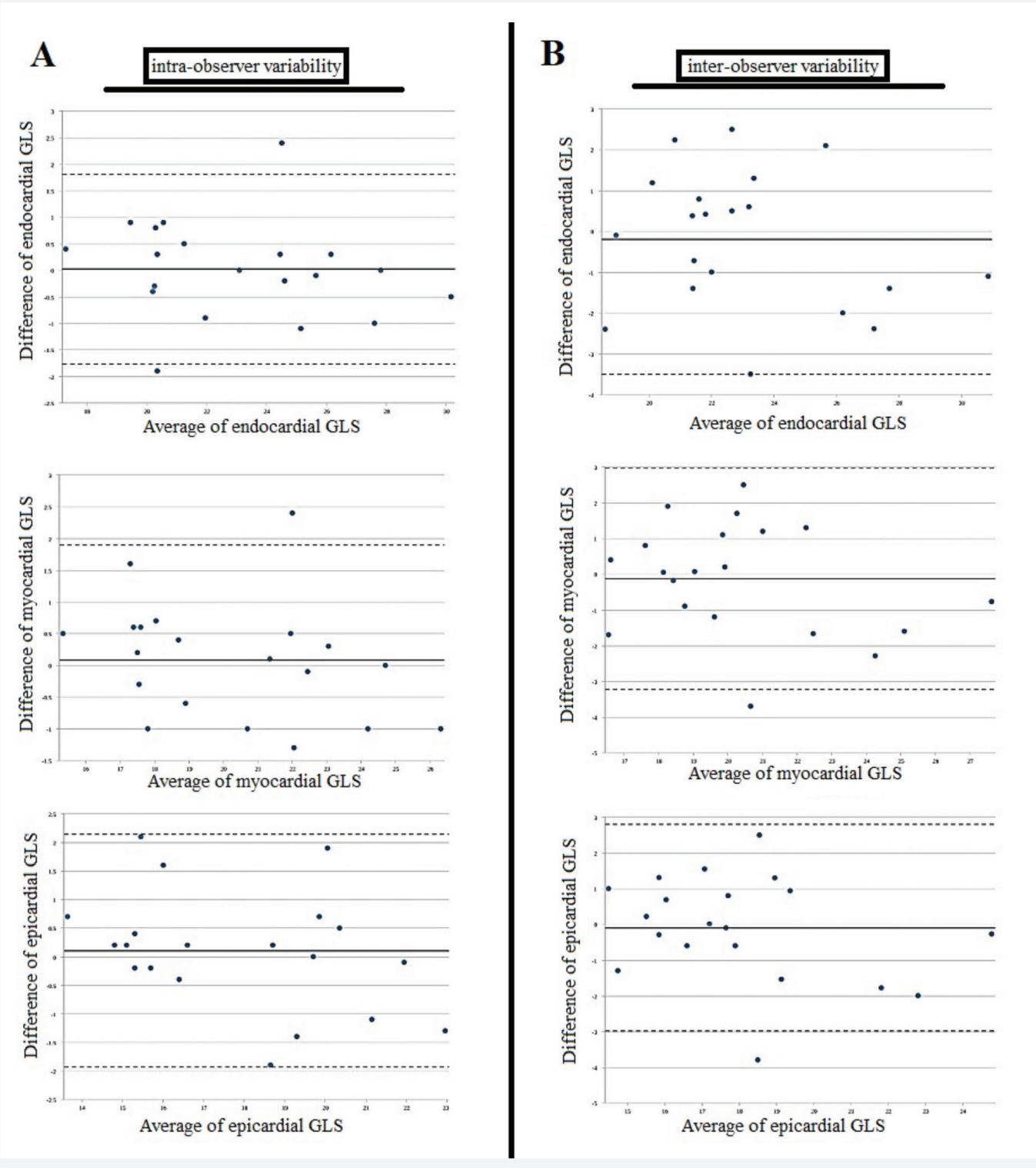


Figure 4. Intra-observer and inter-observer variability statistics are shown in the Bland / Altman Chart. A-intra-observer variability, B-inter-observer variability

GLS: Global longitudinal

due to MI. We excluded patients with previous MI, wall motion abnormalities, moderate to severe valvular disease, pulmonary hypertension, bundle branch block, and atrial fibrillation. Blood pressure and medication were similar, and all patients were euvolemic. We believe that these factors did not significantly influence our study. Although the limits of the normal range of GLS and LSS were not clearly defined in our study, cut-off values were identified similar to the studies performed by Nagata et al.[21] and Shi et al.[22] with the same software (GLSendo: -19.5 %, GLSmyo: -22.6%, GLSepi: -16.5%). In a recent review, cut off values of -17.82 in acute patients and -17.41 in chronic patients were reported[23].

In a study performed by Hagemann et al.[24] with 80 patients diagnosed with ischemia in MPS were retrospectively evaluated. The groups were divided into true positive and false positive groups. It was found that GLS values were lower in the true positive group and there was no significant difference between the false positive group and the control group. In our study, lower GLS values were found in patients with MPS positivity and severe stenosis (GLS mid myocardial -18.42, -21.66 p<0.001).

Recent studies have used the SS in ACS to determine the severity of CAD. In our study, the SS and stress echocardiography were also evaluated in chronic CAD[25]. The group's syntax scores were classified as <22 (Group 1), 22-32 (Group 2), and> 32 (Group 3) as stated in the guideline. In multiple comparison tests, there was a significant difference only between Group 1 and Group 2 (Table 4). We initially thought that a decrease in peak systolic strain might correlate with a higher group, but no differences were found between the third group and others, likely due to its small size (n=4). Homogeneously distributed groups in future studies may reveal significant differences across all groups.

In our study, regional measurements were lower in the severe CAD group compared to the control group, aligning with previous research. However, no correlation was found between the ischemic coronary artery and low regional values, potentially due to differences among coronary arteries, collateral vessels, and microvascular dysfunction. Thus, we advise against using this for lesion prediction. While echocardiography remains controversial due to interpretation challenges, advancements in analysis programs and automatic calculations have made it easier for even inexperienced users to perform image evaluations.

Another issue to be analyzed should be artificial intelligence. Today, there are some studies on the use of artificial intelligence in CAD[26]. Probably, artificial intelligence support will be added to strain echocardiography as well as all imaging techniques in the future. In this way, even more optimal results will be obtained. Recent studies are showing the superiority of coronary computed tomography and MPS over each other[27]. In the future, strain echocardiography will be developed in addition to these examinations and its use will become widespread in the pre-diagnosis.

Study Limitations

Our study has some limitations. There was a difference in gender distribution between groups, and diabetes, which can affect microvascular values, was more common in the severe CAD group. Therefore, a larger study can be planned in a more homogeneous population for these two conditions. Although analysis provides more quantitative and accurate results than visual analysis, it is an operator-dependent technique. It is therefore subject to operator error and subjective assessment. Furthermore, patient echocardiographic image quality varies with many factors, and some images are difficult to process. Our study is prospective and cross-sectional. Multicenter trials with larger patient groups can be designed to overcome these limitations and provide clearer results.

CONCLUSION

In our study, values were lower and significant in all layers in patients with suspected CAD and without wall motion disorder in TTE.

Especially, in patients with preserved LVEF, 2DSTE resting layer-specific GLS was significantly reduced in all myocardium layers in patients with significant CAD. Strain echocardiography will be very useful in diagnosis and follow-up, in addition to ECG, biochemical markers, and standard echocardiographic measurements.

The technique of speckle-tracking echocardiography is open to research and needs to be developed. In this way, it provides advanced patient management in diagnosis, treatment, and follow-up, and it gives us a new perspective on the physiology of the heart.

Ethics

Ethics Committee Approval: The Trakya University Ethics Committee approved this study (decision no: 2018/384-18/26, date: 05.11.2018). Our study was conducted following the Declaration of Helsinki.

Informed Consent: Retrospective study

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ç.K., Concept: Ç.K., M.Y., Design: Ç.K., M.Y., S.K., H.Y.G., Data Collection or Processing: Ç.K., M.Y.,

S.K., Analysis or Interpretation: Ç.K., S.K., Literature Search: Ç.K., M.Y, H.Y.G., Writing: Ç.K., M.Y, H.Y.G., S.K.

REFERENCES

1. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45:3415-537.
2. Buechel RR, Kaufmann BA, Tobler D, Wild D, Zellweger MJ. Non-invasive nuclear myocardial perfusion imaging improves the diagnostic yield of invasive coronary angiography. Eur Heart J Cardiovasc Imaging. 2015;16:842-7.
3. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American society of echocardiography committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. J Am Soc Echocardiogr. 1989;2:358-67.
4. Sutherland GR, Di Salvo G, Claus P, D'hooge J, Bijnens B. Strain and strain rate imaging: a new clinical approach to quantifying regional myocardial function. J Am Soc Echocardiogr. 2004;17:788-802.
5. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010;362:886-95.
6. D'hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, et al. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. Eur J Echocardiogr. 2000;1:154-70.
7. Sanderson JE, Fraser AG. Systolic dysfunction in heart failure with a normal ejection fraction: echo-Doppler measurements. Prog Cardiovasc Dis. 2006;49:196-206.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.
9. Voigt J-U, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2015;16:1-11.
10. Voigt JU, Cvijic M. 2- and 3-Dimensional Myocardial Strain in Cardiac Health and Disease. JACC Cardiovasc Imaging. 2019;12:1849-63.
11. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the cardiac imaging committee of the council on clinical cardiology of the american heart association. Circulation. 2002;105:539-42.
12. Généreux P, Palmerini T, Caixeta A, Cristea E, Mehran R, Sanchez R, et al. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. Circ Cardiovasc Interv. 2011;4:553-61.
13. Vrettos A, Dawson D, Grigoratos C, Nihoyannopoulos P. Correlation between global longitudinal peak systolic strain and coronary artery disease severity as assessed by the angiographically derived SYNTAX score. Echo Res Pract. 2016;3:29-34.
14. Anwar AM. Accuracy of two-dimensional speckle tracking echocardiography for the detection of significant coronary stenosis. J Cardiovasc Ultrasound. 2013;21:177-82.
15. Biering-Sørensen T, Hoffmann S, Mogelvang R, Zeeberg Iversen A, Galatius S, Fritz-Hansen T, et al. Myocardial strain analysis by 2-dimensional speckle tracking echocardiography improves diagnostics of coronary artery stenosis in stable angina pectoris. Circ Cardiovasc Imaging. 2014;7:58-65.
16. Meimoun P, Abouth S, Clerc J, Elmkies F, Martis S, Luycx-Bore A, et al. Usefulness of two-dimensional longitudinal strain pattern to predict left ventricular recovery and in-hospital complications after acute anterior myocardial infarction treated successfully by primary angioplasty. J Am Soc Echocardiogr. 2015;28:1366-75.
17. Zhang L, Wu WC, Ma H, Wang H. Usefulness of layer-specific strain for identifying complex CAD and predicting the severity of coronary lesions in patients with non-ST-segment elevation acute coronary syndrome: Compared with Syntax score. Int J Cardiol. 2016;223:1045-52.
18. Montgomery DE, Puthumana JJ, Fox JM, Ogunyankin KO. Global longitudinal strain aids the detection of non-obstructive coronary artery disease in the resting echocardiogram. Eur Heart J Cardiovasc Imaging. 2012;13:579-87.
19. Yılmaztepe MA, Uçar FM. Layer-specific strain analysis in patients with suspected stable angina pectoris and apparently normal left ventricular wall motion. Cardiovasc Ultrasound. 2018;16:25.
20. Hagemann CA, Hoffmann S, Hagemann RA, Fritz-Hansen T, Olsen FJ, Jørgensen PG, et al. Usefulness of layer-specific strain in diagnosis of coronary artery disease in patients with stable angina pectoris. Int J Cardiovasc Imaging. 2019;35:1989-99.
21. Nagata Y, Wu VC, Otsuji Y, Takeuchi M. Normal range of myocardial layer-specific strain using two-dimensional speckle tracking echocardiography. PLoS One. 2017;12:e0180584.
22. Shi J, Pan C, Kong D, Cheng L, Shu X. Left ventricular longitudinal and circumferential layer-specific myocardial strains and their determinants in healthy subjects. Echocardiography. 2016;33:510-8.
23. Pastore MC, Mandoli GE, Contorni F, Cavigli L, Focardi M, D'Ascenzi F, et al. Speckle tracking echocardiography: early predictor of diagnosis and prognosis in coronary artery disease. Biomed Res Int. 2021;2021:6685378.
24. Hagemann CE, Hoffmann S, Olsen FJ, Jørgensen PG, Fritz-Hansen T, Jensen JS, et al. Layer-specific global longitudinal strain reveals impaired cardiac function in patients with reversible ischemia. Echocardiography. 2018;35:632-42.
25. KARADENİZ M, AYDIN C, DEMİRKIRAN A, ALP Ç. Predictors of severity of coronary artery disease in patients with acute ST-elevation myocardial infarction. Namik Kemal Med J. 2024;12:171-5.
26. Hayıroğlu Mİ, Altay S. The Role of Artificial Intelligence in coronary artery disease and atrial fibrillation. Balkan Med J. 2023;40:151-2.
27. DELİBALTA S, SAYIT AT, ÇELENK Ç. Investigation of coronary artery disease by coronary computed tomography angiography and the diagnostic value of first-pass myocardial perfusion imaging without stress. Namik Kemal Med J. 2023;11:301-7.

CASE REPORT

DOI: 10.4274/nkmj.galenos.2024.70894
Nam Kem Med J 2024;12(4):342-344

Bupivacaine-Induced Kounis Syndrome

Bupivakain İlişkili Kounis Sendromu

Efe YILMAZ, Çağlar KAYA

Trakya University Faculty of Medicine, Department of Cardiology, Edirne, Turkey

ABSTRACT

Bupivacaine is frequently used in daily practice for local anesthesia. The cardiotoxic and arrhythmic effects of bupivacaine are known. Acute allergic attacks and electrocardiographic changes associated with bupivacaine have not been reported in the literature. Kounis syndrome presents with the clinical picture of acute myocardial infarction following an acute allergic attack. Coronary angiography was planned for the patient, who had a known coronary artery bypass graft, with the diagnosis of unstable angina pectoris. After subcutaneous bupivacaine injection applied to the radial area, severe chest pain and electrocardiography changes occurred. No acute occlusive lesion was detected in coronary angiography. In this article, bupivacaine-associated kounis syndrome will be presented.

Keywords: Local anesthesia, bupivacaine, kounis syndrome, acute coronary syndrome, coronary angiography

ÖZ

Bupivakain, günlük pratikte lokal anestezi için sıkça kullanılmaktadır. Bupivakainin kardiyotoksik ve aritmik etkileri bilinmektedir. Literatürde bupivakain ile ilişkili akut alerjik reaksiyonlar ve elektrokardiyografik değişiklikler bildirilmemiştir. Kounis sendromu, akut alerjik bir atak sonrasında akut miyokard enfarktüsü klinik tablosu ile kendini gösterir. Koroner arter bypass grefti olan ve stabil olmayan angina pektoris tanısı konan hastaya koroner anjiyografi planlandı. Radial bölgeye uygulanan subkutan bupivakain enjeksiyonu sonrasında şiddetli göğüs ağrısı ve elektrokardiyografi değişiklikleri meydana geldi. Koroner anjiyografide akut tıkayıcı lezyon tespit edilmedi. Bu makalede, bupivakain ile ilişkili kounis sendromu sunulacaktır.

Anahtar Kelimeler: Lokal anestezi, bupivakain, kounis sendromu, akut koroner sendrom, koroner anjiyografi

INTRODUCTION

Medications given during anesthesia can act as antigens, which can trigger anaphylactic reactions. Bupivacaine, as it is known, is an anesthetic drug administered subcutaneously to provide local anesthesia to patients. Bupivacaine amide derivative is a local anesthetic agent. Hypersensitivity and anaphylaxis can be observed after bupivacaine injection. It can also cause a type 4 hypersensitivity reaction[1]. When allergy, hypersensitivity, and anaphylactoid effects occur, cardiovascular effects may manifest as kounis syndrome[2]. Kounis syndrome may present with coronary vasospasm and acute coronary syndrome[3]. In this article, we present a case of ST elevated myocardial infarction without significant anaphylaxis after subcutaneous administration of bupivacaine.

CASE REPORT

A sixty-four-year-old male patient was admitted to our emergency department with chest pain ongoing for the last three days. In his history, it was learned that he had known hypertension, hyperlipidemia, and 3 vascular coronary artery bypass grafts applied in 2018. Troponin and electrocardiography (ECG) follow-ups were performed. The patient's presenting ECG was determined as normal sinus rhythm (Figure 1A). Troponin tests were negative. However, he was admitted to our clinic with the diagnosis of unstable angina pectoris because

Address for Correspondence: Efe YILMAZ MD, Trakya University Faculty of Medicine, Department of Cardiology, Edirne, Turkey
E-mail: drefeyilmaz@gmail.com **ORCID ID:** orcid.org/0000-0003-2976-3063
Received: 15.05.2024 **Accepted**: 24.07.2024

he had cardiac pain which did not go away. Radial coronary angiography was planed for the patient. Before coronary angiography, local anesthesia was applied to the radial region with 3 mg bupivacaine. Then, the patient's pulse was observed to be 30 on the monitor. Concomitant feelings of deterioration, back pain, and facial flushing developed. When the measured blood pressure is 70/30 mmHg, 1 mg of atropine is applied. Afterwards, the patient developed branch-block tachycardia with a pulse rate of 150 beats/min. Then, ST elevation was seen on the ECG (Figure 1B). Femoral angiography was decided and coronary angiography was performed with local anesthesia with lidocaine. No acute total occlusion was observed in coronary bypass grafts and native vessels (Figure 2). Finally, all complaints regressed and the control troponin value of the patient was found to be 6,893. During the follow-up, medical treatment was arranged and the patient was discharged. The patient provided written informed consent for the publication of this article.

DISCUSSION

If there is a sudden onset of chest pain and allergic symptoms accompanying ECG changes, kounis syndrome should be considered. Kounis and avras first defined it as allergic angina[4]. Two subtypes have been identified. Type 1 coronary artery disease has been described in patients with normal coronary arteries without predisposing factors. Coronary vasospasm, endothelial dysfunction, or microvascular angina have been blamed for the release of allergic mediators in this type. In the other type, thrombosis was blamed for acute allergic attacks causing rupture of the existing stable plaque[5]. In our patient, type 1 kounis syndrome triggered by an acute allergic attack after bupivacaine was considered.

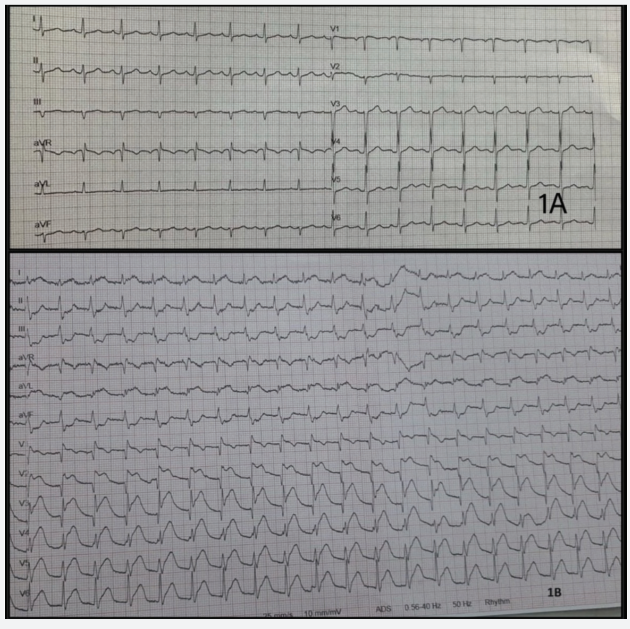


Figure 1. A) Electrocardiography at admission. B) Electrocardiography after local bupivacaine injection

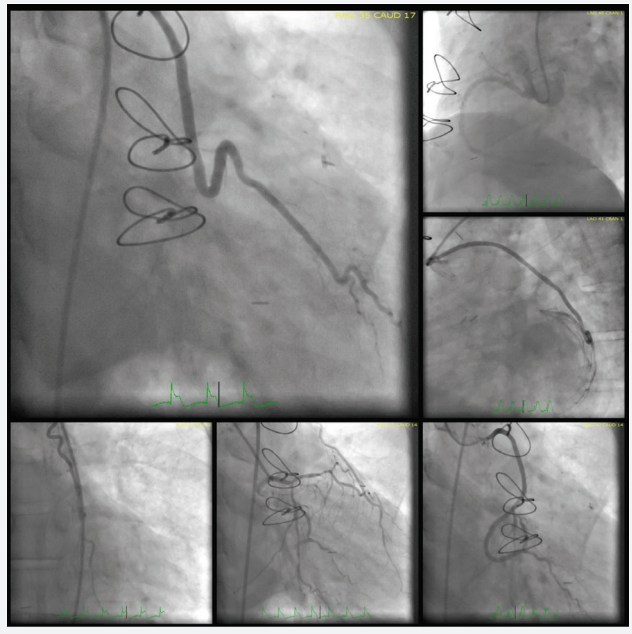


Figure 2. Coronary angiography was performed, and native coronary artery and bypass graft vessels were detected as normal

Bupivacaine is known to have a cardiotoxic effect by inhibiting voltage-gated ion channels. All local anesthetic agents have negative inotropic effects. Bupikain can cause electromechanical dissociation and severe ventricular arrhythmias in particular[6]. In this case, it has been shown that bupivacaine may cause acute chest pain, ECG change, and myocardial infarction triggered by allergy in addition to these known effects.

Local anesthetic drugs are used in many different areas. After the use of these drugs, it is necessary to take an ECG for patients with allergic symptoms with chest pain and sweating. It should be borne in mind that drugs such as bupivacaine can cause acute myocardial infarction without causing significant anaphylaxis. It is important to see the coronary anatomy in these patients. It should be anticipated that an acute allergic reaction may lead to a rupture in patients with stable plaque and they may have a myocardial infarction presenting with a thrombus.

CONCLUSION

In the literature, kounis syndrome developed against the combination of amikacin, bupivacaine and fentanyl has been reported[1]. However, no patient who developed kounis

syndrome directly due to bupivacaine has been reported. Therefore, it should be kept in mind that local anesthetics, which we frequently use and do not usually have side effects, may have situations like the one in this case.

Ethics

Informed Consent: The patient provided written informed consent for the publication of this article.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Y., Ç.K., Concept: E.Y., Ç.K., Design: E.Y., Ç.K., Data Collection or Processing: E.Y., Ç.K., Analysis or Interpretation: E.Y., Ç.K., Literature Search: E.Y., Ç.K., Writing: E.Y., Ç.K.

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

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Kounis NG, Kounis GN, Soufras GD. Amikacin, bupivacaine, fentanyl and Kounis syndrome. J Pharmacol Pharmacother. 2014;5:169-71.
2. Kounis NG. Coronary hypersensitivity disorder: the Kounis syndrome. Clin Ther. 2013;35:563-71.
3. Kaya Ç, Altay S. Quetiapine induced acute coronary syndrome: Possible Kounis syndrome. J Clin Psychiatry Cog Psychol. 2018;2:11-3.
4. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. Br J Clin Pract. 1991;45:121-8.
5. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol. 2006;110:7-14.
6. Mather LE, Chang DH. Cardiotoxicity with modern local anaesthetics: is there a safer choice? Drugs. 2001;61:333-42.

2024 Referee Index

Abidin Şehitoğullari
Ahmet Çarhan
Ahmet Küçükarda
Ali Delibaş
Ali Duman
Ali Gökyer
Ali Hakan Kaya
Ali Kandeğer
Ali Öztürk
Alihan Oral
Alıye Çelikkol
Altemur Karamustafaoğlu
Arzu Altunçekiç
Arzu Ayraler
Aslı Özbek Bilgin
Atakan Erol
Aygül Çeltik
Ayhan Atıgan
Ayla Arslan
Aylin Aydın Sayılan
Ayşe Berna Anıl
Ayşe Özlem Mete
Ayşe Zeynep Yılmazer Kayatekin
Barış Yılbaş
Başak Büyük
Bedia Sultan Önal
Beray Gelmez Taş
Bestegül Çoruh Akyol
Betül Öğüt
Beyhan Özyurt
Bülent Bilir
Bülent Sabri Cığalı
Burak Açıkel
Burcu Tokuç
Cafer Sadık Zorkun
Cahit Bağcı
Cemil Kavalci
Cemile Özsürekçi Gülbaş
Çiğdem Özdemir
Çiğdem Binay
Cihan Aydın
Cihan Özgür
Damla Binnetoğlu
Damla Hepduman
Dilek Solmaz
Dott Danılo De Gregorio
Eda Çelik Güzel
Elif Serap Esen
Elif Deniz Şafak
Elif Er Gülbezer
Emel Çalışkan
Emir Çelik
Enver Özdemir
Ercan Akşit
Ercan Babur
Esra Kazak
Esra Okyar
Esra Zerdali
Evrim Şenkal
Eyüphan Gencel
Eyyüp Çavdar
Fatih Mehmet Uçar
Fatih Tanrıverdi
Figen Kaptan Aydoğmuş
Gamze Varol
Gazi Zorer
Gül Teksin
Gündüz Yümün
Hadi Sasani
Hale Öktem
Hülya Çaşkurlu
Hülya Duran
İlkçe Akgün Kurtulmuş
İlknur Erdem
İlknur Ucuz
İnci Yılmaz Nakir
Istemi Serin
Kemal Kef
Kenan Bek
Kenan İltümür
Kubilay Karaboyun
Leyla Arvas
Lütfi Çağatay Onar
Mahcube Çubukçu
Mahmut Fırat Kenanoğlu
Mehmet Hilmi Doğu
Mehmet Yılmaz
Menekşe Karahan
Mesut Ayer
Mesut Engin
Mihrali Karademir
Müfide Okay Özgeyik
Muhammed Yayla
Muhammet Cemal Kızılarslanoğlu
Mustafa Akyürek
Mustafa Kadıhasanoğlu
Mustafa Serhat Şahinoğlu
Nadir Emlek
Nagehan Didem Sarı
Nergiz Bayrakcı
Nurnehir Baltacı Bozkurt
Oğuzhan Bol
Onur Hurşitoğlu
Osman Celbiş
Özge Şahmelikoğlu Onur
Özgür Kızılca
Özkan Alan
Pınar Tosun Taşar
Rafet Eren
Ramazan Güven
Ramazan Kocaaslan
Remzi Abalı
Rıdvan Karaali
Rıdvan Mercan
Rıfat Özmen
Rıza Sonkaya
Rukiye Yasak Güner
Şafak Eray
Şebnem Şenol Akar
Seda Uğraş Harman
Sedat Yıldız
Selahattin Çalışkan
Selma Tekin
Serhat KARAMAN
Serhat Örün
Serkan Menekşe
Serkan Yazıcı
Sevil Karabağ
Sevnaz Şahin
Sibel İlgün
Sinharib Citgez
Sonay Göktaş
Süha Serin
Süheyla Görar
Süleyman Ahbab
Süleyman Emre Koçyiğit
Süleyman Özer
Tahir Şevval Eren
Tamer Tunçkale
Tuba Özgöçer
Tuğçe Büşra Erdem
Tuna Sezer
Ülfiye Çelikkalp
Umut Uyan
Volkan Erdoğu
Yakup İriağaç
Yalçın Hacıoğlu
Yeliz Mercan
Yener Koç
Zafer Dağtaş
Zeynep Tosun