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The European Research Journal 2024;10(2):157-165 Original Article

DOI: https://doi.org/10.18621/eurj.1373134 *Cell Biology*

The protective and antiapoptotic effects of *Hypericum triquetrifolium* Turra against cyclophosphamide-induced lung injury in rats: in vitro evaluation

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ABSTRACT

Objectives: *Hypericum triquetrifolium* Turra (HTT) has been traditionally used in medical treatments due to its sedative, antiseptic, antiinflammatory, and anthelmintic properties. The present study aims to investigate the lung-protective and antiapoptotic effects of HTT against cyclophosphamide (CP)-induced lung injury in rats.

Methods: Thirty-five Sprague Dawley rats were categorized into 5 groups, each consisting of seven members. Phenolic acid and flavonoid contents of this plant were determined. The lung tissue samples cultivated from the rats were examined in histopathological and immunohistochemically for the apoptosis markers of Caspase-3, Bax, and Bcl-2.

Results: Histopathological results indicated that structural defects, bleeding areas, and edema had occurred in the lungs of the CP-Alone Group. Besides, Caspase-3 and Bax positivity of the lung cells had also increased while Bcl-2 positivity had decreased. On the other hand, in the HTT+CP Group, HTT was shown to have reversed the aforementioned changes positively.

Conclusion: Based on in vivo results, HTT could be a strong protective candidate for CP-induced lung injury and apoptosis

Keywords: Cyclophosphamide, *Hypericum triquetrifolium*, immunohistochemical, apoptosis, rats

The lung is vulnerable to the detrimental effects of various xenobiotics, such as drugs, natural toxins, and environmental pollutants [1]. Alkylating antineoplastic groups of drugs are potent drugs that can damage the balance of antioxidant-oxidants [2]. Cyclophosphamide (CP) is an oxazaphosphorine derivative of alkylating nitrogen mustard typically used as a chemotherapeutic drug in treating cancer [3]. Research shows that the damage CP causes to healthy tissues, including the kidney, liver, lung, and testicle, limits the use of this drug in cancer treatment [4, 5].

Inadequacy of detoxifying enzymes in the lung tissue is accepted to be the main reason for lung toxicity caused by CP [6]. It has been reported that CP exposure causes biochemical and physiological distur-

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bances by disrupting the redox balance after oxidative stress [7, 8]. CP is a generally prescribed anticancer drug applied in the treatment of various neoplastic diseases. Cytotoxic effects of CP are due to chemically reactive metabolites that produce cross-linking, which alkylate DNA and protein [9]. Reactive oxygen species (ROS) have essential roles in the pathogenesis of acute and chronic lung damage. Because oxygen is vital for living, the cells that cover the airways and the surface area of the alveolus always need oxygen. Known as pulmonary defense cells, neutrophils, monocytes, and macrophages tend to be effectively inclined to convert molecular oxygen to ROS [10, 11] Studies have shown CP to cause inflammatory reactions in the lungs of rats apart from causing acrolein/ROS formation, increasing lipid peroxidation, and accumulating neutrophils while the drug is being metabolized [3].

Species of *Hypericum*, also known as the Clusioid clade, belong to the Hypericaceae family [12]. There are known to be many bioactive compounds in the methanolic extracts of Hypericum species [13, 14]. A member of the Hypericaceae family, *Hypericum triquetrifolium* Turra (HTT) has been traditionally used in medical treatments due to its sedative, antiseptic, anti-inflammatory, and anthelmintic properties [15]. Furthermore, HTT has flavonoid and phenolic compounds with such properties as chlorogenic acid, hyperoside, quercitrin, quercetin, and routine apart from having antioxidant properties [16, 17]. Besides, the antioxidant property of HTT helps to prevent or reduce the progression of many oxidative stress-mediated diseases [13]. All these taken into account, the present study investigates whether the protective effects of HTT extract can decrease CP-induced toxicity on the lung tissue of rats thanks to in vivo studies.

METHODS

Drug and Chemicals

Endoxan, Cyclophosphamide Monohydrate, and C0768 (CP) were commercially obtained from Sigma-Aldrich, Taufkirchen, Germany. 500 mg CP was dissolved in bi-distilled water (25 mL) before being injected into the rats, each of them was given a single dose of 150 mg/kg of CP intraperitoneally.

Plant Extraction

Samples of HTT were collected during the seeding periods (between August and September 2015), which were then stored in the herbarium of Mardin Artuklu University. Afterward, 20 g of seed powder was extracted three times using 200 ml of absolute methanol, upon which 4.0 g of crude extract was obtained and then stored at -20ºC prior to use the onset of the experiment. Next, this extract was dissolved with 0.2% dimethyl sulfoxide (DMSO) to produce 100 mg/kg HTT. It was filtered for high-performance liquid chromatography (HPLC) via a membrane filter with a pore of 0.22 µm (Carl Roth GmbH, Karlsruhe, Germany). HPLC analyses of phenolic acid and flavonoid were performed using a Waters model 2690 gradient pump with Waters 2487 UV detector and XTerra RP18 column (150 Å~ 3.9 mm, 3.5 µm) [18, 19].

Animals

Male Sprague Dawley rats were provided from the Experimental Animals Lab. Ind. Trade. Corp. Co., which received approval from the Experimental Animal Ethics Committee of Eskişehir Osmangazi University (Protocol No. 444-1/2015). 220±20 g healthy, 3-4 months old male rats were kept in normal environmental conditions, including 25±2 °C room temperature, 60-70%, humidity, and 12 h light-dark cycles. Care was taken to make sure that these animals could reach standard pellet feed and water easily.

Experimental Groups

Five groups of seven rats each were formed from the 35 total animals. Group 1 (the control) received 0.5 mL of saline, Group 2 was given 150 mg/kg of CP, and Group 3 was administrated 100 mg/kg of HTT. Group 4 received HTT+CP, and Group 5 received 0.2 mL of DMSO (0.2%).

Chemical and medication dosages were chosen and prepared for the injection. Every injection was intraperitoneal (i.p). Group 1: Control rats received 0.5 ml of so-called normal saline (SF) over 6 days. Group 2 rats received SF treatment for five days before receiving a single dosage of CP on the sixth day. For six days, rats in Group 3 received the appropriate HTT-dose treatment. Rats in Group 4 received the appropriate dose of HTT. A single dose of CP was given on the sixth day. Group 5 received 0.2% DMSO treatment for 6 days. Blood samples were collected through

heart puncture under ketamine/xylazine anesthesia to evaluate serum parameters before the animals were euthanized on the seventh day (Table 1).

Histological Examination

Lungs from experimental albino rats were processed using an automated tissue processor after being formalin-preserved. Dehydration and fixation served as the processing's first two steps. During fixation, the tissue is submerged for 48 hours in 10 percent buffered formalin before the fixative is washed away with distilled water for 30 minutes. The tissues were then given two cycles of 100 percent alcohol for one hour each to dehydrate them. Initially, the tissues were exposed to 70% alcohol for 120 minutes, then to 90% alcohol for 90 minutes. After dehydration, the samples were cleaned in multiple xylene changes. During the operation, tissue was submerged for one hour in a mixture of 50% xylene and 50% alcohol, then for another 1.5 hours in pure xylene. The samples were then impregnated with molten paraffin wax, blacked out, and embedded [20]. Slices made from 4-5 M paraffin were stained using hematoxylin and eosin. Following conventional HE staining, morphological parameters were evaluated using light microscopy. A pathologist who was unaware of the groups evaluated lung injury using histological abnormalities like alveolar congestion, alveolar wall edema, inflammatory cell infiltration, and bleeding.

The pathologist also recorded the histopathology grade for the tissues in the left lung, which was based on the aforementioned reference [21]. Each benchmark was rated between 0 (normal) and 4 (severe), where 0 indicates no harm or a very minor injury, 1, 2, 3, and 4 are mild, serious, medium, and extremely serious injuries, respectively. The diffuse alveolar injury standard (DAS) score is the name of this approach. The sum of all scores was used to establish the overall score for the pathology of lung tissues.

Table 1. The protocol devised for all the study groups and the chemicals used

Groups	Treatment	Number of animals
Control	Control (saline i.p.)	7
CP	150 mg/kg	7
HTT	100 mg/kg	7
CP + HTT	150 mg/kg + 100 mg/kg	7
DMSO	0.2% (0.2 mL)	7

CP=Cyclophosphamide, HTT= *Hypericum triquetrifolium* Turra, DMSO=dimethyl sulfoxide

Immunohistochemistry Examination

The 5-m sections were deparaffinized, rehydrated, and subjected to antigen retrieval using a variety of newly discovered methods. The samples were cleaned with PBS and then blocked with 10% goat serum. The primary antibody (1:500; anti-Bax, anti-Caspase-3, and anti-Bcl-2 antibody; Abcam, Cambridge, UK) was incubated with the samples for 24 hours at 40°C. After washing the samples, the secondary antibody was incubated with them for 90 minutes at room temperature (1:1500; goat anti-rabbit IgG; Abcam). The slides were examined using the Leica DM500 Biological Microscope after the samples had been cleaned (Caspase-3 (Thermo Fischer), Bcl-2 (Abcam), and Bax (Abcam)

Statistical Analysis

The findings were defined as means±S.E.M. The statistical analyses used were One Way Analysis of Variance and Kruskal-Wallis One Way Analysis of Variance on Ranks Test. The data obtained for the contents of the plant seed material were subjected to ANOVA. All analyses were carried out in triplicates.

RESULTS

Lung tissue samples cultivated from the rats were not only histopathologically but also immunohistochemically analyzed for Bax, Bcl-2, and Caspase-3 on a routine basis.

Content of the Seed of Hypericum triquetrifolium

The levels of all the compounds detected in *H. triquetrifolium* were hyperoside (HT), kaempferol, quercetin, quercitrin, rutin, amentoflavone, chlorogenic acid, and apigenin-7-O-glucoside were examined and presented in Table 2. Considering this table, the compound with the largest amount of *H. triquetrifolium* was determined to be that of Hyperoside (HT) (8.42 mg/g DW).

Histological Evaluations

Table 2. Compounds available in *Hypericum triquetrifolium* (mg/g DW)

Compounds	*H. triquetrifolium*
Hyperoside (HT)	**8.42**
Kaempferol	0.02
Quercetin	1.91
Quercitrin	2.76
Rutin	3.72
Amentoflavone	0.006
Chlorogenic acid	2.07
Apigenin-7-O-glucoside	0.14

Lung tissues of the experimental groups (Control, 0.2% DMSO, and 100 mg/kg HTT) had all normal histology as presented in Table 2, Fig. 1A. Serious damage was observed in the lung tissues of the rats injected CP (150 mg/kg), including structural defects, obstruction, edema foci, bleeding areas, and alveolar cell injuries, as presented in Table 3, Fig. 2A. However, this damage greatly improved in the group injected CP+HTT as presented in Fig. 3A.

Apoptotic Evaluations

The lung tissue samples of Control, CP, HTT, CP+HTT, and DMSO groups were immunohistochemically stained to determine the density and concentration of Bax, Caspase-3, and Bcl-2 apoptotic markers. A comparison of the CP Group with Control, HTT, and DMSO Groups revealed that while the number of the positively-stained cells in Bax and Caspase-3 had increased, those of Bcl-2 had decreased. On the other hand, the number of the positively-stained cells had decreased in Bax and Caspase-3 while they increased in Bcl-2 as shown in Figs. 1-6.

Histological damage scores of the lung tissues are presented in Table 3.

DISCUSSION

This study aims to investigate whether or not HTT can

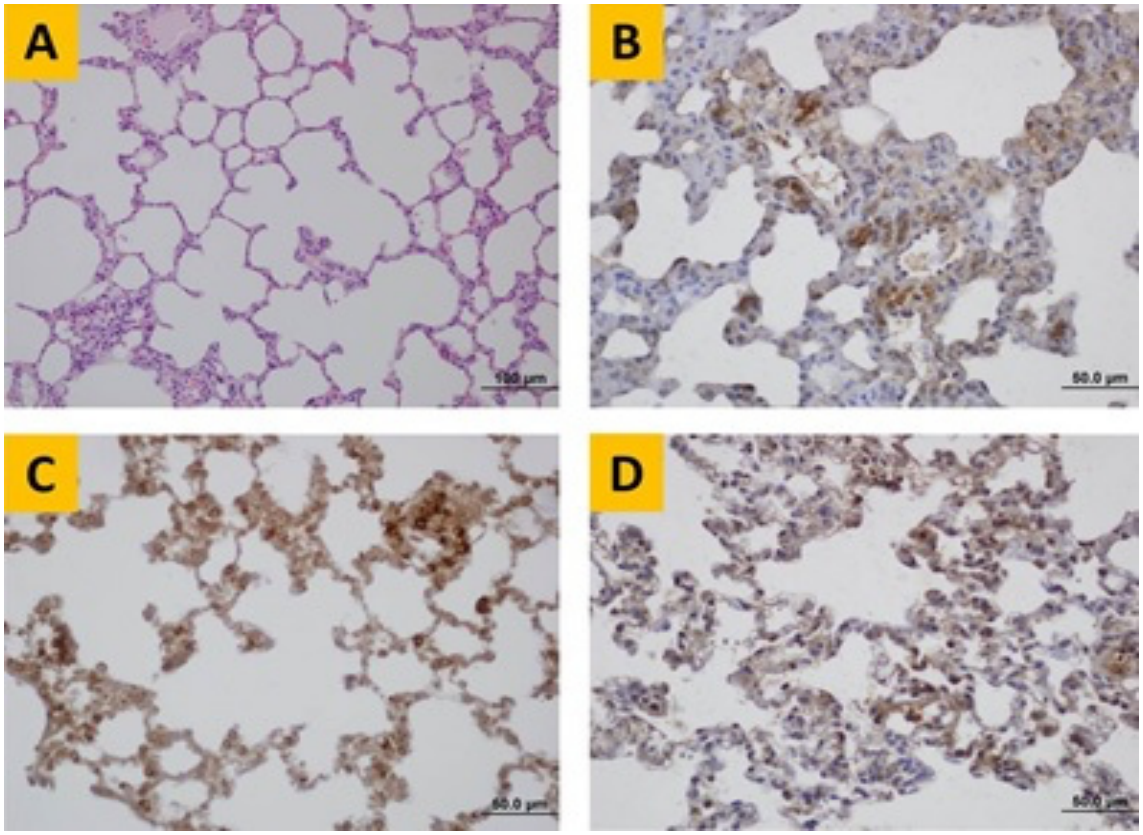

Fig 1. (A) Images of Control, HTT, and DMSO groups (B) Caspase-3 (C) Bcl-2 (D) Bax. Bars are between 50-100 µm.

Table 3. Histological damage scores of the lung tissues

Groups	Hemorrhage	Edema	Congestion
Control	0 (0-0)	0 (0-0)	0 (0-0)
CP	3* (2-3)	3* (2-3)	3* (2-3)
HTT	0 (0-0)	0 (0-0)	0 (0-0)
CP+HTT	0 (0–0)	0 (0-1)	0 (0–1)
DMSO	0 (0-0)	0 (0-0)	0 (0-0)

Data are shown median (minimum-maximum). CP=Cyclophosphamide, HTT= *Hypericum triquetrifolium* Turra, DMSO=dimethyl sulfoxide,

*P<0.001 compared to Control, significant differences

recover CP-induced lung damage thanks to *in vitro* studies. In this study, in addition to apoptosis, severe damage was detected in the lung tissues of the CP Group, including structural defects, obstruction, bleeding areas, edema foci, and alveolar cell injuries, which are in agreement with the literature (Table 3). Suddek *et al*. [3], showed that the rats given CP suffered damage and/or edema, congestion, macrophages infiltration, and neutrophilic in the interalveolar septa. One other study reported alveolar cell injuries, alveolar septa thickness, erythrocytes, and polymorphonuclear cells in the alveolar lumen in histopathological examination of lung tissues in rats given CP [22]. Previous studies have also reported that CP causes apoptosis in the liver, kidney, bladder, and testicles [5, 7, 13]. However, no studies are available in the literature on CP-induced apoptosis. In our CP Group, while the number of the positively-stained cells in Bax and Caspase-3

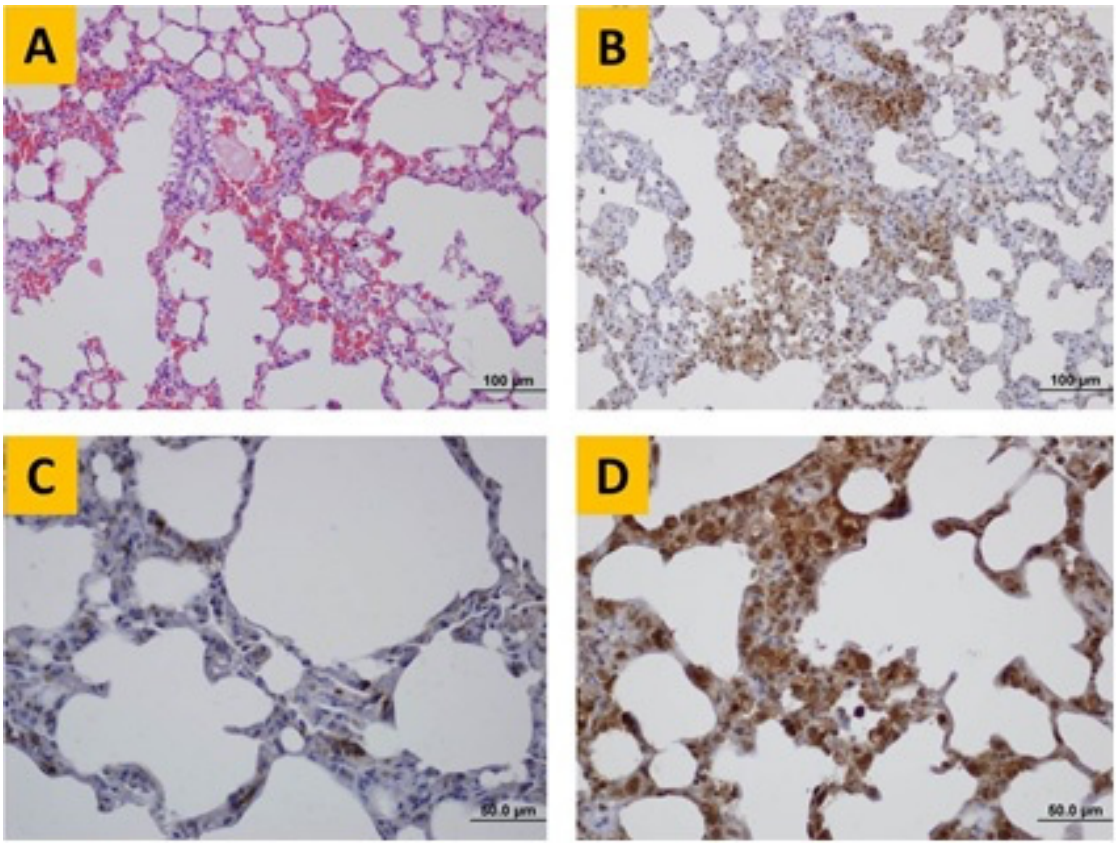

Fig 2. A) Images of CP (B) Caspase-3 (C) Bcl-2 (D) Bax groups. Bars are between 50-100 µm.

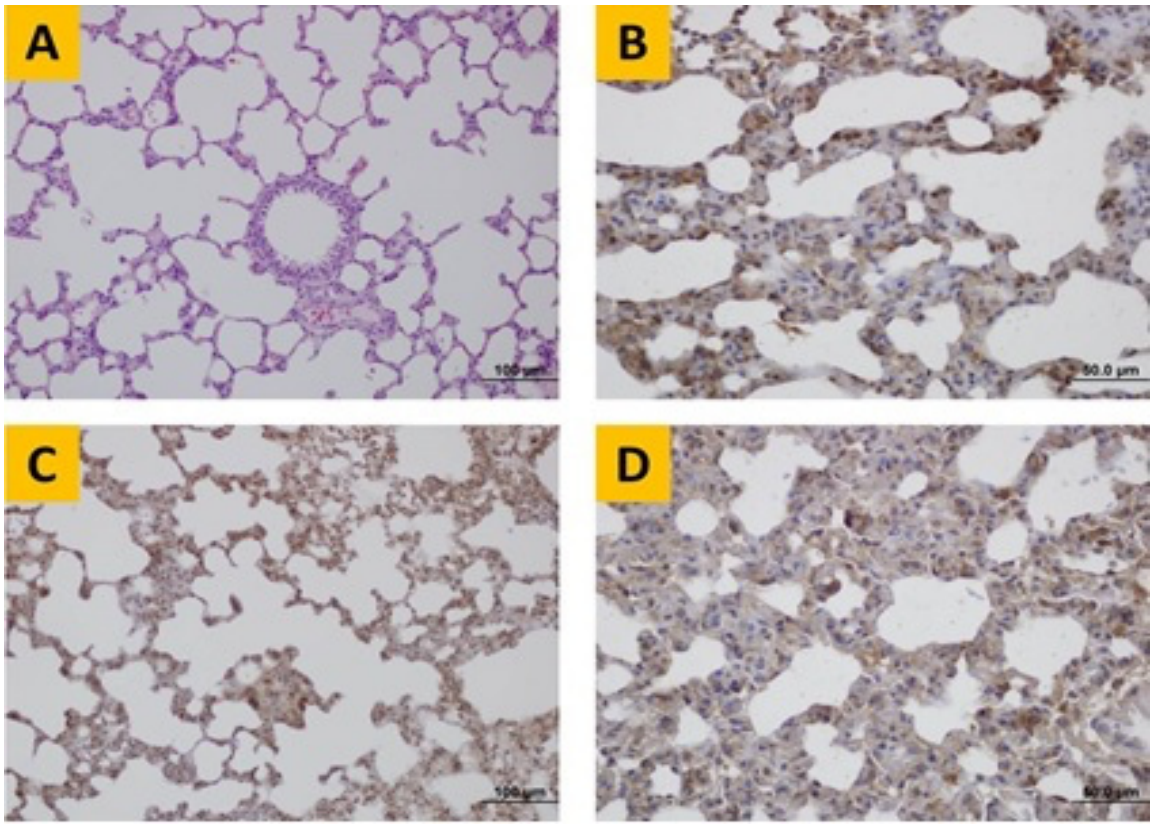

Fig 3. **(A) Images of CP+HTT (B) Caspase-3 (C) Bcl-2 (D) Bax groups. Bars are 50-100 µm.**

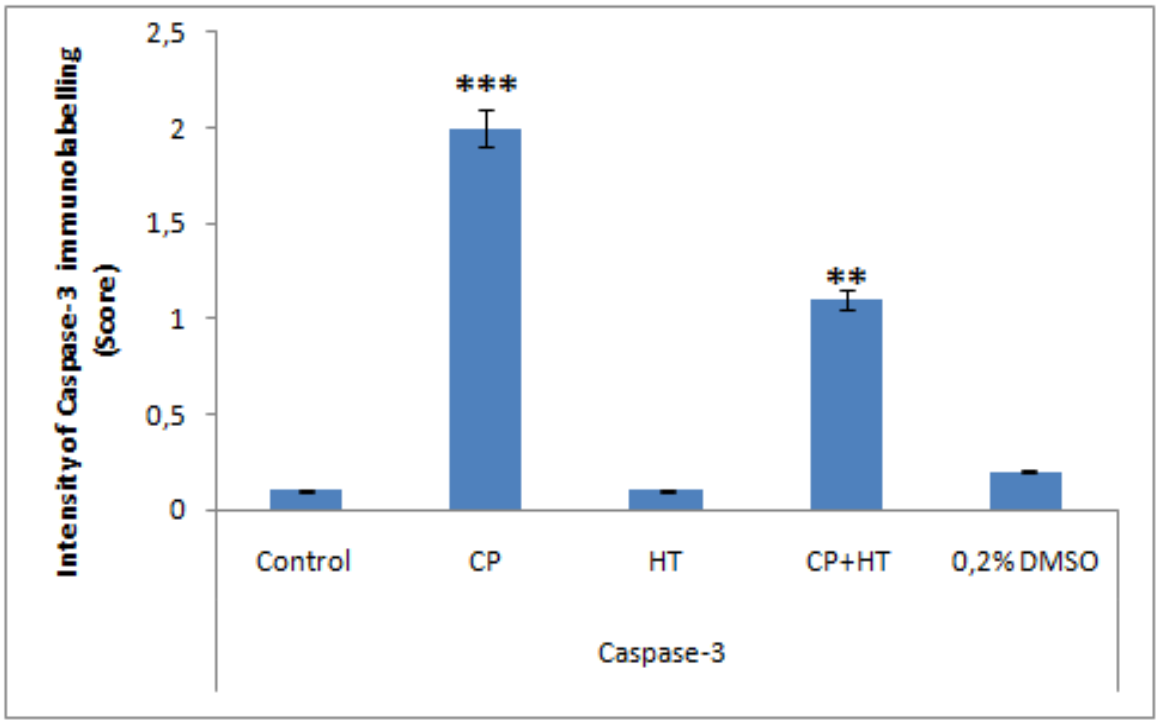

Fig 4. **Intensity of the immunolabeling score of the activated Caspase-3 positive cells in the groups. ***P<0.001 significant difference compared to control group, **P<0.01 different compared to control group.**

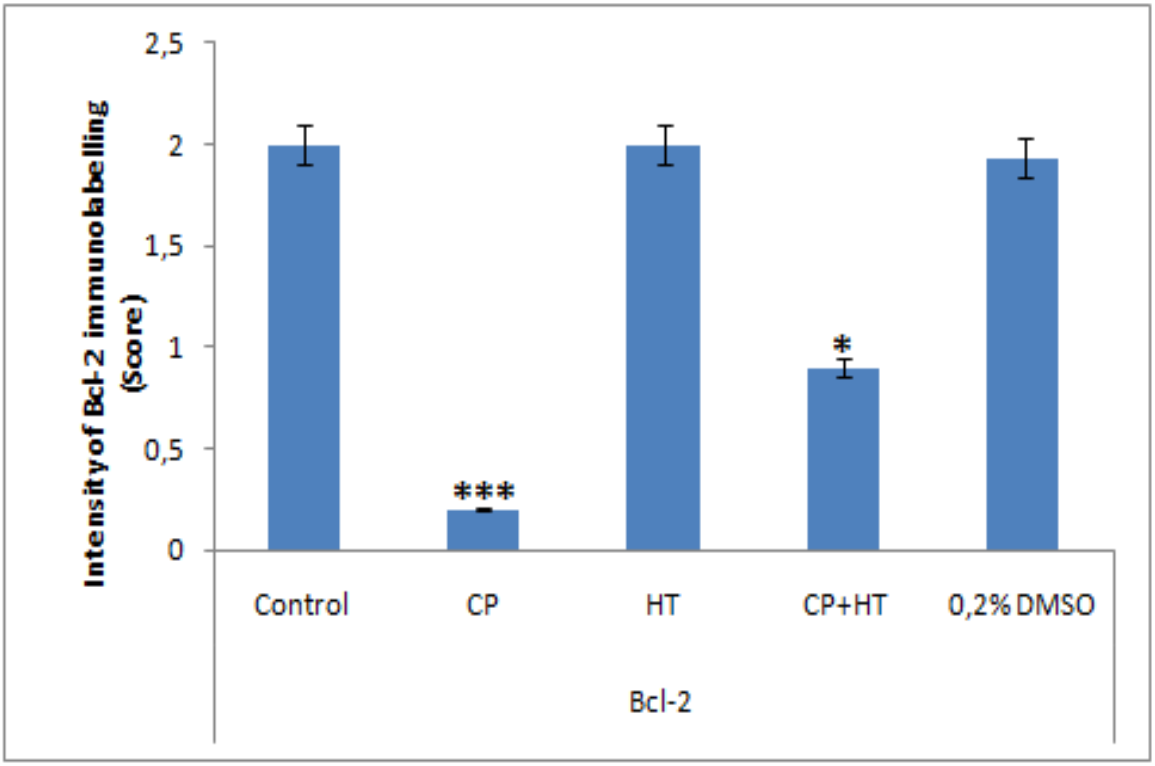

Fig 5. Intensity of the immunolabeling score of the activated Bcl-2 positive cells in the groups. ***P<0.001 significant difference compared to control, *P<0.05 different compared to control group.

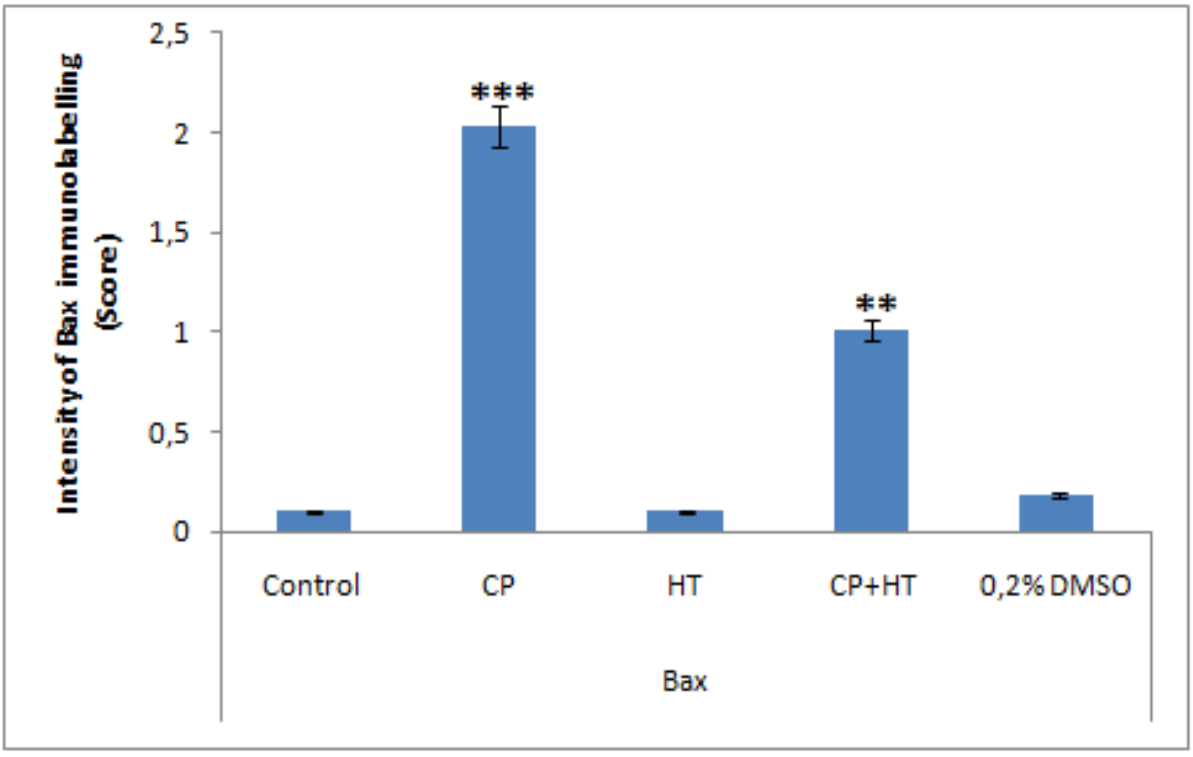

Fig 6. Intensity of the immunolabeling score of the activated Bax positive cells in the groups. ***P<0.001 significant difference compared to control, **P<0.01 different compared to control group.

had increased, those of Bcl-2 had decreased (Figs. 1-6).

High doses of CP are required to stop tumors from becoming resistant to anti-carcinogenic drugs. On the other hand, excessive doses raise the possibility of hazardous side effects while simultaneously extending survival [23]. HTT is known for its phenolic and flavonoid compounds showing antioxidant and anti-apoptotic properties [24]. The anti-oxidative activities of HTT can help suppress or decrease the side effects of many oxidative stress-induced diseases [25]. An experimental study reported that 100 mg/kg HTT achieved significant success in improving CP-induced testicular damage and apoptosis [13]. Also, Yildiz *et al*. [26] reported that CP-related cardiotoxicity, Bax, and Caspase-3 expressions decreased in CP + HTT Group while significantly increasing Bcl-2 expressions, suggesting that not only CP toxicity but also apoptosis intensity must have decreased in the cells. Our study is the first of its kind in the literature in that there are no studies available on the protective or curative effect of HTT upon lung injury.

Severe inflammatory reactions are caused by the acute effect of CYP on the lungs of rats. These reactions include the generation of acrolein during drug metabolism, neutrophil buildup, ROS creation, and increases in lipid peroxidation [27]. HTT and CP were co-administered to the rats, it was observed that this application resulted in a positive effect upon the expressions of Bcl-2. In conclusion, this study suggests that the CP-related increase in Bcl-2 expressions can be prevented by the addition of HTT. These results are consistent with the histopathological results of the present study (Figs. 1-6). The research team has shown in past studies that HTT works through anti-inflammatory and anti-apoptotic pathways to protect against a variety of experimentally produced tissue toxicities [13, 26]. HTT may inadvertently prevent apoptosis. Additionally, by limiting the loss of GSH, it can boost antioxidant levels, reduce inflammatory processes by lowering intracellular Ca++ and ROS levels, and finally, reduced TNF- and ROS levels can inhibit apoptotic cell death [28].

CONCLUSION

Based on our in-vivo results, we suggest that HTT could be a potential candidate for eliminating the toxic side effects of CP upon the lungs. This study, however, also suggests that further scientific research is necessary to better evaluate the clinical applications of HTT on cancer sufferers.

Authors' Contribution

Study Conception: SCY; Study Design: SCY; Supervision: SCY, CK, VŞ, AA; Funding: SCY, CK, VŞ, AA; Materials: SCY, CK, VŞ, AA; Data Collection and/or Processing: SCY, CK, VŞ, AA; Statistical Analysis and/or Data Interpretation: SCY, CK, VŞ, AA; Literature Review: SCY, CK, VŞ, AA; Manuscript Preparation: SCY, CK, VŞ, AA and Critical Review: SCY, CK, VŞ, AA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Investigation of the relationship between childhood traumas, psychological resilience, cognitive flexibility and emotion regulation skills in adults

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ABSTRACT

Objectives: This paper looked into the relation between childhood traumas, resilience, cognitive flexibility, and adult emotion regulation skills in adults.

Methods: The sample, which is based on the relational screening model, includes 395 participants (female: 202, male: 193). Sociodemographic Information Form, Childhood Trauma Questionnaire, Connor-Davidson Resilience Scale, Cognitive Flexibility Scale and Cognitive Emotion Regulation Questionnaire were applied to the participants to obtain the research data. Data collection was carried out online (google forms) through convenient sampling. The t-test was used to compare the study's quantitative data, and Pearson Correlation analysis was utilized to test the relationship between the scales. Multiple Linear Regression analysis was used for predictive analysis and finally PROCESS was used for mediator role analysis.

Results: The investigation's findings revealed that there is a statistically significant difference between the scores of the two groups compared. Findings showed that there is a moderately positive correlation between acceptance and CTQ scores, a weak positive correlation between acceptance and emotional abuse scores, a weak positive correlation with physical abuse scores, a weak positive correlation with physical neglect scores, a weak positive correlation with emotional neglect scores and weak positive correlation with sexual abuse scores. A weak and negative correlation exists between Putting into Perspective and the CTQ, an even weaker and negative correlation exists between Putting into Perspective and the Emotional Neglect and Sexual Abuse scores. Rumination scores have a weak and negative relationship with emotional abuse scores.

Conclusions: In order to prevent them from serving as the foundation for difficulties with adult mental health, it is crucial to understand the relationship between traumatic childhood events and psychological resilience, cognitive flexibility, and cognitive emotion regulation techniques. In order to assist people, analyze their thoughts and feelings, be aware of negative coping mechanisms, rigid, inflexible cognitive styles, and negative thinking patterns, clinical psychology practices will benefit from research on these characteristics.

Keywords: Childhood traumas, psychological resilience, cognitive flexibility, emotion regulation skills

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The concept of “childhood trauma” includes various traumatic experiences such as social and domestic violence, natural disasters, traffic accidents, child neglect, and emotional, physical, and sexual abuse [1-3]. Any behavior that harms the physical, emotional, mental, and social development of children under 18 years old is considered as abuse; failure to meet their needs such as nutrition, care, supervision and education is considered neglect. Abuse, and neglect in childhood or young adulthood are all examples of childhood trauma. Childhood traumas are behaviors that are intentionally or unintentionally done by an adult and negatively affect a child’s health, physical and psychosocial development. In this context, the important thing is not the intention of the adult but the long-term effects of the action on the child in the early period and the adult period.

Most studies on childhood trauma focused on the effect and treatment of sexual abuse but with less emphasis on child physical abuse [4]. Several community and clinical studies have discovered a link between recollected traumatic experiences from childhood and adult psychiatric disease [5, 6]. Recent studies have established that post-traumatic stress disorder (PTSD) and its inherent comorbidity affect children of all ages as well as adult victims of terrible life experiences [7, 8].

Today, researchers agree that early childhood traumas underlie long-term depression and anxiety disorders, as well as many emotional and psychological disorders. Adult PTSD is connected to childhood abuse and other cumulative traumas. Compared to those without PTSD, those with PTSD had higher rates of childhood maltreatment and abuse [5, 8, 9]. Nevertheless, research has revealed that repeated traumas are linked to greater rates of anxiety, suicidality, divorce, personality disorders, drug misuse, physical sickness, and interpersonal issues [10-14].

A wealth of research-based evidence has shown that childhood trauma reveals neural structure and function, predisposing the individual to later cognitive deficits and psychiatric illnesses such as schizophrenia, major depression, bipolar disorder, post-traumatic stress disorder (PTSD), and substance abuse [15-18]. As a result of micro-traumatic impacts, negative parental attitudes (including a carelessness and excessive protection) have been linked to an increased prevalence of anxiety disorders [6]. Finkelhor and colleagues have proposed that victimization is a "situation" rather than an "event" due to mounting evidence demonstrating the prevalence of collective exposure to violence, maltreatment, and abuse [19].

Compared to cumulative trauma, single event trauma has a different impact. According to studies, up to 87 % of youngsters suffer from PTSD as a result of natural disaster traumas [20, 21]. It has also been proven that childhood maltreatment and abuse have a higher tendency to cause anxiety disorders in adulthood and single event traumas to cause acute PTSD [22].

Emotional regulation is a term that refers to the emotions people experience, when such emotions occur, how the experience is, and the expression of such [23]. Thus, emotional regulation is challenging and it is characterized by awareness, identification and expression of emotional experiences, the ability to pay attention to contextual signals, impulse control, and the use of strategies to regulate emotions in response to emotional state triggers [24].

Deficiencies in emotional regulation skills are associated with greater negative affect, decreased positive affect, and ineffectiveness in managing one's emotions [25]. Individuals' psychological resilience is a dynamic process in which they adjust successfully despite extensive stress or trauma. In regard to childhood experiences, resilience is a complex combination of genetic predispositions, individual, family-related, and environmental risk and protective factors [26, 27]. The literature supporting the significance of protective psychological factors in preventing the negative consequences of childhood traumas is extensive [28]. Children who have experienced various forms of trauma frequently exhibit resilience in the form of protective characteristics that take a variety of different trajectories to promote their healthy development [26, 29, 30]. Psychological resilience is characterized by positive self-esteem, ego flexibility and being able to exert control over the ego [31, 32].

Cognitive flexibility is the ability to switch between rules and concepts even as they change and adapt to the situation. In other words, Individuals' ability to adapt to a continually changing environment is aided by cognitive flexibility and it is at the center of goal-directed behavior. Denis and Vander Wal see cognitive flexibility as a three-dimensional proccess where the tendency to perceive difficult situations as manageable, the ability to recognize that there may be many alternative explanations for human behavior and

events that occur throughout life, and the ability to produce alternative solutions in the face of difficult situations [33]. Recent research has shown increasing interest in understanding factors, including genetics and early life experiences, that may contribute to individual differences in this ability. Being cognitively flexibility is necessary to be able to respond appropriately to new situations in the face of problems [34].

This study discussed whether childhood traumas differ in psychological resilience levels, cognitive flexibility and cognitive emotion regulation strategies of adults. It is important for researchers to identify the characteristics, protective factors, cognitive flexibility and emotion regulation strategies that enable those who have experienced childhood traumas, especially sexual abuse, to develop psychological resilience.

METHODS

Design

Sociodemographic Information Form, Childhood Trauma Questionnaire, Connor-Davidson Resilience Scale, Cognitive Flexibility Scale and Cognitive Emotion Regulation Questionnaire were applied to the participants (n = 395) who constituted the sample of this study. Data collection was carried out online (google forms) through convenience sampling. The association between childhood traumas, psychological resilience, cognitive flexibility, and emotion regulation skills in adults was investigated using a relational screening model.

Participants

The participants in the study are individuals over the age of 18. The study's sample includes 395 adults ranging in age from 18 to 63 years (35 ± 10 years). Two hundred and two (51.1%) participants were female, 48.9% male, 6.6% primary school graduate, 6.8% secondary school graduate, 14.9% high school graduate, 58.5% university graduate, 13.2% postgraduate and above, 52.2% are married, 47.8% are single.

Measures

Sociodemographic Information Form

The form created by the researchers includes information such as age, gender, education level and marital status.

Childhood Trauma Questionnaire (CTQ)

It is a self-report scale developed by Bernstein *et al*. [35]. The scale consists of 28 items, three of which measure denial of trauma, and participants rate each item on a 5-point Likert-type scale. The scale includes five sub-dimensions related to childhood abuse: sexual, physical, emotional abuse and emotional and physical neglect [36]. The accuracy and reliability of the Turkish version of the scale were evaluated, Cronbach's alpha and half-test (Guttman formula) methods were used to measure internal consistency [37]. The Cronbach's alpha value, which shows the internal consistency of the scale, was found to be 0.93 for the group consisting of all participants (n=123), while the Guttman half-test coefficient was 0.97 [36]. In this group, correlations between each item and the total score were found by calculating the Pearson Product Moments Correlation coefficient. Except for item 4 (r=.17), all results were above .30 and most were above .50 [36]. These results show that the internal consistency of the scale is high. The test-retest correlation coefficient of the total score of the CTQ performed on clinical and non-clinical participants at 2-week intervals was 0.90 (in the explanatory factor analysis of p validity, five factors were examined in accordance with the original form of the scale. The CTQ has been verified to be valid and accurate [37].

Connor-Davidson Resilience Scale (CD-RISC)

The scale developed by Connor and Davidson [38] was adapted into Turkish by Karaırmak [39]. CD-RISC consists of 25 items and participants rate each item on a 5-point Likert-type scale. The scale consists of three factors: tenacity and personal competence, tolerance of negative affect, and spiritual influences. It was stated that these three factors explained 52% of the total variance. Higher scores from CD-RISC indicate higher psychological resilience. The reliability of the scale was calculated with the Cronbach's alpha internal consistency method and was found to be .92 for the whole scale. Cronbach's alpha internal consistency coefficient was found to be .94 in this investigation.

Cognitive Flexibility Scale (CFS)

The 12-item scale was created by Martin and Rubin [40] and translated into Turkish by Altunkol [41]. It is a 6-point Likert type (1-Strongly Disagree, 6-Strongly Agree) scale developed to determine the

cognitive flexibility level of an individual. The total score is obtained by summing the answers given to each item. The scale's lowest possible score is 12 and its highest possible score is 72. High scores indicate high cognitive flexibility, while low scores indicate low cognitive flexibility. The Cronbach's alpha coefficients obtained in different studies on the scale range from .72 to .87. It was reported that the test-retest reliability coefficient of the scale was .83 as a result of two applications performed with a one-week interval [40]. The scale is widely used in studies where the level of cognitive flexibility is variable. The Cronbach's alpha coefficient obtained in the adaptation studies of the scale is .81. Again, within the scope of this study, the test-retest correlation coefficient obtained in the application to determine the continuity coefficient of the scale was discovered to be .73. Within the scope of validity studies, criterion-related validity and construct validity studies were conducted and it was seen that the scale met the validity criteria [41].

Cognitive Emotion Regulation Questionnaire (CERQ)

Garnefski *et al*. [42] developed the scale to measure the cognitive emotion regulation strategies that people use after stressful life events or to regulate their emotions in general. It is a self-report scale that can be applied to both clinical and non-clinical samples. The scale is a 5-point Likert type that has 9 subscales, 4 items in each subscale and a total of 36 items. The subscales that make up the scale are "Self-blame", "Acceptance", "Rumination", "Positive refocusing", "Refocus on planning", "Positive reappraisal", "Putting into perspective", "Catastrophizing" and "Blaming others". Each subscale score can range from 4 to 20. Evaluation is made with the scores obtained from the subscales. The Turkish adaptation, validity and reliability of the scale was made by Onat and Otrar [43]. As a result of the statistical analyzes of the study, the test-retest reliability coefficient was found to be "r = 1.00" and the Cronbach Alpha value as "a = 0.784".

Statistical Analysis

Statistical evaluations were analyzed using SPSS (Statistical Package for Social Sciences) 25.0 package program. The kurtosis and skewness values were checked to determine the normality of the distribution. According to George and Mallery [44] skewness and kurtosis values between -2 and +2; and according to Groeneveld and Meeden [45], Moors [46], Hopkins and Weeks [47], and De Carlo [48], skewness and kurtosis values between -3 and +3 are sufficient to meet the normal distribution condition.

After deciding on the normal distribution, it was decided to use parametric analyzes. Descriptive statistical analysis for the demographic variables employed in this study was immediately determined after the normality analysis. The relationship between Pearson Correlation analysis and Childhood Trauma Questionnaire, Connor-Davidson Resilience Scale, Cognitive Flexibility Scale and Cognitive Emotion Regulation Questionnaire were investigated.

For predictive analysis, Multiple Linear Regression analysis and mediation analyses were performed with PROCESS. The confidence interval used for all analyses was determined as 95%.

It has been observed that the Childhood Trauma Questionnaire is (mean±standard deviation [44.30±17.04]), Emotional Abuse subscale is (8.33±3.66), Physical Abuse subscale (8.72±3.85), Physical Neglect subscale (9.30±4.43), Emotional Neglect subscale (9.71±4.86), Sexual Abuse subscale (8.23±3.78), Connor-Davidson Resilience Scale is (67.99±18.20), Tenacity and Personal Competence subscale is (42.30±11.87), Tolerance of Negative Affect subscale is (18.28±5.46), Spiritual Influences subscale is (7.42±2.93), Cognitive Flexibility Scale is (53.86±9.19), Acceptance subscale is (12.83±3.57), Positive Refocusing subscale is (12.59±3.41), Refocus on Planning subscale is (15.16±3.19), Positive Reappraisal subscale is (14.75±3.22), Putting into Perspective subscale is (13.13±3.57), Rumination subscale is (14.37±3.24), Self-blame subscale is (11.29±3.14), Catastrophizing subscale is (10.33±3.87), Blaming Others subscale is (11.02±3.42).

RESULTS

The findings revealed a moderate, positive relationship between Acceptance and CTQ scores (r=.328, P<0.01), a weak, positive relationship between Acceptance and Emotional Abuse scores (r=.296, P<0.01), a weak, Physical Abuse scores (r=.275, P<0.01), Physical Neglect scores (r=.280, P<0.01),

Table 1. The relation between Cognitive Emotion Regulation Questionnaire and Childhood Trauma Questionnaire

	CTQ	Emotional abuse	Physical abuse	Physical neglect	Emotional neglect	Sexual abuse
Acceptance	.328**	.296**	.275**	.280**	.274**	.232**
Positive refocusing	-0.046	-0.005	-0.048	-0.060	-0.041	-0.031
Refocus on planning	-.310**	-.170**	-.199**	-.325**	-.363**	-.182**
Positive reappraisal	-.289**	-.166**	-.191**	-.279**	-.380**	-.134**
Putting into perspective	-.114*	-0.070	-0.079	-0.069	-.128*	-.121*
Rumination	0.049	.107*	0.061	-0.002	0.015	0.038
Self-blame	.255**	.229**	.217**	.217**	.213**	.179**
Catastrophizing	.407**	.363**	.298**	.377**	.381**	.249**
Blaming others	.276**	.234**	.181**	.252**	.278**	.182**

CTQ= Childhood Trauma Questionnaire, **P<0.01, *P<0.05 Pearson correlation test

Emotional Neglect scores (r=.274, P<0.01), and Sexual Abuse scores (r=.232, P<0.01) (Table 1).

There is a moderate, negative relation between Refocus on Planning and CTQ scores (r=-.310, P<0.01), a weak, negative relationship between Refocus on Planning and Emotional Abuse scores (r=-.170, P<0.01), Physical Abuse scores (r=-.199, P<0.01), and Sexual Abuse scores (r=-.182, P<0.01). A moderate, negative relationship between Refocus on Planning and Physical Neglect scores (r=-.325, P<0.01), and Emotional Neglect scores (r=-.363, P<0.01) (Table 1).

There is a weak, negative relationship between Positive Reappraisal and CTQ scores (r=-.289, P<0.01), a weak, negative relationship between Positive Reappraisal and Emotional Abuse scores (r=-.166, P<0.01), Physical Abuse scores (r=-.191, P<0.01), Physical Neglect scores (r=-.279, P<0.01), and Sexual Abuse scores (r=-.134, P<0.01). A moderate, negative relationship between Positive Reappraisal and Emotional Neglect scores (r=-.380, P<0.01) (Table 1). There is a weak, negative relationship between Putting into Perspective and CTQ scores (r=-.114, P<0.01), Emotional Neglect scores (r=-.128, P<0.01), and Sex-

Table 2. The relation between Cognitive Emotion Regulation Questionnaire and Connor-Davidson Resilience Scale

	CD-RISC	Tenacity and personal competence	Tolerance of negative affect	Spiritual influences
Acceptance	-.205**	-.224**	-.181**	-0.028
Positive refocusing	0.091	0.080	0.072	.107*
Refocus on planning	.317**	.336**	.252**	.137**
Positive reappraisal	.350**	.359**	.295**	.169**
Putting into perspective	0.079	0.073	0.056	0.091
Rumination	0.061	0.032	0.072	.114*
Self-blame	-.121*	-.158**	-0.089	0.054
Catastrophizing	-.207**	-.253**	-.130**	-0.019
Blaming others	-0.073	-.121*	-0.025	0.080

CD-RISC= Connor-Davidson Resilience Scale, **P<0.01, *P<0.05 Pearson correlation test

Tablo 3. The relation between Cognitive Emotion Regulation Questionnaire and Cognitive Flexibility Scale

	CFS
Acceptance	-.269**
Positive refocusing	.102*
Refocus on planning	.454**
Positive reappraisal	.419**
Putting into perspective	0.005
Rumination	0.054
Self-blame	-.225**
Catastrophizing	-.365**
Blaming others	-.233**

CFS= Cognitive Flexibility Scale, **P<0.01, *P<0.05 Pearson correlation test

ual Abuse scores (r=-.121, P<0.01). There is a weak, negative relationship between Rumination and Emotional Abuse scores (r=-.107, P< 0.01). There is a weak, positive relationship between Self-blame and CTQ scores (r=.255, P<0.01), a weak, positive relationship between Self-blame and Emotional Abuse (r=.229, P<0.01), Physical Abuse scores (r=.217, P<0.01), Physical Neglect scores (r=.217, P<0.01), Emotional Neglect scores (r=.213, P<0.01), and Sexual Abuse scores (r=.179, P<0.01) (Table 1).

There is a moderate, positive relationship between Catastrophizing and CTQ scores (r=.407, P<0.01), a moderate, positive relationship between Catastrophizing and Emotional Abuse scores (r=.363, P<0.01), Physical Neglect scores (r=.377, P<0.01), and Emotional Neglect scores (r=.381, P<0.01), a weak, positive relationship between Catastrophizing and Sexual Abuse scores (r=.249, P<0.01) and Physical Abuse scores (r=.298, P<0.01). There is a weak, positive relationship between Blaming Others and CTQ scores (r=.276, P<0.01), a weak, positive relationship between Blaming Others and Emotional Abuse scores (r=.234, P<0.01), Physical Abuse scores (r=.181, P<0.01), Physical Neglect scores (r=.252, P<0.01), Emotional Neglect scores (r=.278, P<0.01), and Sexual Abuse scores (r=.182, P<0.01) (Table 1).

The findings revealed a weak, negative relationship between Acceptance and CD-RISC scores (r=-.205, P<0.01), a weak, negative relationship between Acceptance and Tenacity and Personal Competence scores (r=-.224, P<0.01), and Tolerance of Negative Affect scores (r=-.181, P<0.01) (Table 2). There is a weak, positive relationship between Positive Refocusing and Spiritual Influences scores (r=.107, P<0.01). There is a moderate, positive relationship between Refocus on Planning and CD-RISC scores (r=.317, P<0.01), a moderate, positive relationship between Refocus on Planning and Tenacity and Personal Competence scores (r=.336, P<0.01), a weak, positive relationship between Refocus on Planning and Tolerance of Negative Affect scores (r=.252, P<0.01), and Spiritual Influences scores (r=.137, P<0.01) (Table 2).

There is a moderate, positive relationship between Positive Reappraisal and CD-RISC scores (r=.350, P<0.01), a moderate, positive relationship between Positive Reappraisal and Tenacity and Personal Competence scores (r=.359, P<0.01), a weak, positive relationship between Positive Reappraisal and Tolerance of Negative Affect scores (r=.295, P<0.01), a weak,

Tablo 4. The relation between Connor-Davidson Resilience Scale, Cognitive Flexibility Scale and Childhood Trauma Questionnaire

	CTQ	Emotional abuse	Physical abuse	Physical neglect	Emotional neglect	Sexual abuse
CD-RISC	-,333**	-,207**	-,231**	-,377**	-,361**	-,160**
Tenacity and Personal Competence	-,362**	-,238**	-,226**	-,405**	-,411**	-,170**
Tolerance of Negative Affect	-,254**	-,155**	-,208**	-,283**	-,259**	-,119*
Spiritual Influences	-,128*	-0,032	-,133**	-,174**	-0,096	-0,084
CFS	-,453**	-,298**	-,306**	-,477**	-,518**	-,220**

CTQ= Childhood Trauma Questionnaire, CD-RISC= Connor-Davidson Resilience Scale, CFS= Cognitive Flexibility Scale, **P<0.01, *P<0.05 Pearson correlation test

positive relationship between Positive Reappraisal and Spiritual Influences scores (r= 169, P<0.01). There is a weak, positive relationship between Rumination and Spiritual Influences scores (r=.114, P<0.01). There is a weak, negative relationship between Self-blame and CD-RISC scores (r=-.121, P<0.01), a weak, negative relationship between Self-blame and Tenacity and Personal Competence scores (r=-.158, P<0.01). There is a weak, negative relationship between Catastrophizing and CD-RISC scores (r=-.207, P<0.01), a weak, negative relationship between Catastrophizing and Tenacity and Personal Competence scores (r=-.253, P<0.01), and Tolerance of Negative Affect scores (r=-.130, P<0.01). There is a weak, negative relationship between Blaming Others and Tenacity and Personal Competence scores (r=-.121, P<0.01) (Table 2).

There is a weak, negative relationship between CFS and Acceptance scores (r=-.269, P<0.01), a weak, positive relationship between CFS and Positive Refocusing scores (r=.102, P<0.01), a moderate, positive relationship between CFS and Refocus on Planning scores (r=.454, P<0.01), a moderate, positive relationship between CFS and Positive Reappraisal scores (r=.419, P<0.01), a weak, negative relationship between CFS and Self-blame scores (r=-.225, P<0.01), a moderate, negative relationship between CFS and Catastrophizing scores (r=-.365, P<0.01), a weak, negative relationship between CFS and Blaming Others scores (r=-.233, P<0.01) (Table 3).

The findings revealed a negative relationship between CD-RISC and CTQ scores (r=-.333, P<0.01), negative relationship between CD-RISC and Emotional Abuse scores (r=-.207, P<0.01), Physical Abuse scores (r=-.231, P<0.01), Physical Neglect scores (r=-.377, P<0.01), Emotional Neglect scores (r=-.361, P<0.01), and Sexual Abuse scores (r=-.160, P<0.01) (Table 4). There is negative relationship between Tenacity and Personal Competence and CTQ scores (r=-.362, P<0.01), negative relationship between Tenacity and Personal Competence and Emotional Abuse scores (r= -.238, P<0.01), Physical Abuse scores (r=-.226, P<0.01), and Physical Neglect scores (r=-.405, P<0.01), Emotional Neglect scores (r=-.411, P<0.01), and Sexual Abuse scores (r=-.170, P<0.01). There is a weak, negative relationship between Tolerance of Negative Affect and CTQ scores (r=-.254, P<0.01), a weak, negative relationship between Tolerance of Negative Affect and Emotional Abuse scores (r=-.155, p<0.01), Physical Abuse scores (r=-.208, p<0.01), Physical Neglect scores (r=-.283, P<0.01), Emotional Neglect scores (r=-.259, P<0.01), and Sexual Abuse scores (r=-.119, P<0.01). There is a weak, negative relationship between Spiritual Influences and CTQ scores (r=-.128, P<0.01), a weak, negative relationship between Spiritual Influences and Physical Abuse scores (r=-.133, P<0.01), and Physical Neglect scores (r=-.174, P<0.01). There is a negative relationship between CFS, CD-RISC and CTQ scores (r=-.453, P<0.01), negative relationship between CFS and Emotional Abuse scores (r=-.298, P<0.01), Physical Abuse scores (r=-.306, P<0.01), Physical Neglect scores (r=-.477, P<0.01), Emotional Neglect scores (r=-.518, P<0.01), and Sexual Abuse scores (r=-.220, P<0.01) (Table 4).

Table 5. The relation between Connor-Davidson Resilience Scale and Cognitive Flexibility Scale

	CFS
CD-RISC	.515**
Tenacity and personal competence	.519**
Tolerance of negative affect	.478**
Spiritual influences	.202**

CD-RISC= Connor-Davidson Resilience Scale, CFS= Cognitive Flexibility Scale, **P<0.01 Pearson correlation test

The findings revealed positive relationship between CFS and CD-RISC scores (r=.515, P<0.01), positive relationship between CFS and Tenacity and Personal Competence scores (r=.519, P<0.01), Tolerance of Negative Affect scores (r=.478, P<0.01), and Spiritual Influences scores (r=.202, P<0.01) (Table 5).

DISCUSSION

Significant results were found in the study, which examined whether childhood traumas differed in psychological resilience levels, cognitive flexibility and cognitive emotion regulation strategies of adult individuals in a non-clinical sample. There a significant positive relation between childhood traumas and acceptance subscale of cognitive emotion regulation was discovered. Also, a significant positive relation with catastrophizing and a significant negative relation with refocus on planning was discovered. Memory, deci-

sion-making, behavioral, and relational decisions are all influenced by emotion. Social problems, physical sickness, and a number of psychopathological illnesses can all be caused by emotional dysregulation [49]. It may be possible to buffer people who have experienced childhood trauma from stressors by using more adaptive emotion management techniques (acceptance and refocusing on planning) and fewer maladaptive ones (catastrophizing).

Childhood trauma is known to increase the likelihood of developing PTSD as a result of subsequent events. Numerous studies have examined the relationship between earlier traumatic exposure and PTSD brought on by more recent trauma [50, 51]. It has been documented that early victimization in life has a detrimental impact on a raped woman's likelihood of developing PTSD and how long it will last. Similar results have been observed in soldiers engaged in war [1, 52]. A meta-analysis of 77 studies also revealed a study on PTSD risk factors, showing a history of childhood trauma as a risk factor after adult trauma. Regardless of gender, trauma type, or population analyzed, the meta-analysis found a positive association between populations [53]. Mostly, people with PTSD frequently diagnosed a variety of emotional issues. When recalling the traumatic experience, individuals first express negative emotional reactions like grief, shame, guilt, or rage, and these feelings are taken into consideration as diagnostic criteria [54]. Second, evidence backs up the link between PTSD and emotional value constructs. For example, regression, experiential avoidance, alexithymia, and dissociation have proven to be a relevant predictor of resilience [55-59].

A significant positive relation was found between refocus on planning subscale of cognitive emotion regulation and psychological resilience, and between refocus on planning and tenacity and personal competence subscale of psychological resilience. A significant positive relationship was also discovered between positive reappraisal subscale of cognitive emotion regulation and psychological resilience, and between positive reappraisal and tenacity and personal competence subscale of psychological resilience. This study lends to the theory that resilience has multiple dimensions and that a person can simultaneously be complexly traumatized and resilient [60]. Strategies of psychological resilience and emotion regulation make it easier for most individuals to lead a purposeful life despite the difficult conditions, experiences, and past traumatic experiences.

A significant positive relation was found between refocus of planning and positive reappraisal subscales of cognitive emotion regulation and cognitive flexibility, and a significant negative relation between catastrophizing subscale of cognitive emotion regulation and cognitive flexibility. The relation between cognitive flexibility subscales as the ability of an individual to change thoughts and actions in response to demands arising from situations [61] and functional and dysfunctional subscales of cognitive emotion regulation was also found in our study. Cognitive emotion regulation improves an individual's ability to organize and adapt to living conditions. Cognitive emotion regulation skills include self-blame, acceptance, rumination, positive refocusing, refocus on planning, positive reappraisal, putting into perspective, catastrophizing and blaming others as a cognitive method of controlling emotions and coping strategies. Before people react emotionally to the events they encounter, they reflect their emotions by going through a cognitive process. Difficulty in regulating emotional experience and expression according to contextual situations refers to a sense of difficulty in controlling the effects of emotional arousal, thoughts, behaviors, and interactions on order and quality [62].

Difficulties in emotion control were discovered to buffer the relationship between the severity of PTSD symptoms and substance usage in individuals who had experienced childhood maltreatment [63]. Similar to this, numerous studies have shown that the severity of PTSD symptoms is positively correlated with higher levels of overall emotion dysregulation as well as with particular dimensions like non-acceptance of emotions, difficulty engaging in goal-directed behavior in the face of challenging life circumstances, difficulty controlling behaviors in the face of distress, limited access to efficient emotion regulation strategies, and lack of emotional clarity [64-66]. These data indicate the link between PTSD symptoms and emotional dysregulation. Additionally, studies have demonstrated that childhood trauma can result in the development of maladaptive emotion regulation mechanisms that establish the foundation for the onset and maintenance of depression [67]. Evidence also suggests that the capacity to control emotions is developed early in life [68]. The relationship between maladaptive emotion

regulation mechanisms and depression in response to childhood trauma has been examined in research on the mediating role of emotion regulation [69, 70]. A study showed that there is a connection between negative childhood experiences and cognitive emotional regulation and cognitive function [71]. Another study confirmed the assumption that negative childhood experiences affect children's general cognitive abilities and executive functioning [72].

According to the research findings, A significant negative relationship was discovered between psychological resilience and childhood traumas, and emotional neglect, physical neglect subscales. There's also a significant negative correlation between childhood trauma subscales and tenacity and personal competence subscale of psychological resilience, and between cognitive flexibility and psychological resilience. Social acceptance, social support, good relationships, and secure living situations during adolescence are environmental elements that presumably promote good mental health and shield against PTSD despite traumatic experiences [29, 73-75]. Positive family traits are linked to successful post-traumatic kid adjustment. One of the most effective protective factors against early life traumas has been good parenting [76]. It has also been highlighted that hope is an important variable in resilience [77].

A significant negative relation was found between cognitive flexibility and emotional abuse, physical abuse, and neglect subscales. A significant positive relation was found between cognitive flexibility and psychological resilience subscales. The incidence of adverse childhood experiences is high, and cognitive flexibility is significantly affected by negative childhood experiences [78]. Negative childhood experiences can also be described as triggers for poor emotion regulation [79]. Research findings are consistent with evidence for a link between negative childhood experiences and emotional regulation problems and decreased emotional awareness [80]. It was found that there is a significant relation between childhood distress and emotion regulation [81].

Limitations

The limitations of this study are that 395 people living in Turkey constitute the sample of this study and that the research data only consists of the data obtained from the measurement tools used. Studies on childhood traumas and their results show that psychological resilience, cognitive flexibility and emotion regulation skills are determinants in the context of risk and protective factors in evaluating mental health.

CONCLUSION

From this point of view, it is important to reveal the relation between traumatic childhood experiences and psychological resilience, cognitive flexibility and cognitive emotion regulation strategies so that they do not form the basis of adult mental health problems. Research on these variables will contribute to clinical psychology practices in terms of helping individuals to examine their thoughts and emotions, and to be aware of negative coping and rigid, inflexible cognitive styles and negative thinking patterns. Research findings in the context of psychological resilience, cognitive flexibility and emotion regulation concepts and processes will be guiding instead of ineffective coping strategies of past experiences in the face of negative and stressful life events.

Authors' Contribution

Study Conception: KG; Study Design: KG, ZGD; Supervision: KG, ZGD; Funding: N/A; Materials: N/A; Data Collection and/or Processing: CSY; Statistical Analysis and/or Data Interpretation: KG; Literature Review: KG, ZGD, CSY; Manuscript Preparation: CSY and Critical Review: KG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

Ethics Approval and Consent to Participate

The 1964 Declaration of Helsinki and its updates, as well as any other relevant ethical principles, are followed in all techniques employed in studies involving human beings. Participants in this study gave their full, informed permission. This study approved by Üsküdar University Non-interventional Research Ethics Committee (Date: 26.03.22021, Decision no. 2021-45).

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Comparison of testicular stiffness values obtained by ultrasound shear-wave elastography and magnetic resonance elastography in normal healthy volunteers

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ABSTRACT

Objectives: This study aimed to contribute to the standardization of elastography by comparing stiffness values obtained from ultrasound shear wave elastography (SWE) and magnetic resonance elastography (MRE) of the testicular parenchyma in healthy volunteers.

Methods: A total of 22 healthy volunteers (44 testes) were included in this study. Of the 26 cases analyzed, four were excluded from the study due to the exclusion criteria. The testicular parenchyma of the included patients was evaluated using MRE and SWE examinations. Pearson's correlation test was used to calculate the correlation between age and stiffness values, testicular volumes and stiffness values, and stiffness values from both examinations.

Results: The mean SWE stiffness of the right testes was 5.560±3.1 kPa and the mean SWE stiffness of the left testes was 5.361±2.9 kPa. The mean MRE stiffness of the right testes was 6960.11±460 Pa and the mean MRE stiffness of the left testes was 6560.19±310 Pa. There was no significant correlation between SWE and MRE stiffness values (P=0.096). There was also no significant statistical correlation between SWE and MRE stiffness values and testicular volumes (P=0.17 and P=0.093, respectively).

Conclusion: No statistical correlation was found between the stiffness values obtained by SWE and those obtained by MRE in the normal testicular parenchyma. Additionally, no conclusive relationship between stiffness levels, age, or testicular volume was discovered.

Keywords: Elastography, magnetic resonance imaging, stiffness, testis, ultrasonography

Ultrasonography (USG) is the most sensitive and specific examination method for the testes. However, it is limited to evaluating the surrounding vascular structures and arteries supplying the testicular parenchyma with Doppler, roughly observing the intraparenchymal structures on a greyscale, and providing objective data on the testicular parenchyma only for easily visible peripheral and intraparenchymal mass lesions and apparent vascular abnormalities [1, 2].

Although normal radiological findings are detected on greyscale USG and color Doppler examination of the testicular parenchyma in a small number of patients presenting with infertility, obvious abnormal-

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ities in the testicular parenchyma, its size and volume, and pathological conditions other than varicocele are uncommon radiological findings in infertility [1].

It is not possible to detect more micro-level abnormalities in the testicular parenchyma on greyscale USG examination, except for space-occupying lesions in the parenchyma or point calcifications, known as microlithiasis and inflammatory processes. However, varicocele, atrophy, and parenchymal grayscale abnormalities have not been detected in many patients with infertility. As the testis is not a suitable organ for biopsy, hardness remains a measurable parenchyma parameter [2].

Elastography is a sonographic imaging technique that provides qualitative and/or quantitative information regarding tissue stiffness. It is based on the degree of deformation of the analyzed lesion compared with the surrounding tissue. Images are obtained in color tones from red to blue, or vice versa, and from soft to hard, depending on the tissue stiffness. This color map provides both relative and qualitative data. Shear wave elastography (SWE) is a newly developed real-time sonographic imaging technique that provides quantitative information (in N/m2 or kPa) on the elasticity of soft tissues by sending transverse waves to the examined tissue [2].

Elastography is considered the gold standard radiological method for testicular imaging and has been used as an additional diagnostic examination in recent years because it offers additional parameters while remaining faithful to the basic principles of ultrasonography. However, the procedure is operator dependent and a wide range of unstandardized data has been presented in the literature. Therefore, the idea of standardizing this examination by comparing it with magnetic resonance elastography (MRE), which works with a similar logic but with different physical laws, has emerged. These comparison and standardization studies have been carried out extensively on liver imaging, in which elastography is extensively used.

METHODS

Ethical Issues, Settings, and Study Design

Our study was conducted at the Radiology Department of BHT Clinic Istanbul Tema Hospital, with the approval and permission of the Academic Board and

Fig. 1. Touch panel and button panel of GE Logic S8 brand/model USG device with elastography software (elastography button is circled in red on the right) and a 9 Mhz linear probe with hardware elastography features (shown from two different directions on the left).

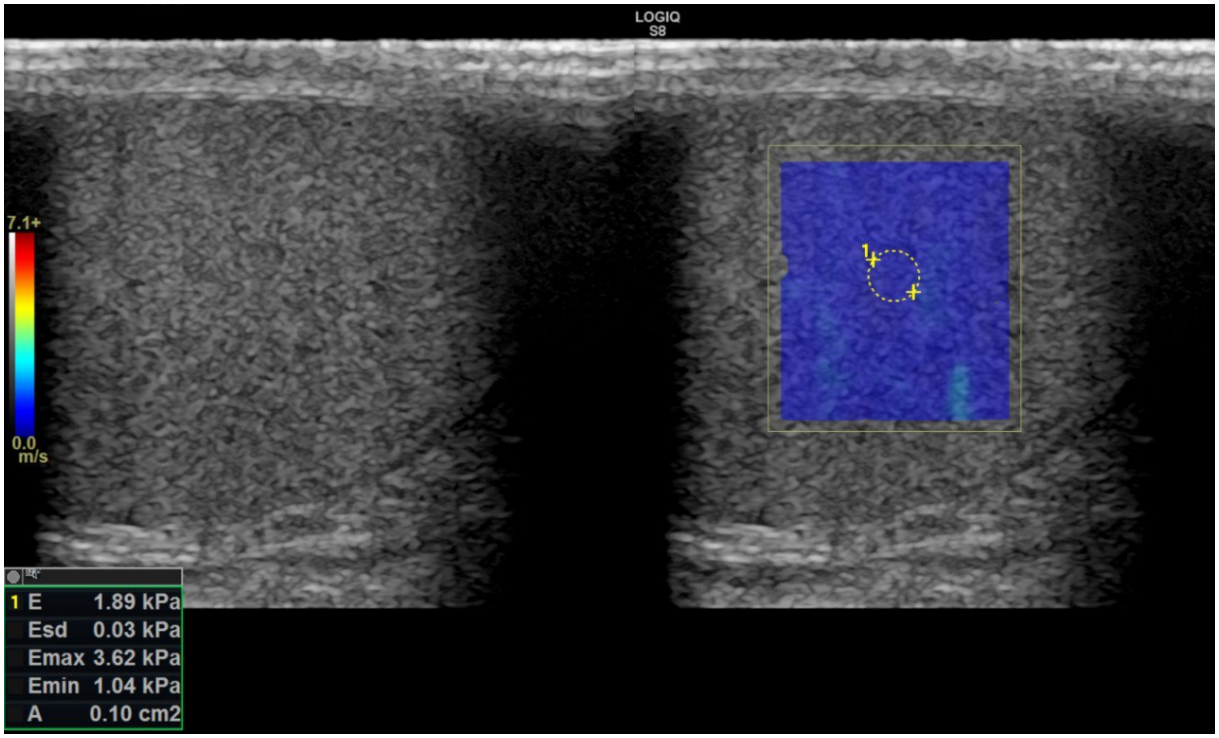

Fig. 2. SWE: Elastography image in the right window and simultaneous greyscale image in the left window. In the image on the right, a 0.1 cm2 ROI area (area surrounded by yellow dots numbered 1) was measured from the central part of the testis within the colored blue elastogram window. In the lower-left corner of the image, there are measurement values in units of kPa.

Ethics Committee of Istanbul Nişantaşı University (Date: 14.08.2023, No: 2023/33-12).

A total of 26 healthy volunteers were examined using SWE and MRE with permission from the university and hospital between August and November 2023. Our exclusion criterion was the presence of a herniated scrotal and/or epididymal abnormality on USG and/or magnetic resonance imaging (MRI). Four cases were excluded from the study due to microlithiasis in the testis, cysts in the epididymis, incidental and asymptomatic small testicular size (atrophy or hypoplasia), and hydrocele. Thus, 22 cases (44 testes) were evaluated in the present study. The obtained data were comparatively evaluated. SWE and MRE examinations were evaluated by two radiologists with more than 10 years of experience in scrotal USG and MRI and more than 2 years of experience in elastography.

Fig. 3. The apparatus called "passive driver," which is one of the extra equipment for MRE examination, is shown from the back, front, and side in three images from left to right.

Fig. 4. The so-called "active driver", which is an additional component of the MRE examination, is shown.

USG SWE Device, Technique, Assessment, Data Collection and Outcomes

The study was conducted using a General Electric (GE) brand Logic S8 model (2019) USG device with elastography software, utilizing a 9 MHz linear probe with elastography hardware (Fig. 1).

Ultrasonographic examination was performed with the patient in the supine position and the penis was positioned on the abdomen with a blanket covering it, ensuring that it was removed from the examination area.

Light pressure was applied to measure the three dimensions of each testis while in the supine posture. Testicular volume was estimated by the USG machine using the following method, based on comparable earlier investigations: Volume of testis = width × length × height × 0.523, expressed in milliliters (mL) [3, 4].

After completing the greyscale USG test, the radiologist initiated the SWE examination. Two-dimensional SWE was performed with the patient in a supine resting state. The probe was held as steady as possible during the SWE evaluation to minimize artifacts and inaccurate measurements. The right window displays the elastography image, whereas the left window displays the simultaneous grayscale image (Fig. 2). Elastographic examinations were conducted with minimal compression for at least 5 seconds to reduce motion artifacts. ROIs (regions of interest) were placed to measure a round area of 0.1 cm2 in the central part of the normal testicular parenchyma, as it is known that measurements become more standardized in this region, and the area becomes smaller in SWE [4, 5].

The ROI area (0.1 cm2 was our study's most optimum measurable standard (Fig. 2). Quantitative data mean (Emean) was obtained in kPa from the normal testicular parenchyma. In our study, the SWE images saved in our PACS archive and the measurements made during the procedure were retrospectively reviewed. The measured values were obtained in kPa units in the SWE. However, to compare them statistically with the values in Pa units in MRE, they were multiplied by 1000 to obtain the Pa value equivalents.

Real-time SWE measurements were performed during the examination and evaluated by transferring the data to the closed-circuit Clear Canvas Picture Archiving and Communication Systems (PACS) mod-

Fig. 5. **In the leftmost picture, the passive driver device shown in Figure 2 is observed in the suprapubic region. In the central picture, it is fixed with a coil, and in the rightmost picture, it is observed with a coil placed on it.**

ule in our hospital. Data from both examinations were collected and documented.

MRI and MRE Protocols Assessment, Data Collection, and Outcomes

All MRE examinations were conducted on a 3 Tesla General Electric Signa Architect MRI scanner with commercially available software and hardware (GE Healthcare, Waukesha, WI, and Resoundant Inc., Rochester, MN) [6, 7].

Technically, there are two non-standard extra hardware apparatuses in the MR device: a special device called a "passive driver" (Fig. 3) and another device called an "active driver" (Fig. 4) for elastography [7].

The subjects were positioned supine, head first, with a body AIR coil centered at the level of the region of interest [6]. Mechanical shear waves at 60 Hz were generated by using an active driver system outside the

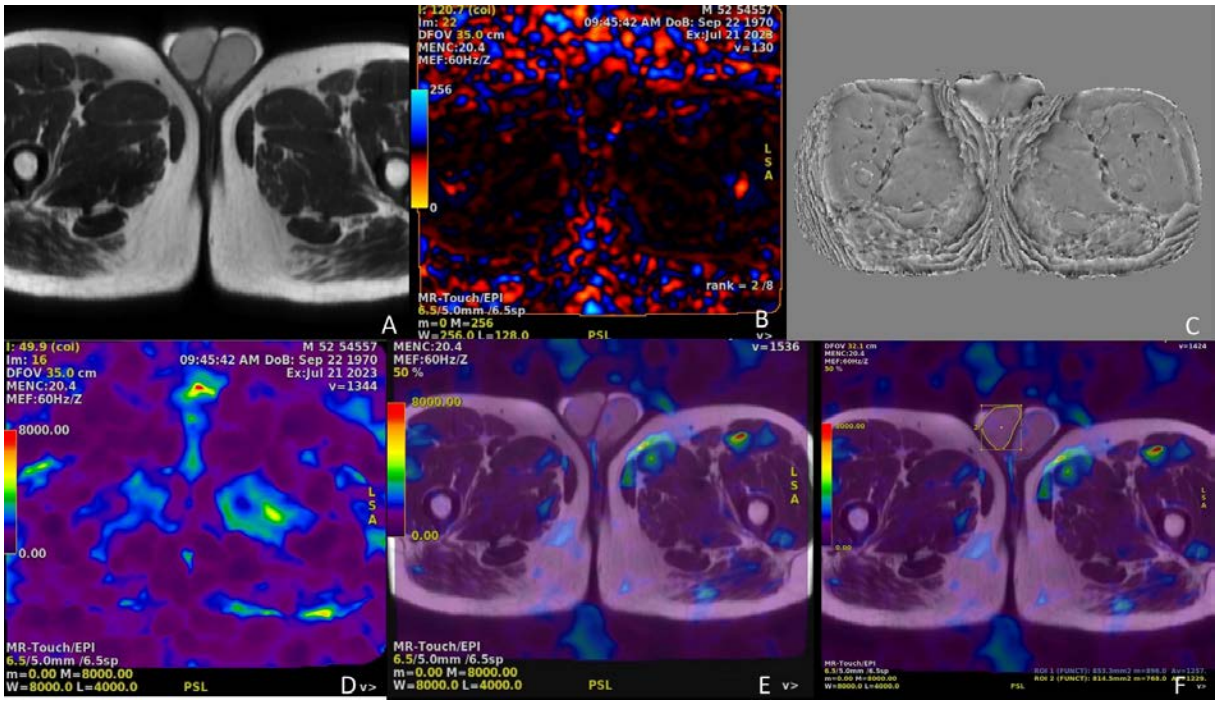

Fig. 6. **In the top row, the leftmost image (A) is the axial spin-echo T2 sequence image, the middle image (B) is the elastography dynamic pressure color map, and the rightmost image (C) is the wave image. The leftmost image (D) is the stiffness color map and the middle image (E) is the elastography fusion image. In the rightmost image (F), the right testicular parenchyma was surrounded by a yellow line border and the left testicular parenchyma was surrounded by a blue line border, and measurements were made in Pa units from all of these areas of both testicular parenchymas over the fusion image.**

MRI room. A rigid passive driver secured against the anterior wall of the pelvis was used to transmit mechanical vibrations from the active transducer to the body (Fig. 5). A rigid driver is the standard device used in the FDA-cleared commercially available implementation of MRE technology. An experienced MRI technologist performed the MRE examinations in this study.

The propagating shear waves were imaged using a motion-sensitized imaging sequence. A (Spin-Echo echo planar imaging (SE-EPI) sequence was used to acquire axial wave images with the following parameters: repetition time (ms)/echo time (ms), 50/23; continuous sinusoidal vibration, 60 Hz; field of view, 32-42 cm; matrix size, 256 × 64; flip angle, 30°; section thickness, 10 mm; four evenly spaced phase offsets; and four pairs of 60-Hz trapezoidal motion-encoding gradients with zeroth and first moment nulling along the through-plane direction. All processing steps were applied automatically, without manual intervention, to yield quantitative images of tissue shear stiffness in kilopascals. The MR elastographic images were interpreted by staff radiologists in the Department of Radiology.

MRE images were processed using commercially available MR-Touch software (GE Healthcare, Waukesha, WI, and Resoundant Inc., Rochester, MN, USA) to generate magnitude, phase, and wave maps (Fig. 6) [6, 7]. Six relative stiffness images were reconstructed for each slice location. The resulting data were measured using ROIs in the muscle on anatomical T1 images and copied onto MRE stiffness maps to measure the stiffness values (or elastograms) in the Pascals.

Statistical Analysis

The MRE and SWE mean stiffness values were statistically analyzed in the Pascals. The SWE and MRE data were compared using the analysis of variance test, and chi-square and binary comparisons were performed using Student's t-test. Pearson's correlation test was used to calculate the correlation between age and stiffness values, testicular volumes and stiffness values, and stiffness values from both examinations. Statistical analysis was performed using SPSS v.23.0 (IBM Corp., Armonk, NY, USA). Two-tailed values of $P<0.05$ were considered statistically significant.

RESULTS

The youngest patient was 23 years old, and the oldest patient was 48 years old, with a mean age of 36.2±11 years). When analyzing the right testicular volumes of our patients, the largest value was 15 mL, and the smallest value was 12 ml. The mean right testicular volume was 13.4±3.1 ml. When analyzing the volumes of the left testes, the largest volume was 15.2 ml, and the smallest was 11 mL. The mean left testicular volume was 13.6 ± 3.2 mL (Table 1). No significant correlation was observed between age and testicular volume (Table 2).

When analyzing US-E stiffness values, the smallest stiffness value for the right testis, was 4.216 kPa, the highest stiffness value was 7.312 kPa, and the mean stiffness value was 5.560±3.1 kPa. For the left testis, the smallest and highest stiffness values were 4.324 kPa, 6.914 kPa, and 5.361±2.9 kPa (Table 3).

Because MRE stiffness values were given by the MR device in Pascal (Pa) units, data were collected in this unit. When analyzing the MRE values, it was observed that the smallest stiffness value for the right testis was 5302.12 Pa, the highest stiffness value was 9211 Pa, and the mean stiffness value was 6960±460 Pa. For the left testis, the smallest stiffness value was 5562 Pa, the highest stiffness value was 8913 Pa, and the average stiffness value was 6560±310 Pa (Table 4).

In the statistical correlation analysis performed between the testicular volume obtained from USG and the SWE stiffness values and the stiffness values measured by MRE ($P=0.17$ and $P=0.093$, respectively), and were found to be greater than 0.05, respectively (Table 5). This indicates that there were no statistically significant differences between the parameters.

When statistically correlating the SWE and MRE

Table 1. Smallest, largest and mean volumes of both testes volume (mL)

	Right	Left
Min.	12	11
Max.	15	15.2
Mean±SD	13.4±3.1	13.6±3.2

Max.=maximum, Min.=:minimum, SD=standart deviation, mL= milliliter

Table 2. Table showing the relationship between testicular volume and age

Age (years)	Right testis volume (mL)	Left testis volume (mL)
36.2±11	13.4±3.1	13.6±3.2
	P=0.083	P=0.27

Data are shown as mean±standard deviation. P value (Pearson's correlation coefficient), mL= milliliter

Table 3. SWE stiffness values (kPa)

	Right	Left
Min.	4.216	4.324
Max.	7.312	6.914
Mean±SD	5.560±3.1	5.361±2.9

SWE=shear wave elastography, kPa=kilopascal, Max.=maximum, Min.=:minimum, SD=standart deviation

Table 4. MRE stiffness values (Pa)

	Right	Left
Min.	5302.12	5562.23
Max.	9211.10	8913.22
Mean±SD	6960.11±460	6560.19±310

MRE=magnetic resonance elastography, Pa=pascal, Max.=maximum, Min.=:minimum, SD=standart deviation

Table 5. Binary comparison between USG volume versus US-E stiffness and MRE stiffness

USG volume (mL)	SWE stiffness (kPa)	MRE stiffness (Pa)
	P=0.17	P=0.093

USG=ultrasonography, SWE=shear wave elastography, MRE=magnetic resonance elastography, kPa=kilopascal, Pa=pascal. P value (Pearson's correlation coefficient)

Table 6. Binary comparison of each mean SWE stiffness and MRE stiffness values four each testis

Device	Mean stiffness value	P value
SWE	5.431 kPa	0.096
MRE	6763.44 Pa	

SWE=shear wave elastography, MRE=magnetic resonance elastography, kPa=kilopascal, Pa=pascal

P value (Pearson's correlation coefficient)

stiffness values of the cases, no significant correlation was found between the values (Table 6).

DISCUSSION

Numerous studies have been conducted on different normal distributions of testicular volume for different age groups [7-9]. When analyzing the testicular volumes of our patients, we observed that they were within the normal range for adults. This is because we included subjects from the normal population in the study. All of our patients were in the young and early middle age groups. When comparing age and testicular volume, no significant statistical correlation was found, which is consistent with most other data in the literature [9-13].

SWE is a relatively novel, reliable, and non-invasive imaging technique that provides data on histopathological alterations in many tissues. It offers a valuable quantitative assessment of tissue stiffness and is extremely helpful in assessing parenchymal diseases. SWE has been used in very few comparative investigations of the impact of varicocele on testicular parenchyma [14, 15].

When analyzing the SWE stiffness values, it was observed that they were similar to those in the literature. Most studies in the literature, especially in adults, aim to identify conditions that do not cause significant abnormalities in the testicular parenchyma on grayscale USG examination, especially varicocele. Although our number of cases and, therefore, our sample size was small, our similar stiffness value findings with the literature revealed that most pathologies that do not give significant findings in the testicular parenchyma on greyscale USG do not give significant findings on SWE.

No significant difference was found in the statistical analysis of the volume obtained by ultrasonographic calculation by measuring three dimensions compared to SWE and MRE. This result is consistent with data in the literature [13].

The MRI device provided the MRE stiffness values in the pascals. Currently, MRE is mostly used for the liver, and researchers who use this examination also use the Pascal unit. The MRE devices and software were calibrated to provide stiffness values in the Pascals.

The use of MRI of the testis in the literature is mostly to create a multiparametric examination for recognizing malignant lesions [16]. Although the use of US-E for testes is considerable in the literature, the same is not the case for MRE. We did not find any MRE studies of the testes in the literature. The MRE component of our study is a preliminary study. This may be criticized because it may produce meaningless results for statistical sampling and power analysis. However, since MRE is a test whose standards are not fully established, except for liver fibrosis, only pioneering studies can contribute to the literature. Similarly, there is only one study in the literature on the spleen, consisting of 16 patients [17].

In the statistical comparative analysis of the data obtained for each testicle, there was no significant correlation between SWE and MRE findings (P=0.096). This nonsignificant correlation may be due to several factors and limitations. One of the most important of these factors is that the current MRE modality is not standardized enough to perform testicular examination.

Limitations

The lack of data on the MRE examination of the testes in the literature constitutes our most significant limitation. Another limitation is the small number of patients. Another limitation is that we performed MRE measurements from the whole parenchyma and SWE measurements from a single location.

CONCLUSION

In our study, we compared the MRE and SWE stiffness values of normal testicular parenchyma but did not find a statistically significant correlation between the two values. In addition, no significant correlation was found between stiffness values and age and testicular volume. The lack of a significant correlation may be attributed to the limitations and absence of standardized application standards for MRE in testicular examinations. Further research with more patients under more standardized conditions is needed to confirm this result. Despite the small number of patients, our study is significant, as it pioneers the literature on this subject.

Authors' Contribution

Study Conception: SP, LK; Study Design: SP, LK; Supervision: SP, LK; Funding: SP, LK; Materials: SP, LK; Data Collection and/or Processing: SP, LK; Statistical Analysis and/or Data Interpretation: SP, LK; Literature Review: SP, LK; Manuscript Preparation: SP, LK and Critical Review: SP, LK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The relationship between immun staining and progression markers in IgA nephropathy

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ABSTRACT

Objectives: To determine the relationship between immunofluorescence microscopy findings and progression markers at the time of diagnosis in immunoglobulin A (IgA) nephropathy.

Methods: Fifty-two patients with pathological diagnosis of primary IgA nephropathy by showing mesangial and mesangiocapillary IgA-dominant immune deposits in immunofluorescence microscopy were included in the study. At the time of biopsy, biochemical and hematological data, Oxford MEST score and immunofluorescent staining findings were recorded. The serum IgA/C3 ratio was calculated. The immunofluorescence results of the total group were compared with the markers of progression at the time of diagnosis, estimated glomerular filtration rate (eGFR), hematuria, proteinuria, creatinine, and serum IgA/C3 ratio.

Results: The mean age of the study group was 39.9±12.3 years and 55.8% were male. eGFR, albumin, hemoglobin, IgM were significantly lower, and uric acid and hematuria were significantly higher in those with proteinuria above 1 g compared to those with low proteinuria. A positive correlation was found between IgA, C3 and lambda staining and hematuria. There was a positive correlation between C3 staining and creatinine, and a positive correlation with hematuria. A correlation was found between Kappa staining and eGFR.

Conclusions: Correlation was found between IgA, C3 and lambda staining and hematuria at the time of diagnosis in IgA nephropathy.

Keywords: Immunoglobulin A nephropathy, immunostaining, hematuria

Immunoglobulin (IgA) nephropathy is the most common primary glomerular disease worldwide, but its geographic distribution varies greatly [1]. In addition to mild cases with abnormal urine findings, it shows a wide clinical spectrum in the form of rapidly progressive renal failure [2-4]. In a period of 20-30 years, end-stage renal disease develops in one third of the cases [5].

The Oxford classification is very important, as the prognosis and choice of treatment depend on the interpretation of the biopsy material. MEST score; M: mesangial hypercellularity (M0=<50%, M1=>50%), E: endocapillary hypercellularity (E0=absent, E1=present), S: segmental glomerulosclerosis (S0=absent, S1=present), T: tubular atrophy /interstitial fibrosis (T0=<25%, T1=26-50%, T2=>50%). An increase in total score during biopsy was found to be associated with poor prognosis [6, 7].

The complement system is an important component of innate and adaptive immunity and a comple-

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ment to antibody-triggered responses. Classical (C1), alternative (D, B, Properdin) and lectin (mannose-binding)-stimulated [8, 9]. IgA nephropathy (IgAN) is thought to arise due to autoimmunity involving abnormal activation of both alternative and mannose-binding lectin (MBL) pathways. MBL, an important protein in innate immunity, functions as a pattern recognition molecule to recognize carbohydrate patterns of microorganisms and activate complement via the lectin pathway.

After multiple adjustments, MBL deficiency IgAN was independently associated with poor outcomes [10]. Both local glomerular and systemic complement activation play a key role in the pathogenesis and clinical presentation. Serum complement levels are indicative of the degree of activation. The role of autoimmunity was emphasized in the most recent 4-hit hypothesis study [11-19]. Both IgA and C3 play important roles in IgAN pathogenesis [20].

The pathogenesis of light chains in glomerulopathies, where the main site of catabolism is kidney, is not clear. IgAN is characterized by increased plasma IgA1 levels and predominant mesangial polymeric IgA1 deposits. Increased binding of polymeric lambda IgA light chain to human mesangial cells may be responsible for disease immunity. Again, the production of IgA1 and IgA2 by mesangial cells may be a factor contributing to mesangial deposition [21].

It is still unclear whether the IF staining findings given alongside the Oxford classification have a predictive value [22]. IgA/C3 was expressed as a predictive biomarker [20, 23]. We planned to investigate the relationship between IF staining and progression markers eGFR, proteinuria, hematuria, creatinine and serum IgA/C3.

METHODS

Fifty-two cases diagnosed as primary IgAN because of mesangial and mesangial-capillary dominant immunofluorescent IgA deposition in kidney biopsy performed in our clinic between 2017 and 2020 were retrospectively included in the study. Those with secondary cause of IgAN were not included in the study. Demographic data such as age and gender at the time of biopsy, mean arterial pressure (MAP), urea, creatinine, estimated glomerular filtration rate (eGFR), albumin, hemoglobin, cholesterol, uric acid, serum IgG, IgA, IgM, C3, C4, IgA/IgG and IgA/C3 ratios, hematuria (>5 erythrocyte/hpf), leukocyturia (>5wbc/hpf), 24-hour urine proteinuria were recorded. eGFR was calculated with the CKD-EPI formula.

All kidney biopsies were evaluated by light and immunofluorescence (IF) microscopy. After the biopsy, the tissue, which quickly reaches the pathology unit in physiological saline, was frozen with snap-frozen in liquid nitrogen for IF, and 4µ sections were made. Sections were stained for at least 2 slides for IgG, IgA, IgM, C3, C1q, kappa and lambda. Pathology reports included IF staining between 0-3(+) and Ox-

Table 1. Demographic characteristics and laboratory result of the total group

Variables	n=52
Age (years)	39.88±12.34)
Gender, n (%)	
Females	23 (44.2)
Males	29 (55.8)
MAP (mmHg)	99.65±12.27
Laboratory	
Creatinine (mg/dL)	1.06 (1.46)
eGFR (mL/min)	76.0 (82.63)
Albumin (g/dL)	4.02 (0.60)
Hemoglobin (g/dL)	12.35 (2.33)
Cholesterol (mg/dL)	184.94±50.24
Uric acid (mg/dL)	6.07±1.72
IgG (mg/dL)	1134.55±385.24
IgA (mg/dL)	353.43±148.26
IgM (mg/dL)	107.29±52.32
C3 (mg/dL)	139.85±26.40
C4 (mg/dL)	32.77±10.05
Hematuria	18.0 (45.75)
Leukocyturia	3.0 (5.0)
IgA/IgG	0.31 (0.19)
Proteinuria	1431 (1925)

Data are shown as mean±standard deviation or median (interquartile range) or n (%). MAP=Mean arterial pressure, eGFR=estimated glomerular filtration rate, Ig=immunoglobulin, C=complement, Hematuria >5 erythrocyte/hpf, Leukocyturia=(wbc/hpf), proteinuria=mg/24 hours.

Table 2. Comparison of proteinuria ≥1g and proteinuria <1g diagnosed with IgAN

	Proteinuria ≥1 (n = 34)	Proteinuria <1 (n = 18)	Statistics (t, z or χ^2)	P value
Age (years)	41.52 ± 12.1	37.05 ± 12.5	1.250	0.217
Gender, n (%)			0.014	0.982
Females	15 (65.2)	8 (34.8)		
Males	19 (65.5)	10 (34.5)		
MAP (mmHg)	100.82±11.04	97.44±14.40	.943	0.350
Laboratory				
Creatinine (mg/dL)	1.52 (2.50)	0.96 (0.45)	-1.170	0.077
eGFR (mL/min)	56.0 (83.23)	90.80 (33.53)	-2.616	**0.009**
Albumin (g/dL)	4.04 (.87)	4.33 (0.41)	-2.646	**0.008**
Hemoglobin (g/dL)	11.87 (3.13)	13.25 (2.49)	-2.098	0.**041**
Cholesterol (mg/dL)	192.02±54.30	171.55±39.48	1.412	0.164
Uric acid (mg/dL)	6.41±1.78	5.42±1.43	2.037	**0.047**
CRP (mg/dL)	3.20 (10.59)	2.00 (6.57)	-2.213	**0.027**
IgG (mg/dL)	1099.8±404.3	1200.1±347.8	-0.892	0.377
IgA (mg/dL)	358.0±141.5	344.7±164.1	0.304	0.762
IgM (mg/dL)	95.9±40.2	130.5±64.7	-2.440	**0.018**
C3 (mg/dL)	136.9±27.0	145.3±25.0	1.148	0.257
C4 (mg/dL)	33.9±10.6	30.5±8.5	1.019	0.315
Hematuria (rbcs/hpf))	26.0 (45.0)	5.5 (19.7)	-2.040	**0.041**
Leukocyturia (wbc/hpf)	3.0 (5.0)	3.0 (5.75)	-0.481	0.630
IgA/IgG	0.35 (0.20)	0.29 (0.12)	-1.135	0.256
IgA/C3	2.68±1.19	2.40±1.12	0.813	0.420
Immunostaining				
IgA	3 (1)	3 (1)	-0.278	0.781
IgG	3 (1)	--	-1.873	0.061
IgM	0 (1)	0 (1)	-0.826	0.409
C3	2 (2)	2 (1.25)	-0.614	0.539
Kappa	0.0 (1)	1 (2)	-0.737	0.461
Lambda	1 (2)	1 (2)	0.246	0.805
MEST				
M	1 (0)	1 (0)	-0.48	0.962
E	1 (1)	0.5 (1)	-0.809	0.418
S	1 (0.25)	1 (1)	-1.152	0.249
T	1 (2)	0 (1)	-2.061	**0.039**

Data are shown as mean±standard deviation or median (interquartile range) or n (%). MAP=Mean arterial pressure, eGFR=estimated glomerular filtration rate, Ig=immunoglobulin, IgAN=IgA nephropathy, C=complement, CRP=C-reactive protein, Hematuria >5 erythrocyte/hpf, Leukocyturia=(wbc/hpf), M=mesangial hypercellularity, E=endocapillary hypercellularity, S=segmental glomerulosclerosis, T=tubular atrophy /interstitial fibrosis

ford-MEST scoring (pre-2017 scoring). M; Mesangial proliferation M0<50% or, M1>50%, E; Endocapillary hypercellularity E0=absent or E1=present, S; Segmental sclerosis S0=absent or S1=present, T; Tubular atrophy/interstitial fibrosis was evaluated as T0=0-25%, T1=26-50%, T2>50%. The other tissue piece was fixed with 10% formalin and 4µ sections were taken in paraffin blocks. Periodic acid Schiff was stained with hematoxylin eosin and trichrome. Results could not be given because C4d staining could not be performed routinely in our hospital. Pathology samples were evaluated twice. The IF results of the total group were compared with the progression markers, eGFR, hematuria, proteinuria, creatinine and IgA/C3, at the time of diagnosis. According to the C3 and IgA storage density, the categorical data as 0, +, ++, +++ were converted into numerical data as 0, 1, 2, and 3 positive. C3 storage was evaluated as<2+ and ≥2+.

The study was carried out with the permission of Clinical Research Ethics Committee of Ankara Training and Research Hospital (Date: 14.12.2022, Decision No: E-22-1145). Informed consent was obtained from all patients included in the study, which was conducted in accordance with the principles of Helsinki.

Statistical Analysis

Analyses were conducted using BM Statistical Package for the Social Sciences 22.0 version (IBM SPSS Corp.; Armonk, NY, USA). All data were first checked for normality of distribution using the Kolmogorov-Smirnov and Shapiro-Wilk test. Normally distributed data are presented as the mean±standard deviation and others were represented as the median and inter-quartile range. Pearson chi-square and Fisher's exact test were used for categorical variables.

Table 3. Morphologic variables of Oxford-MEST classification.

n = 52	n	%
M (0/1)	3/49	5.8/94.2
E (0/1)	22/30	42.3/57.7
S (0/1)	15/37	28.8/71.2
T (0/1/2)	22/18/12	42.3/34.6/23.1

M=mesangial hypercellularity, E=endocapillary hypercellularity, S=segmental glomerulosclerosis, T=tubular atrophy/interstitial fibrosis

Spearman correlation was used for correlation analysis. Uni and multivariance regression analysis was used for factors affecting progression markers. P<0.05 was accepted as the significant level.

RESULTS

Demographic and laboratory data of 52 cases in total are presented in Table 1. Of 55.8% the cases were males, and the mean age was 39.9±12.3 years. Hypertension was seen in 8%, new onset diabetes mellitus in 3.8%., had no history of autoimmune disease.
When we evaluated the total group according to the rate of proteinuria, which is the most important marker of progression, those with proteinuria of 1 gram or more (65.3% of 34 cases) compared to those with less than 1 gram, e-GFR (z=-2.616, P=0.009), albumin (z=-2.646, P=0.008), serum IgM (z=-2.440, P=0.018) and hemoglobin (z=-2.098, P=0.041) were significantly lower, uric acid (t=2.037, P=0.047) and hematuria (z=-2.040, P=0.041) was found to be

Table 4. Frequency of deposited antibody intensity scores

Immunostaining	0	+	++	+++
IgA	0	2	16	34
IgG	46	3	1	1
IgM	35	12	4	1
C3	5	14	19	14
Kappa	27	13	11	1
Lambda	19	10	19	2

Ig = immunoglobulin, C = complement

Tablo 5. Relationship between immunofluorescent staining and progression markers

IF (n = 52)	IgA		IgG		IgM		C3		Kappa		Lambda	
	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value
Creatinine	-0.033	0.81	0.193	0.170	0.003	0.981	0.270	**0.053**	-0.266	0.056	-0.283	**0.042**
eGFR	-0.027	0.847	0.142	0.317	-0.041	0.771	-0.226	0.107	0.325	**0.019**	0.226	0.107
Hematuria	0.403	**0.003**	0.208	0.138	-0.142	0.315	0.329	**0.017**	0.037	0.755	0.367	**0.007**
IgA/C3	0.134	0.343	0.044	0.758	-0.142	0.315	0.258	0.065	0.126	0.364	0.135	**0.**340
Proteinuria	0.008	0.955	0.213	0.129	0.165	0.241	0.098	0.488	-0.148	0.255	0.010	0.947

IF = immunofluorescent staining, eGFR = estimated glomerular filtration rate, Ig = immunoglobulin, C = complement

significantly higher. There was no significant difference between mean arterial pressure, creatinine, hemoglobin, cholesterol, serum IgA and IgG, leukocyturia, IgA/IgG, IgA/C3, age and gender. There was no difference in IF staining between the groups. In comparison of MEST score, T score was found to be significant in the group with proteinuria ≥1g (z=-2.061, P=0.039) (Table 2).

The distribution of Oxford-MEST variables in the study group is given in Table 3, and the antibody density in the pathology samples is given in Table 4.
Correlation analysis of IF staining at the time of diagnosis and laboratory data revealed that there was a statistically significant positive correlation between C3 storage and creatinine in the total group (r=0.270, P=0.053). There was also a positive correlation between C3 storage and hematuria (r=0.329, P=0.017) and a positive correlation between IgA storage and hematuria (r=0.403, P=0.003). There was a positive correlation between lambda storage and hematuria (r=0.367, P=0.007), a negative correlation was found with creatinine (r=-0.283, P=0.042) and a positive correlation was found between kappa storage and e-GFR (r=0.325, P=0.019) (see Table 5).

No correlation was found between MEST score and serum IgA/C3 and IF findings. In binary regression analysis, in which we evaluated the effects of IF staining parameters on progression markers, it was determined that C3 storage had a borderline effect on creatinine. No significant effect was found between other IF staining parameters and progression markers (Table 6).

DISCUSSION

Diagnosis of IgA nephropathy is based on kidney biopsy in which immune deposits are shown in the glomerular mesangium in immunofluorescent microscopy [1]. Clinically, hematuria and proteinuria are important findings. Proteinuria was over 1 gram in 65.3% of the study group. In this group, hematuria and uric acid level were found to be significantly higher than the group with proteinuria less than 1 gram, while eGFR and albumin levels were significantly lower. These findings are closely related to progression and clinical outcome [2-5].

Since the prognosis and choice of treatment de-

Table 6. The binary logistic analysis of the predictors of the C3 staining in IgAN

Progression Markers	Exp(B)	95% CI for EXP(B)		P value
Creatinine	3,117	0,991	9,804	**0.052**
eGFR	1,033	0,998	1,070	0.670
Hematuria	0,999	0,993	1,005	0.821
IgA/C3	3,720	0,743	18,638	0.110
Proteinuria	1,000	1,000	1,000	0.382

eGFR = estimated glomerular filtration rate, Ig = immunoglobulin, IgAN = IgA nephropathy, C = complement

pend on the interpretation of the biopsy material, the Oxford classification, which expresses the morphological findings in light microscopic examination, is important [20]. According to data from previous studies, the degree of renal failure, morphological variants of the Oxford classification, and the degree of proteinuria were potential predictors of progression. In the study of Nasri *et al*. [24], there was no relationship between IgA, IgG, IgM and C3 immune stores, proteinuria and age. In this study, no relationship was found between IF findings and proteinuria and age. Again, the relationship between IgA deposition and MEST score with E and S, and IgM deposition with S was not found in our study. It was not found in our study, as was the case in the study, which showed that IgG deposition was not associated with the MEST score. We could not find the relationship between IgA and C3 deposition and E in our study. The relationship between C3 deposits and serum creatinine was found to be borderline correlation in our study. Although no relationship was found between IF and MEST score, the relationship between C3 storage and creatinine, one of the progression markers, shows the increasing importance of C3 storage [24, 28].

There may be other factors that can predict the progression and outcome of IgA nephropathy. It was presented that mesangial C3 deposition is an independent risk factor in progression and its role in the pathogenesis of complement activation [16, 21]. In recent studies, IgA/C3 ratio was also presented as predictive [17, 22, 23]. In our study, in which we investigated the relationship between IF staining intensity and progression markers in the light of these literatures, a positive correlation was found between C3 deposition and creatinine and hematuria immunohistologically. In the study by Nasri *et al*. [24], it was stated that the presence of C3 storage reached the endpoint more rapidly. In the study of Lang *et al*. [17], it was stated that serum IgA/C3 and glomerular C3 deposition may be useful markers of IgA nephropathy progression. In our study, a positive correlation was found between kappa deposition and e-GFR in the total group. Again, a positive correlation was found between IgA, C3 and lambda staining and hematuria. The correlation between IF staining and hematuria in the total group may reflect the fact that hematuria reported in epidemiological studies is a risk factor for proteinuria and that the level of hematuria is an independent indicator of progression to chronic kidney damage [21, 22, 25-27]. Initially, microscopic hematuria was associated with an 87% increase in the risk of end-stage renal disease, while macroscopic hematuria was associated with a 32% reduction [27].

The correlation between C3 storage and creatinine at the time of diagnosis appears to be compatible with the predictive value of C3 storage. The effect of C3 storage and creatinine in the regression analysis also supports this. [13, 28]. The positive correlation between IgA, C3, and lambda deposition and hematuria seem to contribute positively to the progression markers at the time of diagnosis in IgAN.

Limitations

The limitations of our study are that it is retrospective, single-center and the study group is small. Other limitations are the MEST score before 2017 and the inability to perform C4d staining in our pathology unit.

CONCLUSION

In order for IF staining to be used in IgA nephropathy,

the definition and reproducibility of immunofluorescence should be clarified. Does immunostaining have an independent prognostic value? Not known. The limited correlation between C3 storage and creatinine and the positive correlation between IgA, C3 and lambda storage and hematuria suggest that microscopic hematuria should be given importance in follow-ups in addition to proteinuria. More comprehensive studies are needed to elucidate the subject.

Ethics Committee Approval

The study was carried out with the permission of Clinical Research Ethics Committee of Ankara Training and Research Hospital (Date: 14.12.2022, Decision No: E-22-1145).

Authors' Contribution

Study Conception: SKŞ; Study Design: SKŞ, RB; Supervision: SKŞ, RB; Funding: SKŞ; Materials: SKŞ; Data Collection and/or Processing: SKŞ, RB; Statistical Analysis and/or Data Interpretation: SKŞ, RB; Literature Review: SKŞ, RB; Manuscript Preparation: SKŞ and Critical Review: SKŞ, RB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Does health literacy affect the decision to have gestational diabetes screening test?

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ABSTRACT

Objectives: The main objective of this study is to assess the relationship between the level of Health Literacy and the patient's decision to refuse the Gestational diabetes mellitus screening test.

Methods: This cross-sectional study was conducted at a high-volume public hospital from March 2020 to September 2020 with women between 24-28 weeks of gestation. Demographic characteristics and gestational diabetes mellitus screening status were recorded for each woman. The European Health Literacy Survey Questionnaire was used to assess health literacy.

Results: A total of 364 women were included in the study. Two hundred and three (55.7%) women accepted the gestational diabetes mellitus screening test, and 44.2% did not. Health care, disease prevention, health promotion subscales, and the general scale scores were higher in the gestational diabetes mellitus screening group (P=0.001, P=0.024, P=0.01, and P=0.003, respectively). It was determined that a 1-point increase in the health care score decreased the probability of rejecting the gestational diabetes mellitus screening by 1.03 times (P=0.003).

Conclusions: Lower health literacy levels were associated with higher rates of gestational diabetes mellitus screening test rejection.

Keywords: Gestational diabetes, health literacy, surveys and questionnaires

Gestational diabetes mellitus (GDM) has been defined as glucose intolerance with onset or first identified during pregnancy. GDM, the most common medical disease during pregnancy, affects approximately 20 million live births worldwide [1]. The prevalence of GDM is reported as 6% of all pregnancies in the United States [2]. In Turkey, the prevalence of GDM is approximately 7.7%, according to a systematic review [3].

Screening and diagnosis of GDM aim to identify women at risk for an adverse pregnancy outcome. GDM is associated with many fetal and maternal complications: preeclampsia, gestational hypertension, polyhydramnios, macrosomia, increased risk of birth trauma, perinatal mortality, increased frequency of operative birth, fetal cardiomyopathy, and neonatal respiratory and metabolic problems [4]. Women who develop GDM during pregnancy have an increased

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risk of developing type 2 and type 1 diabetes in the long term [5]. Early diagnosis is important, and effective management of GDM has been demonstrated to enhance pregnancy outcomes and reduce the risk of perinatal complications [6].

GDM screening is universally recommended for all pregnant women between 24-28 weeks of pregnancy [7]. GDM screening can be performed in one of two options: the International Association of Diabetes and Pregnancy Working Groups (IADPSG) 1-stage screening approach (currently preferred by the American Diabetes Association) and the 2-stage Carpenter-Coustan screening approach (recommended by the American College of Obstetricians and Gynecologists) [8]. In the one-step approach, the diagnosis of GDM is done with OGTT with 75g of glucose. The two-step approach includes an initial 1-hour non-fasting 50-gram glucose challenge test. If blood glucose higher than the threshold value is detected, a 3-hour fasting diagnostic oral glucose tolerance test is performed [9, 10].

Health literacy (HL) is defined as "the degree to which individuals can obtain, process, and understand basic health information and services needed to make appropriate health decisions" [11].

Patients with low health literacy have difficulty accessing health care and understanding medical advice [12]. Low levels of health literacy are associated with poorer health outcomes, including increased rates of chronic disease. A factor that can contribute to low levels of health literacy is inadequate education, which can lead to a lack of knowledge about health-related issues and difficulty understanding health information [13].

We hypothesized that women with low health literacy are more likely to refuse gestational diabetes screening tests. The present study aimed to evaluate the relationship between the rejection of GDM screening tests and health literacy and GDM screening rejection prevalence.

METHODS

This cross-sectional study was conducted in a high-volume public hospital from March 2020 to September 2020. The study protocol was approved by the Uludag University Faculty of Medicine Clinical Research Ethics Committee at the beginning of the study (approval number: 2020-3/21). This study was performed under all ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Voluntary patients who visited the obstetrics outpatient clinic for routine pregnancy follow-up were included. A total of 380 eligible patients were invited, and 16 refused to participate in the study. A total of 364 patients were included in the study. The inclusion criteria were to be over the age of 18 and to be able to read and understand Turkish. Exclusion criteria were: having pregestational diabetes and any condition that prevented filling out the questionnaires. Patients at 24-28 weeks of gestation were informed about GDM and adverse pregnancy outcomes, and screening was recommended for all patients. The two-stage screening was applied to the patients included in the study. Whether or not the patients accepted the screening test was recorded.

The socio-demographic information regarding age, body mass index (BMI), smoking status (yes: still smoking, no: quit smoking before pregnancy, quit smoking: quit smoking during pregnancy), education level, reading habits (yes: regularly reading magazines, newspaper, book), employment status, comorbid diseases (hypertension, thyroid diseases, cardiac diseases, Etc.), family structure, income status (low income <2500 Turkish Liras (TL)/month, moderate income: 2500-7500 TL/month, high income >7500 TL/month) and presence and type of health insurance were recorded for each patient.

The Turkish version of the European Health Literacy Survey Questionnaire (HLS-EU-16) was used to assess health literacy. The HLS-EU-16 questionnaire is a validated measurement tool for evaluating HL levels in Turkey [14]. HLS-EU-Q16 comprises 16 items that provide to evaluate difficulties in understanding, evaluating, and implementing issues related to processing related to health care, disease prevention, and health promotion. Each item was rated on four points Likert scale (I do not know: 0, very difficult: 1, difficult: 2; easy: 3, and very easy: 4 points). Survey questions were divided into subgroups and assessed as follows: health care (HC): questions 1-7; disease prevention (DP): questions 8-12; and health promotion (HP): questions 13-16.

Written consent was obtained from each patient before their inclusion in the study.
The HLS-EU-16 questionnaire was applied to the patients with face-to-face interviews between patients and clinicians.

Statistical Analysis

Post-hoc power analysis was performed using the available findings of the study. The mean HC score of the patients who underwent GDM screening was 35.01±10.06, and the mean value of the patients who did not have GDM screening was 31.79±10.15. The power value was determined using the corresponding effect size value. The 85% power value obtained from the study at the α=0.05 level was determined as n = 203 in the GDM screening group and n=161 in the non-GDM screening group.

The compliance of continuous variables to normal distribution was examined using the Shapiro-Wilk test. Age and scores of the general and subscales of the HL-EU-Q16 scale are expressed as mean±standard deviation and median (minimum: maximum) values. Categorical variables are expressed with n (%) Pearson's chi-square. Fisher's exact and Fisher-Freeman-Halton tests were used for intergroup comparisons of categorical variables. The Mann-Whitney U test was used to compare the scores of the general and subscales of the HL-EU-Q16 scale between groups. Internal consistency of the general and subscales of the HL-EU-Q16 scale was examined using the Cronbach alpha reliability coefficient.

Logistic regression analysis was performed to investigate the factors that may cause not having a GDM screening test. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows. Version 21.0. Armonk. NY: IBM Corp.) program was used for statistical analysis. The type I error level was determined as 5% in statistical analysis.

RESULTS

During the study period, 380 eligible women applied to the outpatient clinic for routine pregnancy follow-up, of which 16 were excluded because they refused to participate. The final analysis was made with the data of a total of 364 patients. Of the 364 patients included in the study, 203 patients (55.76%) accepted to have the GDM screening test, and 161 of them were rejected to have.

The mean age of patients was similar between the two groups (28.18±5.75 years versus 28.12±5.48 years, respectively, P=0.975). BMI and the presence of the chronic disease did not differ between patients who accepted a GDM screening test and those who did not (P=0.07 and P=0.43, respectively).

There was no difference between the groups regarding smoking habits (P=0.850). The education level was observed to vary between patients who had GDM screening and those who did not (P=0.014). The distribution of the patients according to their education level is shown in Table 1. In subgroup analyses according to education level, it was determined that the proportion of participants with a level of education below high school differed between the two groups (P=0.004). There was no difference between patients with high school and post-high school education and those who did not have GDM screening (P=0.172 and P=0.064, respectively). Similarly, there was no difference between both groups according to income status, reading habits, family structure, employment status, and presence of health insurance (P=0.145, P=0.719, P=0.283, P=0.920, and P=0.613, respectively). The socio-demographic characteristics of both groups are shown in Table 1.

Cronbach alpha reliability of the subscale for health care was calculated as 0.76 (Table 2). It was seen that the reliability of the healthcare subscale is at a good level. The reliability of the Cronbach alpha scale for disease prevention and health promotion scale was found to be 0.68 and 0.64, respectively. These reliability values were at an acceptable level. Finally, the Cronbach alpha reliability for the general scale was found to be 0.86. Its reliability for the general scale was at a good level.

A comparison of HLS-EU-Q16 scale scores between GDM screening and refusing groups was presented in Table 3. It was determined that the scale scores of the health care, disease prevention, and health promotion subscales were higher in the group that had GDM screening (P=0.001, P=0.024, and P=0.010, respectively). Again, it was determined that the general scale score was higher in the group that had GDM screening (P=0.003).

Table 1. Socio-demographic characteristics of the participants

	GDM Screening		
	Accepted (n=203)	**Refused (n=161)**	**P value**
Age (years)	28.18±5.75 28 (17:44)	28.12±5.48 28 (18:42)	0.975[a]
BMI (kg/m^2)	28.15±4.47 27.54 (13.32-40)	29.01±4.06 28.39 (19.05-42.54)	0.070[a]
Presence of chronic disease	18 (8.90%)	10(6.20%)	0.345[b]
Smoking status			
Yes	13 (6.40%)	10 (6.20%)	0.850[b]
No	150 (73.90%)	120 (74.50%)	
Quit smoking	8 (3.90%)	9 (5.60%)	
Never smoked	32 (15.80%)	22 (13.70%)	
Educational status			
Under high school	74 (36.50%)	83 (51.60%)	**0.014[b]**
High school	73 (36%)	47 (29.20%)	
Above high school	56 (27.60%)	31 (19.30%)	
Employment status			
Working	47 (23.20%)	38 (23.60%)	0.920[b]
Not working	156 (76.80%)	123 (76.40%)	
Income status*			
Low income	2 (1%)	6 (3.70%)	0.144[c]
Moderate income	156 (76.80%)	126 (78.30%)	
High income	45 (22.20%)	29 (18%)	
Reading habits			
Yes	173 (85.20%)	135 (83.90%)	0.719[b]
No	30 (14.80%)	26 (16.10%)	
Family structure			
Nuclear family	187 (92.10%)	143 (88.80%)	0.283[b]
Extended family	16 (7.90%)	18 (11.20%)	
Health insurance			0.631[c]
General health insurance	180 (88.70%)	138 (85.70%)	
Private health insurance	3 (1.50%)	4 (2.50%)	
Green card**	2 (1%)	4 (2.50%)	
None	18 (8.90%)	15 (9.30%)	

Data are expressed as mean±standard deviation or n (%) or median (minimum- maximum), GDM=Gestational Diabetes Mellitus, BMI=Body Mass Index, TL = Turkish Lira

[a]Mann Whitney U test, [b]Pearson Chi-Square test, [c]Fisher-Freeman-Halton Test

*Low income is <2500 TL month, Moderate income: 2500-7500 TL/month and High income >7500 TL/month **Green card is a document that is given to people in Turkey who are in need and do not have health insurance so that they can receive health services free of charge.

Table 2. Distribution of HL-EU-Q16 general and subscales

Health literacy	Insufficient	Problematic	Sufficient	Excellent	Cronbach α
Health care	17.90%	21.40%	36.80%	23.90%	0.76
Disease prevention	26.60%	16.90%	34.60%	25.80%	0.68
Health promotion	11.50%	7.70%	54.40%	26.40%	0.64
Total	19.50%	21.40%	37.90%	21.20%	0.86

Data expressed as n %. HL=Health Literacy

To determine the risk factors thought to be effective in GDM screening, variables were first examined with univariate logistic regression analysis, and variables meeting the P<0.25 criterion after the analysis were included in the multivariate logistic regression model. After the logistic regression analysis of the relevant variables, the variables that meet the P<0.25 criterion were determined as BMI, educational status, income status, family structure, HC, DP, HP, and general health literacy. These variables were included in the multivariate logistic regression model. The analysis result of the last step was presented in Table 4, and the risk factors thought to have an impact on rejecting GDM screening were reported in Table 4. The forward selection approach was used as the variable selection method. The risk factors thought to be effective in rejecting GDM screening were listed in the table. When the analysis results were examined, it was seen that the logistic regression model obtained in the last step was compatible with the data (Hosmer and Lemeshow test P=0.347), and the logistic regression model obtained was also significant (P=0.003). It was determined that a 1-point increase in the HC score decreased the probability of rejecting the GDM screening by 1.03 times.

DISCUSSION

This study aims to determine the relationship between the GDM screening test acceptance rate and HL. In this study, 55.76% of the patients who applied to the outpatient clinic accepted to have a GDM screening test in our hospital. In a recent study by Hocaoğlu *et al*. [15], the reasons why some patients in Turkey rejected the GDM screening test were evaluated. The study was performed on 312 patients of any gestational age 42.5% of patients under 28 weeks and 37.8% of patients over 28 weeks agreed to have the test. Hocaoğlu *et al*. [15], in their study, questioned the

Table 3. Comparison of HLS-EU-Q16 scale scores between GDM screening and refusing groups

	GDM Screening		
	Yes (n=203)	No (n=161)	P value [a]
Health care	35.01±10.06 35.71 (2.38-50)	31.79±10.15 3.33 (4.76-50)	**0.001**
Disease prevention	33.75±11.83 33.33 (3.33-50)	31.20±11.90 33.33 (3.33-50)	**0.024**
Health promotion	37.70±8.66 33.33 (8.33-50)	35.27±9.18 33.33 (12.50-50)	**0.010**
Total	35.29±8.93 34.38 (9.38-50)	32.47±9.14 33.33 (11.46-50)	**0.003**

Data are expressed as mean±standard deviation or n (%) or median (minimum-maximum), GDM=Gestational Diabetes Mellitus

[a]Mann Whitney U test

Table 4. Factors affecting the likelihood of rejection of GDM screening (n= 64)

	Univariate Model				Multivariate Model			
	OR	95% CI		P value	OR	95% CI		P value
Age	1	0.97	1.04	0.929				
BMI	0.96	0.91	1	0.064				
Chronic Disease (Reference Coefficient: Yes)	0.68	0.31	1.52	0.347				
Smoking (Reference Coefficient: Yes)								
No	0.96	0.41	2.27	0.929				
Quit smoking	0.68	0.19	2.41	0.554				
Never smoked	1.12	0.42	3	0.823				
Educational Status (Reference Coefficient: Above High School)								
Under high school	0.50	0.29	0.86	0.012				
High school	0.85	0.49	1.50	0.572				
Employment Status (Reference Coefficient: Working)	0.98	0.60	1.59	0.920				
Income status (Reference Coefficient: High Income)								
Low Income	0.22	0.04	1.14	0.071				
Moderate income	0.80	0.47	1.35	0.397				
Reading Habits (Reference Coefficient: Yes)	0.90	0.51	1.59	0.719				
Family Structure (Reference Coefficient: Nuclear family)	1.47	0.73	2.99	0.285				
Health Insurance (Reference Coefficient: None)								
General health insurance	2.40	0.39	14.97	0.349				
Private health insurance	2.61	0.47	14.45	0.272				
Green card	1.50	0.16	14.42	0.725				
Health care	1.03	1.01	1.05	0.003	1.03	1.01	1.05	**0.003**
Disease Prevention	1.02	1	1.04	0.043				
Health Promotion	1.03	1.01	1.06	0.011				
Health Literacy	1.04	1.01	1.06	0.004				

GDM= Gestational diabetes mellitus, OR= Odds ratio. CI= Confidence interval
χ^2=8.97; P=0.003

reasons for patients' refusal to test and found that the most frequently indicated reason was the belief that GDM screening test is harmful to themselves and the baby.

GDM screening rates in various countries are available in the literature. In our study, screening test rates seem lower than most countries in the literature. For example, the rate in Israel is 89%; in a US study, including women who benefit from health insurance is 68%, which has been reported as 30% in Lombardy / Italy [16-18].

In our study, it was observed that the education level varies between patients who had GDM screening and those who did not. When subgroup analysis was made according to education level, we demonstrated a positive association between the level of education under high school and rejection of the screening test (36.5% versus 51.6%). In a study by van der Heide *et al*., using data from 5136 adults, examined the relationship between education and health literacy and showed a significant relationship between health literacy and education level. They pointed out that those who completed their tertiary education had a higher level of health literacy than those who had completed secondary education [19].

According to a European study of 8000 people by Sørensen *et al*. [20], financial deprivation, low social status, low education status, or old age had been seen in higher proportions of people with limited health literacy [20]. Contrastingly, in our study, there was no difference between the groups regarding employment status, income status, reading habits, family structure, and health insurance. We explained this because the Sørensen *et al*.'s study [20] was multinational and conducted with data from 8000 patients.

The possible reason for the discrepancy in our findings is that our study was conducted in a tertiary hospital in the city center. In our study, there was no significant difference in socio-demographic characteristics of the groups who had and did not have the screening test, except for the level of education; this gave us a significant advantage: we were able to analyze health literacy and subgroup scores without bias due to socio-demographic characteristics.

In a manual about the problem of health literacy, it was reported that patients with low health literacy skills have poorer health status than those with adequate skills, even after controlling for a variety of socio-demographic variables [21]. This supports the findings of our study and highlights the importance of HL.

Stafford *et al*. [22] investigated the associations between health literacy and postpartum outcomes. They found that women in the lowest health literacy group were less likely to plan to breastfeed.

Endres *et al*. [23], in their study investigating the relationship between health literacy and planned pregnancies in women with pregestational diabetes, found that women with low health literacy were significantly more likely to have an unplanned pregnancy. Pirdehyghan *et al*. [24] conducted a study on the relationship between HL and glycemic control in pregnant women with GDM. And they concluded that low HL was associated with insufficient glycemic control. Low health literacy is associated with poorer health status; this is consistent with the results of our study.

As a result of mutually evaluating the groups that accepted and did not accept to have GDM screening, we determined that the scores on health care, disease prevention, and health promotion scales were higher in the group that had the screening test. It was determined that a 1-point increase in the HC score decreased the probability of rejecting the GDM screening by 1.03 times ($p = 0.003$). In addition, the results of the logistic regression model created with the risk factors that are thought to be effective in rejecting the GDM screening can also call for more awareness in the healthcare community about the importance of GDM diagnosis and the need for health education materials that encourage screening. Seeking methods to alleviate the impact of poor health literacy on health results is a crucial measure to be taken.

Limitations

Our study has some strengths and limitations. The prospective design of our study strengthened the power of the results. There were also limitations of the study: we included patients living in the city center so that the results may reflect only some of the population in terms of socio-demographic characteristics.

CONCLUSION

We found the HL score of the patients who accepted the screening test significantly higher than those who did not want to have the test. Among the socio-demo-

graphic characteristics, it was determined that the patients with less than a high school education were significantly higher in the group who did not have the GDM test. Further large, multicenter studies are needed to determine the knowledge and attitudes of the pregnant population on the importance of GDM and GDM screening.

Authors' Contribution

Study Conception: ÖÖU; Study Design: ÖÖU, ZA, SRO, GO; Supervision: ÖÖU; Funding: ÖÖU, ZA, SRO; Materials: ÖÖU, ZA, SRO; Data Collection and/or Processing: ÖÖU, ZA, SRO; Statistical Analysis and/or Data Interpretation: ÖÖU, SRO, HO, GO; Literature Review: ÖÖU, ZA, SRO; Manuscript Preparation: ÖÖU, SRO, HO, GO and Critical Review: ÖÖU, ZA, SRO, HO, GO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Can plethysmography have a greater place in the diagnosis, treatment and follow-up of chronic venous insufficiency?

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ABSTRACT

Objectives: Chronic venous insufficiency (CVI) is one of the most common venous diseases. CVI is an important clinical picture with a high prevalence, low quality of life, and high diagnosis and treatment costs. Therefore, diagnosis, follow-up, and treatment are important for the patient's socioeconomic and life quality. In this study, we aimed to better examine a test used in the diagnosis, treatment, and follow-up of CVI.

Methods: In this retrospective study, 683 patients diagnosed with CVI, who had endovenous laser ablation (EVLA) indications were evaluated between June 2013 and November 2018. EVLA procedure performed on all patients. Preoperative, postoperative 1st and 6th month Doppler USG (ultrasonography), plethysmography, and VCSS (Venous Clinical Severity Score) questionnaire was made to all patients.

Results: As a result of our study, we found that there was a significant difference between the preoperative plethysmography and VCSS results of the patients and the postoperative 1st and 6th month results. With the significant difference in the VCSS questionnaire, we have shown that plethysmography gives accurate results in the diagnosis and treatment of CVI since it is an individual, quantitative, and easy test.

Conclusions: EVLA is an effective and safe method in patients with venous insufficiency. Since Doppler USG is person and device dependent, we think that plethysmography, which can be used in every clinical setting and provides quantitative results independent of the person, can be used more frequently in the diagnosis and treatment of venous insufficiency. In addition, we think that plethysmography can be used as a valuable additional method in the diagnosis and follow-up of such patients, due to the venous hemodynamic data that Doppler USG cannot provide.

Keywords: Chronic venous disease, plethysmography, endovenous laser ablation

Chronic venous insufficiency (CVI) is one of the most common vascular diseases. It describes the morphological and functional disorders in the venous system. CVI is an important clinical picture with a high prevalence, reducing the patient's quality of life and high cost of diagnosis and treatment [1, 2].

It has a wide range of symptoms that can result in itching, burning, restlessness, discoloration, swelling in the legs, prominent veins, venous ulcers in the ankles. In general, the biggest effect is to reduce the pa-

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tient's quality of life. However, because it is a non-life-threatening and non-specific disease, it is a disease that tends to be overlooked by patients and doctors [3]. Treating CVI is very important in improving the patient's venous hemodynamics and clinic. Clinical worsening in patients awaiting or delayed elective surgery has been shown in many studies [4]. It is important to eliminate this mechanical leakage before permanent and irreversible damage occurs [4].

Treatment of saphenofemoral junction insufficiency can be grouped under 3 main headings as medical, open surgery, and endovascular treatments. Open surgery; high ligation at the saphenofemoral junction (SFJ) stripping of the above-knee great saphenous vein (GSV) and pack excisions have been the gold standard until today [5]. With the development of endovascular treatments, increasing experience, and seeing the results; endovascular treatments, which are alternatives to open surgery, have begun to take their place in new guidelines.

A good anamnesis and clinical examination are usually sufficient for the diagnosis. Information such as the severity, anatomical location and extent of the regurgitation are revealed by Doppler USG examination [6]. Invasive, standard venography, computerized tomographic venography, and magnetic resonance venography are available but not widely used [7]. In addition, plethysmographic tests can be used to determine venous hemodynamics. Strain-gauge venous occlusion plethysmography (SGVOP) provides objective data about venous outflow and venous capacity [3, 8]. Plethysmographic methods have been frequently used in many studies on venous insufficiency, especially in medical treatment efficacy studies [9, 10].

Although venous hemodynamic measurements are considered important evidence in proving efficacy, they are not widely used in practice today. The presence and severity of the regurgitation, as well as the saphenous diameter in measurements made with Doppler USG, play a key role in determining the treatment, but venous hemodynamics in the entire leg is not considered. This means ignoring the changes in venous volume in the process of venous hypertension, which we consider the initial pathology of the disease. In this study, we aimed to evaluate the place of plethysmography in the diagnosis of CVI and in the follow-up of the patient clinic and venous hemodynamics after EVLA.

METHODS

This retrospective study was conducted in Bursa Arrhythmia and Heart Hospital by scanning and documenting the files of patients diagnosed with CVI, who had EVLA indication and EVLA procedure performed in June 2013 and November 2018. Regional Ethics Committee approval was obtained for this retrospective review study (Uludag University Clinical Research Ethics Committee, Date: 10 November 2022, Decision no. 2022-17/25).

Patients with reflux of more than 0.5 seconds at the saphenofemoral junction detected by Doppler USG and with a GSV greater than 5.5 mm were included in the study. Patients who had the insufficiency but have no complaints, whose GSV diameter is more than 10 mm, patients with a doubled saphenous vein, patients with anterior or posterior accessory saphenous vein varicose veins, patients with excessive bend in the saphenous magna, patients with femoral or popliteal vein insufficiency, patients with previous deep vein thrombosis, patients using oral anticoagulants such as warfarin, patients with peripheral artery disease (ankle-brachial index below 0.9) were excluded from the study.

Between June 2013 and November 2018, 683 patients who were randomly selected and diagnosed with GSV insufficiency by Doppler USG were included in the study. EVLA was applied in a standard way to all patients with EVLA indications. Venous Capacity (VC), Venous Refilling Time (VRT), and Venous Pump Capacity (VPC) measurements were made with SGVOP at preoperative (VC-0, VRT-0, and VPC-0) and postoperative 1st (VC-1, VRT-1, and VPC-1)and 6th months (VC-6, VRT-6, and VPC-6). Doppler USG was performed at 1 month for the evaluation of the procedure.

VCSS was used to evaluate patients' clinical state. VCSS records of the patients were made. Preoperative and postoperative measurements were compared with each other and statistical significance was checked. All EVLA procedures were performed by the same surgeon, and SGP measurements were performed by the same technician.

Statistical Analysis

Whether the data were suitable for normal distribution was examined using the Shapiro-Wilk test. De-

Table 1. Frequency distribution regarding the demographic characteristics of the participants

	Data
Gender, n (%)	
Female	408 (59.7)
Male	275 (40.3)
Age (year)	53.30±15.13 53 (28-80)
GSV diameter (mm)	7.57±1.18 7.70 (5.5-9.5)
GSV length (cm)	20.23±6.82 20 (9-32)

Data are shown as mean±standard deviation or median (minimum-maximum) or number (percent). GSV= Great saphenous vein

scriptive statistics for categorical variables are given as frequency and percentage. Descriptive statistics for continuous variables are given as median (minimum-maximum) for those that do not conform to the normal distribution. In the comparison of dependent groups, Wilcoxon sign-rank test was used for those who did not comply with the normal distribution. Statistical analysis was done in SPSS 22.0 package program. The level of significance was taken as α=0.05.

RESULTS

The mean age of 683 patients included in the study was 53.30±15.13 years, with 408 (59.7%) females and 275 (40.3%) males (Table 1).

When the preoperative measurements were compared with the postoperative 1st and 6th month measurements, a statistically significant improvement was found in all parameters (P<0.001). Similarly, when the postoperative 1st month and 6th month measurements were compared, a statistically significant improvement was found in all parameters (P<0.001) (Table 2).

DISCUSSION

Chronic venous insufficiency (CVI) is a pathology that occurs as a result of deterioration of the hemodynamics and anatomy of the venous system in the lower extremities. Clinically, it can be defined as a very common condition that includes various subjective symptoms such as pain, itching, restlessness in the legs, swelling of the legs, cramps, and skin changes [2, 4].

The main pathology constituting chronic venous insufficiency is insufficiency, occlusion, or the combination of these two factors. The result is increased

Table 2. Comparison of venous capacity, venous refilling time, venous pump capacity, venous clinical severity score variables in the treatment group according to their pre-treatment values

	(n=683)	Binary comparisons	P value
VC-0 (%)	7.90 (4.8-10.7)	(VC-0)-(VC-1)	**< 0.001**
VC-1 (%)	6.70 (4.0-9.1)	(VC-0) - (VC-6)	**< 0.001**
VC-6 (%)	7.00 (4.1-9.4)	(VC-1) - (VC-6)	**< 0.001**
VRT-0 (seconds)	15.50 (5.2-24.0)	(VRT-0) - (VRT-1)	**< 0.001**
VRT-1 (seconds)	24.70 (15.7-37.2)	(VRT-0) - (VRT-6)	**< 0.001**
VRT-6 (seconds)	25.20 (16-38)	(VRT-1) - (VRT-6)	**< 0.001**
VPC-0 (%)	4.80 (0-8)	(VPC-0) – (VPC-1)	**< 0.001**
VPC-1 (%)	2.50 (1.1-3.9)	(VPC-0) – (VPC-6)	**< 0.001**
VPC-6 (%)	2.60 (1.1-4.0)	(VPC-1) – (VPC-6)	**< 0.001**
VCSS-0	6.00 (1-11)	(VCSS-0) – (VCSS-12)	**< 0.001**
VCSS-6	3.00 (1-5)		

Data are shown as median (minimum-maximum). VC= venous capacity, VRT= venous refilling time, VPC= venous pump capacity, VCSS= venous clinical severity score variables, 0= Preoperative, 1= postoperative 1st month, 6= postoperative 6th month, 12= postoperative 12th month

ambulatory venous pressure, in other words, venous hypertension [4].

Treatment of the disease may start with lifestyle changes depending on the severity and symptoms of the disease and may require medical and surgical treatment.

We aimed to see the stage of the disease and the clinic of the patient after surgery by performing presurgical scoring tests and SGVOP in patients diagnosed with venous insufficiency and having severe symptoms in our clinic. Thus, in addition to anamnesis, physical examination and Doppler USG in the diagnosis, treatment option, and follow-up of CVI we planned to evaluate whether an objective test such as SGVOP could be used more in the clinic.

Venous valves are bicuspid. They are important structures in the venous system that ensure that the flow is unidirectional and in the opposite direction to gravity. Venous blood moves against gravity with the muscle pump function created by ambulation and the effect of venous valves. Venous valves prevent the transmission of venous pressure created by the pump function of the muscle to the superficial veins and capillaries and when the venous pressure drops at the end of muscle contraction, they prevent the backflow of blood in the venous system [11]. The deterioration of any component in this valve system appears as venous insufficiency.

The first step in the diagnosis of venous insufficiency is a detailed history and physical examination. Then, color Doppler ultrasonography (USG), and plethysmography, which are non-invasive imaging methods, are important in the diagnosis. In the third step, invasive computed tomography (CT) venography, magnetic resonance (MR) venography and venography are used, which require the use of opaque materials.

The VCSS system includes 10 clinical definitions scored from 0 to 3, consisting of pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, number of active ulcers, duration of active ulceration, size of ulcer and use of compressive therapy, which can be used to assess changes in response to treatment [12]. In our study, as in other studies, it was used for subjective identification in terms of clinical follow-up [13].

Color Doppler USG is the most commonly used among these methods. It gives sufficient information about the diameter of the target veins, the adequacy of the valves, the beginning of the collaterals, and the presence of the accessory saphenous vein. However, the biggest disadvantages of Doppler USG are it is subjective who is doing the examination and device Also being able to cooperate with the patient is not always possible. In addition, it does not give quantitative value other than flow measurement hemodynamically.

In this article, we used SGP alongside Doppler USG. The reason for using this method is that it is easily accessible, can be done quickly and most importantly, it gives quantitative results independent of the person doing it or the device. It also provides quantitative data on venous hemodynamics such as Venous Capacity, Venous Fill Time and Venous Pump Capacity. In the European Society for Vascular Surgery (ESVS) 2022 guideline, IIb class C level, "Air plethysmography can be considered to quantify reflux and/or obstruction in patients with chronic venous disease, especially when duplex ultrasound results do not match clinical findings." is recommended [14]. However, no recommendations were made about other plethysmographic methods. The development of technology and the increase in sensor sensitivity are progressing in a way that may change these recommendations in the future.

The first step in the treatment of venous insufficiency is patient education. Losing weight, exercising frequently, lifestyle changes, intermittent leg elevation, not standing for a long time or staying seated are indispensable parts of the treatment. Compression therapy comes next. The most commonly used method is compression stockings. In the 2021 Peripheral Arterial and Vein Diseases National Treatment Guidelines, it has been shown as a 1A recommendation for preventing the progression of the disease and relieving symptoms [15].

Venoactive drugs used in medical treatment consist of several heterogeneous drug groups. They can be of vegetable origin or synthetic [16]. The important thing is to know that venoactive drugs will not cure the existing disease, but will only relieve the symptoms. They reduce edema, pain, restlessness, and muscle cramps.

Indications for interventional treatment vary according to the patient's symptoms, objective findings related to varicose veins, and complications. The aim

is to eliminate all varicose veins and the cause of venous hypertension, achieve maximum cosmetic improvement, prevent recurrence, relieve symptoms, prevent complications, and treat the disease.

Although interventional methods vary according to the patient's clinic and venous pathology, they can be grouped as sclerotherapy, transcutaneous laser, endovenous thermal, and mechanical-chemical ablation. Traditional open surgical treatment also maintains its importance in the treatment of venous insufficiency. We preferred the EVLA method for our patients within the indications. EVLA is a safe and effective method that is increasingly used in the treatment of venous insufficiency. The new hemodynamics that will occur after EVLA relieves the patient's complaints and symptoms [17]. However, the same success does not occur in every patient and the importance of pre- and post-treatment evaluation becomes even more important. Plethysmography is a method that can objectively and accurately evaluate venous hemodynamics in a short time [4]. For this reason, we evaluated venous hemodynamics by performing plethysmography on the lower extremity before the operation, after the operation, and 6 months after the operation. Likewise, we compared the results of Doppler USG and plethysmography in the diagnosis, course, and follow-up of the disease.

There is a significant difference and improvement between our venous capacitance, and venous refilling time (VC-0, VRT-0) values in the preoperative evaluation, and our postoperative 1st month (VC-1, VRT-1) values. It was also found a significant difference and improvement between the postoperative 1st (VC-1 and VRT-1) and 6th month (VC6 and VRT6) values, and finally, our evaluation between our preoperative values and our 6th month values (VC0 and VC6, VRT-1 and VRT-6) also significant improvement. This shows that venous hemodynamics changes before and after the operation, and plethysmography presents it quickly and easily with quantitative values.

The significant difference between the preoperative scores of the patients (VCSS-0) and the scores at the 6th month postoperatively (VCSS-6) shows that our surgeries were also clinically successful and significantly reduced the complaints of our patients. We think that the fact that the plethysmographic data of the patients whose scores have changed has also progressed compared to the preoperative period, which shows that plethysmography correctly shows the improvement in venous hemodynamics and that this situation is reflected in the patient's clinic.

Limitations

The main limitation of the study was the small number of patients and the retrospective design.

CONCLUSION

EVLA is an effective and safe method in patients with venous insufficiency and decreased quality of life due to this pathology. Although Doppler USG is the most commonly used method in diagnosis and treatment; It can cause problems in diagnosis and follow-up due to the fact that it depends on the person doing it and the device used. However, it does not provide sufficient information about venous hemodynamics. For this reason, in addition to Doppler USG, we think that plethysmography, which can be used in every clinical setting and provides quantitative and independent results, can be used more frequently in the diagnosis and treatment of venous insufficiency.

Authors' Contribution

Study Conception: HG; Study Design: HG, TT; Supervision: HG; Funding: N/A; Materials: N/A; Data Collection and/or Processing: TT; Statistical Analysis and/or Data Interpretation: TT; Literature Review: TT; Manuscript Preparation: TT and Critical Review: TT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Evaluation of Turkish videos about breast self-examination on YouTube

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ABSTRACT

Objectives: Breast self-examination (BSE) is very important to early detect breast cancer in women in addition to imaging methods. The easiest way to access information concerning how to perform this examination is undoubtedly the internet, and the most popular platform is YouTube. However, the most important disadvantage of this massive platform is the risk of spreading false information since it cannot be audited. This study aimed to evaluate Turkish videos on BSE on YouTube in terms of quality and content.

Methods: On January 17, 2022, a search was conducted on YouTube using the keyword "breast self-examination", and the first 210 videos presented on the first five pages were obtained. After applying the study criteria, 156 were included in the sample and evaluated by two general surgeons in terms of educational value, content, and upload source.

Results: Of the 156 videos, 23 were categorized as useful (14.7%) and 133 as misleading (85.3%). When examined according to the upload source group, universities/professional organizations/non-profit physicians/physicians had the highest rate of misleading videos (96.9%), while stand-alone health information websites had the highest rate of useful videos (24%). There was no significant difference between the upload sources in terms of video length, number of views, content score, or quality score.

Conclusions: The number of useful Turkish videos on BSE is very low. Our results indicate the need for more educational and useful videos to be produced, especially by healthcare professionals who use the YouTube platform.

Keywords: Breast cancer, YouTube, video, usefulness, quality

Breast cancer is the most common cancer in women, with almost two million patients receiving this diagnosis every year [1]. In the USA, breast cancer constitutes the second most common cause of cancer-related deaths in women [2]. From the mid-1980s to 1999, there was an increase in the number of patients diagnosed with breast cancer, associated with the increase in screening in the USA [3]. Breast cancer mortality rates have decreased since the 1970s [4]. It is considered that this decrease in mortality is due to the increase in screening methods that allow for an early diagnosis and the developments in adjuvant therapy [5, 6].

Mammography and, when necessary, breast mag-

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netic resonance imaging are used for breast cancer screening purposes across the world. In addition, breast examination by both clinicians and patients is important in practice. Despite there being no consensus concerning its benefits, breast self-examination (BSE) is essential for patients to become familiar with their breast structure and spot differences early. Although not included in direct screening methods, it is recommended to perform BSE to both increase awareness and support these methods. In fact, the World Health Organization recommends BSE not as a screening method but as a means of raising awareness among women at risk [7].

Certain guidelines have determined how BSE should be performed [8]. To ensure that individuals perform this examination accurately and thoroughly, it is essential to provide them with the appropriate education via healthcare professionals or other audio-visual platforms. Today, the internet, especially social video platforms, offers easy access to patients on many subjects. YouTube is unquestionably the leading and most popular video platform, with two billion views per day. On average, a new video is uploaded every minute, and the typical user spends at least 15 minutes per day on this platform [9].

Undoubtedly, health-related issues are also influenced by YouTube's popularity. The Health Information National Trends Survey reported a significant increase in internet use to access health information. Recent studies have found that eight out of 10 internet users access health information online [10, 11]. However, the greatest disadvantage of platforms such as YouTube is that the information presented does not pass any control mechanism in terms of accuracy and validity. Many researchers have expressed concerns regarding the accuracy and quality of the information available on this platform [12-15]. Many articles have been written on YouTube videos related to vaccination, the human papilloma virus, organ transplantation, swine flu, prostate cancer, and obesity [15-20]. The current study was conducted to evaluate the content, reliability, and quality of the most watched YouTube videos about BSE in Turkish, targeting the audience in Turkey.

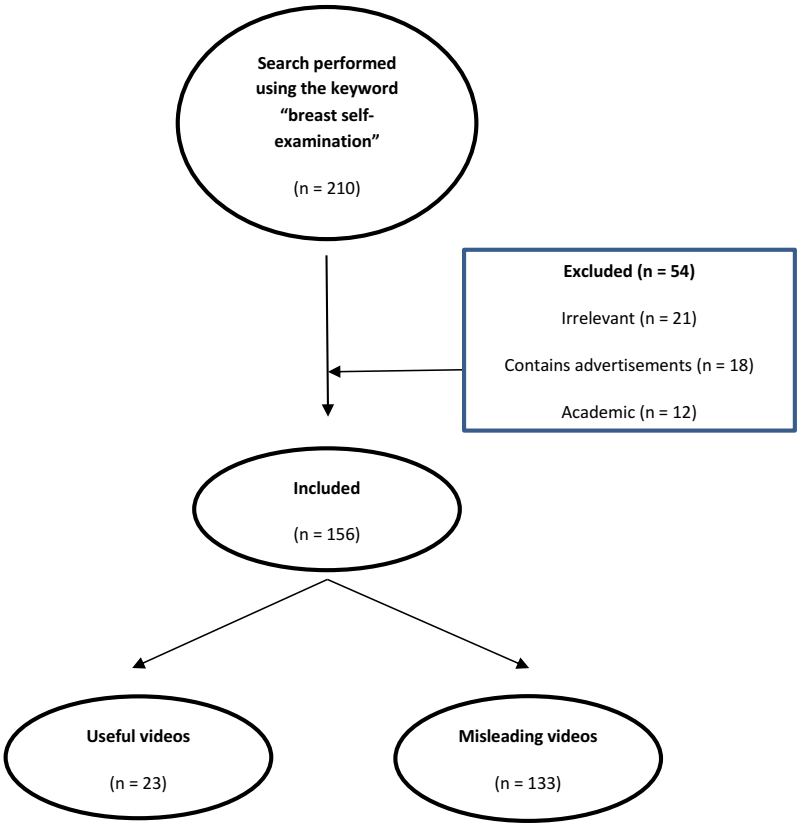

Fig. 1. Consort diagram

METHODS

On January 17, 2022, a search was undertaken on YouTube (https://www.youtube.com; YouTube, LLC, San Bruno, CA, USA) using the keywords "breast self-examination". Videos uploaded before 2017 were not included in the study. The videos were reviewed by two independent general surgeons, and a third general surgeon was consulted to reach a consensus, if necessary. The top 210 videos listed as a result of the search were included in the evaluation (Fig. 1). Only the first five pages were included in the study because previous research has shown that subsequent pages mostly contain unrelated videos and that viewers mostly watch videos presented in the first few pages [21, 22].

Exclusion Criteria includes uploaded videos before 2017, irrelevant, containing advertisements, uploaded for academic purposes, prepared in a language other than Turkish, and duplicated videos.

Video Evaluation

The evaluation of the videos in terms of their educational value was carried out by calculating the total video scores according to the criteria published by Azer [23]. As shown in Table 1, five major and six minor criteria were determined to evaluate the accuracy of the content, the clarity of the message given, whether expert opinion has been received on the subject, the informativeness of the video, and the technical design. Two points are awarded for each of the major criteria and one point for each of the minor criteria. Videos with a total score of 13 and above are categorized as useful, provided that all major criteria are met. These criteria have been successfully used for similar purposes in many previous studies [23-25].
For each video evaluated, the total number of views, time since upload, number of views per day, video length (seconds), and uploader characteristics were recorded. The popularity of the videos was evaluated using the Video Power Index (VPI). The following formulas were used for calculation:

VPI = popularity × views per day / 100

Popularity = number of likes × 100 / (likes + dislikes)

Views per day = total views/time since upload (days)

Characteristics of Upload Source

The videos were divided into four categories according to their upload sources: universities/professional organizations/non-profit physicians/physicians, stand-alone health information websites, medical advertisement/for-profit companies, and individual users.

Up-to-dateness and Accuracy of Video Content

All videos were evaluated by two independent general surgeons for information accuracy, up-to-dateness, and content (Table 2). In case of differences of opinion, a third expert was consulted to reach a consensus.

Video content (comprehensiveness score) was evaluated according to the following eight items, similar to previous studies [26]:

--The most appropriate time for BSE specified

--Complete removal of upper clothing

--Examination being performed in front of a mirror

--Looking at the external appearance of the breasts in the mirror

--Explaining how to perform a manual examination

--Examination being performed separately while lying down, sitting, and standing

--Discussing what to pay attention to during BSE

--Inclusion of the areola-nipple complex and the underarm in the examination.

Comprehensiveness score: Number of items included / 8 × 100 (%)

Statistical Analysis

The Statistical Package for the Social Sciences (IBM SPSS Inc., Chicago, IL, USA) v. 22.0 was used to analyze the data. The Shapiro-Wilk test was used to determine whether the data was normally distributed. Continuous variables were expressed as mean and standard deviation or median (interquartile range), and categorical variables were expressed as numbers and percentages. Kruskal Wallis test was used in the analysis of continuous variables. The Spearman correlation analysis was used to investigate the correlation between the total video score and basic video characteristics. Inter-rater agreement was calculated with Cohen's Kappa score. $P<0.05$ was considered statistically significant in all analyses.

RESULTS

According to the search on YouTube, a total of 210 videos were initially evaluated. Applying the exclusion criteria, 54 videos were excluded from the study. Of these, 21 were irrelevant, 18 contained advertisements, 12 were academic videos, and three were not in Turkish. As a result, 156 videos were included in the sample. Of these videos, 23 (14.7%) were categorized as useful and 133 as misleading (85.3%) (Fig. 1).

The inter-observer agreement of the total video scores for the BSE-related videos was found strong level (Kappa value: 0.841, 95% confidence interval: 0.839-0.842).

The number of views for the videos included in the study was 256 (59-2,680). The mean video length was 164 (110-357) seconds. The mean time since upload was 24 (12-52) months. The mean number of daily views was 0.49 (0.12-2.49). According to these statistics, the mean VPI was found to be 0.49 (0.12-2.49). The mean comprehensiveness score was 50 (25-75), and the mean total video score was 4 (5.5-8). Of the videos, 48.7% were presented by male speakers, 43.6% were presented by female speakers, and the remaining 7.7% did not have audio (Table 2).

When the number of views, video length, time since upload, daily views, VPI, comprehensiveness score, and total video score were examined according to the upload source, these values were determined to be 150 (30-695), 175 (114-686) seconds, 24 (12-48) months, 0.34 (0.07-1.04), 0.34 (0.07-1.04), 50.0 (6.25-75), and 5 (4-6), respectively, for universities/professional organizations/non-profit physicians/physicians; 156 (38-3,310), 163 (111-404) seconds, 27 (15-76) months, 0.53 (0.07-2.17), 0.53 (0.07-2.17), 50 (25.00-87.50), and 7 (4-11), respectively, for stand-alone health information websites; 507 (77-5,569), 146 (93-335) seconds, 28 (12-52) months, 0.77 (0.18-5.63), 0.77 (0.18-5.63), 50 (25.00-87.50), and 6 (4-7), respectively, for medical advertisement/for-profit companies; and 298 (95-1,069), 167 (128-290) seconds, 16 (9-52) months, 0.51 (0.23-2.33), 0.51 (0.23-2.33), 37.50 (25.00-75.00), and 5 (4-12), respectively, for individual users. There was no statistically significant difference between the upload source groups in terms of any of these variables (P>0.05) (Table 2).

Videos classified as useful and misleading were compared according to uploader characteristics. The highest rate of misleading videos belonged to universities/professional organizations/non-profit physicians/physicians (96.9%), with statistically significant differences when compared to stand-alone health information websites and individual users (76%, and 76.1%, respectively, P<0.05). The group with the highest rate of useful videos was stand-alone health information websites (24%). The rate of useful videos in this group was significantly higher than that detected for universities/professional organizations/non-profit physicians/physicians (3.1%, P<0.05) (Table 2).

Data are presented as median (25-75th percentile) or n (%). The Kruskal-Wallis test was applied. The same superscripts (a, b) denote a subset of categories that are not statistically significantly different from each other at the P=0.05 level. The chi-square test was applied.

The content of the videos was also examined to determine whether they covered the following topics: the most appropriate time for BSE, complete removal of upper clothing, examination being performed in front of a mirror, looking at the external appearance of the breasts in the mirror, explaining how to perform manual examination, examination being performed separately while lying down, sitting, and standing, dis-

Table 1. Evaluation of the global quality score of the videos according to Azer's criteria

Major criteria:
1. Scientific accuracy of videos on BSE
2. Quality of images
3. Upload source being clearly specified
4. Clarity of the topic discussed
5. Quality of video sound and absence of background noises
Minor criteria:
1. Video covering the topic specified in the title
2. Designed at the level of medical undergraduate students
3. Reasonable downloading/streaming time
4. Up-to-date information available about the upload source
5. Education goals specified
6. BSM is shown on a real person rather than a picture

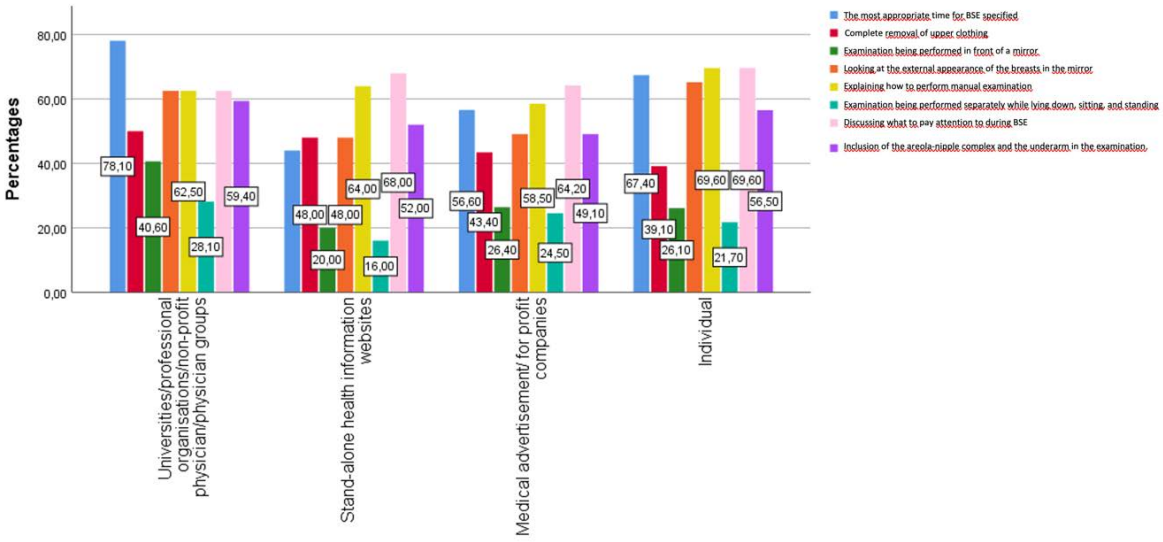

Fig. 2. Characteristics by source of uploads.

cussing what to pay attention to during BSE, and inclusion of the areola-nipple complex and the underarm in the examination. There was no significant difference between the upload source groups in relation to the comprehensiveness score obtained from this evaluation (Fig. 2) However, as the number of covered topics increased, there was a significant increase in the total video score (P<0.001) (Tables 2 and 3).

There was a negative correlation between the total video score and video length (r=-0.225, p = 0.005), number of daily views (r=-0.163, P=0.042), and the VPI (r = -0.163, P=0.042). In addition, the total video score had a positive and significant relationship with the time since upload (r=0.167, P=0.037) and the comprehensiveness score (r=0.422, P<0.001). However, no significant correlation was found between the total video score and total views (r=-0.082, P=0.307) (Table 3).

Spearman's rho correlation test was applied. Statistical significance was demonstrated using the P-value. P<0.05 was considered statistically significant and marked in bold (r: correlation coefficient)

DISCUSSION

The internet is a widely used tool for obtaining information about healthcare. YouTube has a huge amount of data on healthcare. Some of the information presented on this platform is misleading or inaccurate. Considering that YouTube is one of the most accessed websites across the world, it is clear that such misleading information can easily spread and have unfavorable consequences. To prevent this, it is necessary to take steps to increase the quality of uploaded videos and ensure their quality control. In the literature, there are many studies investigating the quality of YouTube videos on medical issues [15-20].

This study evaluated whether the Turkish-titled videos searched with the keyword "breast self-examination" on YouTube complied with the relevant guidelines, provided accurate information, and were educationally useful or misleading. Of the videos that emerged from this search, 74.3% were included in the sample, and 25.7% were excluded. In similar previous studies, the rate of exclusion ranged from 80 to 90% [27, 28]. This shows that although searches are made using related keywords, the content of the videos displayed may be irrelevant to the subject. This may be due to uploads with the purpose of advertising a product or service and attempts to increase the number of views. In the current study, the rate of exclusion was lower than reported in the literature, probably because the search was limited to Turkish-titled videos.

In the literature, different rates of usefulness have been reported concerning YouTube videos on different subjects. For example, the rate of useful videos was found to be over 60% for those with spondylarthritis [29], 62% for those with lung cancer [30], 65.4% for those with asthma [31], and 22% for those on endoscopic transsphenoidal surgery [32]. In addition, Esen

Table 2. Comparison of all parameters between the upload source groups

Characteristics		All videos (n=156)	Universities/professional organizations/non-profit physicians/physicians (n=32)	Stand-alone health information websites (n=25)	Medical advertisement/for-profit companies (n=53)	Individual users (n=46)	P value
Total views		256 (59-2,680)	150 (30-695)	156 (38-3,310)	507 (77-5,569)	298 (95-1,069)	0.233
Video length, second		164 (110-357)	175 (114-686)	163 (111-404)	146 (93-335)	167 (128-290)	0.282
Time since upload (month)		24 (12-52)	21 (12-48)	27 (15-76)	28 (12-52)	16 (9-52)	0.599
Views per day		0.49 (0.12-2.49)	0.34 (0.07-1.04)	0.53 (0.07-2.17)	0.77 (0.18-5.63)	0.51 (0.23-2.33)	0.143
Video power index (VPI)		0.49 (0.12-2.49)	0.34 (0.07-1.04)	0.53 (0.07-2.17)	0.77 (0.18-5.63)	0.51 (0.23-2.33)	0.143
Comprehensiveness score		50 (25-75)	50.0 (6.25-75)	50 (25.00-87.50)	50 (25.00-87.50)	37.50 (25.00-75.00)	0.515
Total video scores		4 (5.5-8)	5 (4-6)	7 (4-11)	6 (4-7)	5 (4-12)	0.442
Speaker gender, n (%)	Man	76 (48.7%)	19 (59.4%)	13 (52.0%)	25 (47.2%)	19 (41.3%)	0.357
	Woman	68 (43.6%)	13 (40.6%)	9 (36.0%)	22 (41.5%)	24 (52.2%)	
	No speaker	12 (7.7%)	0 (0.0%)	3 (12.0%)	6 (11.3%)	3 (6.5%)	
Usefulness, n (%)	Misleading information	133 (85.3%)	31 (96.9%)[a]	19 (76.0%)[b]	48 (90.6%)[a,b]	35 (76.1%)[b]	**0.024**
	Useful information	23 (14.7%)	1 (3.1%)[a]	6 (24.0%)[b]	5 (9.4%)[a,b]	11 (23.9%)[b]	

Table 3. The relationship between total video score and video characteristics

	Total Video Scores	
Characteristic	**R value**	**P value**
Total views	-0.082	0.307
Video length, second	-0.225	**0.005**
Time since upload (month)	0.167	**0.037**
Views per day	-0.163	**0.042**
Video Power Index	-0.163	**0.042**
Comprehensiveness score	0.422	**<0.001**

Spearman's rho correlation test was applied. Statistical significance was demonstrated using the P-value. P<0.05 was considered statistically significant and marked in bold (r: correlation coefficient)

et al. [26] reported the rate of useful videos to be[26]. In our study, this rate was determined to be lower, at approximately 14.7%. According to this result, it can be suggested that the educational quality of BSE videos with Turkish titles on YouTube is very inadequate.

When the distribution of upload sources was examined, 20.5% of the videos had been uploaded by universities/professional organizations/non-profit physicians/physicians, 16.02% by stand-alone health information websites, 33.4% by medical advertisement/for-profit companies, and 29.5% by individual users. In previous studies, the rate of healthcare professionals among video uploaders was reported to be 69% for spondylarthritis videos [29] and 7.7% for asthma videos [31]. Therefore, this rate seems to vary according to the subject of the videos examined in the literature.

Elangovan et al. [29] reported that 96% of useful videos had been uploaded by healthcare professionals. The authors also found that 83% of misleading videos had been uploaded by healthcare professionals. In a study on laryngeal cancer, Enver et al. [33] emphasized that videos uploaded by universities were more useful. Diers et al. [31] determined that a small portion (7.7%) of asthma-related videos had been uploaded by healthcare professionals, but they were more useful than those from other uploaders. Thus, there is no consensus in the literature on this issue. While the videos that were found to be useful in our study had been mostly uploaded by independent health information

websites, misleading videos had been mostly uploaded by universities/professional organizations/non-profit physicians/physicians. This supports the data of some of the studies in the literature, revealing that even if some uploaders are healthcare professionals, there is a need for more useful videos with better quality.

Diers et al. [31] reported that the videos of uploaders other than healthcare professionals were more popular. Meteran et al. [30] determined that misleading videos were more popular (30). In contrast, in our study, there was no significant difference between the upload source groups in terms of total views, video length, time since upload, daily views, VPI, comprehensiveness score, or total video score.

In this study, we determined that the total views, daily views, VPI, and comprehensiveness scores of videos classified as useful according to Azer's criteria were higher when compared to those of misleading videos. This result shows that useful videos attract more attention from viewers. In our study, total views did not have a correlation with the total video score. However, as the time since the video upload and the comprehensiveness score increased, the total video score also increased. In addition, there was a negative relationship between the total video score video length, and daily views.

Limitations

Among the limitations of this study are that videos uploaded to platforms other than YouTube were not evaluated, and videos that were not in Turkish were excluded. Another limitation is that the total video score was calculated subjectively.

CONCLUSION

Based on the results of this research, it is not easy to directly access educational videos about BSE on YouTube. The number of useful Turkish videos about BSE was found to be very low. While we expected to see that the videos uploaded by healthcare professionals would have higher content quality and educational value, we did not observe this. There was no significant difference between the upload source groups in terms of the parameters examined. Therefore, we conclude that healthcare professionals using the YouTube platform should produce more educational and useful videos. We recommend that YouTube videos on BSE be prepared in accordance with the relevant guidelines by prioritizing educational and useful content and taking Azer's criteria into account to increase views and likes.

Authors' Contribution

Study Conception: MEU; Study Design: MEU; Supervision: EB; Funding: EB; Materials: EB; Data Collection and/or Processing: MEU ; Statistical Analysis and/or Data Interpretation: MEU; Literature Review: MEU; Manuscript Preparation: MEU and Critical Review: MEU.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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The European Research Journal 2024;10(2):218-225 Original Article

DOI: https://doi.org/10.18621/eurj.1295895 *Infectious Diseases*

Bibliometric analysis of publications on osteoarticular brucellosis

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ABSTRACT

Objectives: The aim of this investigation was to undertake a thorough bibliometric analysis of publications between 1991 and 2022 to scrutinize and comprehend the research landscape of osteoarticular brucellosis, a zoonotic infection that affects bones and joints.

Methods: We scrutinized the distribution of publications by various criteria, including country, institution, author, and journal. Furthermore, we executed citation analysis, established collaboration networks, and performed keyword co-occurrence analysis.

Results: Our examination discovered 432 documents on this topic indexed in the Web of Science database, with a noticeable surge in publications over time. Turkey, the United States, and Iran were the leading nations in terms of research output. The University of Buenos Aires emerged as the most productive institution. The primary research areas were General Internal Medicine, Infectious Diseases, and Rheumatology. The primary beneficiary of this research was Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT).

Conclusions: This study furnishes valuable insights into worldwide research endeavors on osteoarticular brucellosis. These insights can steer future research directions, emphasizing the necessity for sustained collaboration and funding support to tackle this significant public health issue.

Keywords: Osteoarticular brucellosis, bibliometric analysis, web of science database

The Brucella species causes a zoonotic infection known as brucellosis which presents itself in various forms including osteoarticular brucellosis that affects bones and joints leading to arthritis, spondylitis or even osteomyelitis [1, 2]. In light of its growing prevalence rates infectious diseases specialists need to carry out thorough analyses of available literature regarding research trends and knowledge gaps [3, 4]. This form presents unique challenges when it comes to diagnosis, treatment and prevention hence necessitating advanced comprehension through continued research efforts backed by relevant stakeholders. The study delves into bibliometric analysis from publications made between 1991-2022 spanning multiple geographies institutions documenting authorship roles played across different journals while revealing new insights into global research efforts centred around Osteoarticular Brucellosis.

In addition, analysts have applied tactics like citation analysis, collaboration networks, and keyword co-occurrence analysis to clarify ongoing research themes as well as possible areas where additional knowledge is required.

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METHODS

In this bibliometric search, we gathered information from the Web of Science (WoS) database (Clarivate Analytics, Philadelphia, PA, USA) to obtain the information "osteoarticular" and "brucellosis," "bone and joint" and "brucellosis," "brucellosis and arthritis," "brucellosis and osteoarticular manifestations," "brucellosis and bursitis," and "brucellosis and tenosynovitis." We conducted these searches on titles, descriptions, keywords, and WoS with KeyWords Plus. We saved titles, document types, publication years, authors, organizations, keywords, abstracts of each record, H-index, and citations in WoS publications as TXT files.We imported them into Microsoft Office Excel 2023 (Los Angeles, CA, USA). We received the data for this study on April 23, 2023 and the material was reviewed and analyzed.

In cases where authorship is not provided, we accept that the original work and the authors are the same. Likewise, we distributed publications from a school that was the school of the first author. For articles with more than one co-author, only the first coauthor is considered. We use the address to identify the type of partnership. We analyzed the data published between 1991 and 2022, excluding the publication in 2023, as the year is not yet over.

Statistical Analysis

We use the tool VOSviewer 1.6.18 for Microsoft Windows systems to view country coordination and content. We base our data collection on data identified through advertising, e.g., country, citation and keywords).

RESULTS

Based on the search method used in this study, the findings revealed that 470 documents on this topic were indexed in the Wos database between 1991 and 2022. Three hundred eighty-three documents are articles, and 49 are review articles. We analyzed only these 432 documents.

Most publications on osteoarticular brucellosis were indexed in the Science Citation Index Expanded (SCI-Expanded), accounting for 79.06% of the total records. The Emerging Sources Citation Index (ESCI) accounted for 20.24% of the publications. A tiny percentage of publications were indexed in the Social Sciences Citation Index (SSCI) and Arts & Humanities Citation Index (A&HCI), with 0.47% and 0.24%, respectively. These findings emphasize that most research on osteoarticular brucellosis is concentrated in science and emerging sources, with minimal representation in social sciences and arts & humanities databases.

The most cited article on this topic was published in 1996, titled "Complications associated with Brucella melitensis infection: A study of 530 cases" by Colmenero *et al*. [2]. The most common keywords in the analyzed publications were "brucellosis," "osteoarticular involvement," "brucella," "treatment," and "epidemiology."

These findings show the distribution of publications on osteoarticular brucellosis across different years, with a general increase in publications over time. The highest number of publications was in 2019, with 7.87%. In more recent years, there has been a

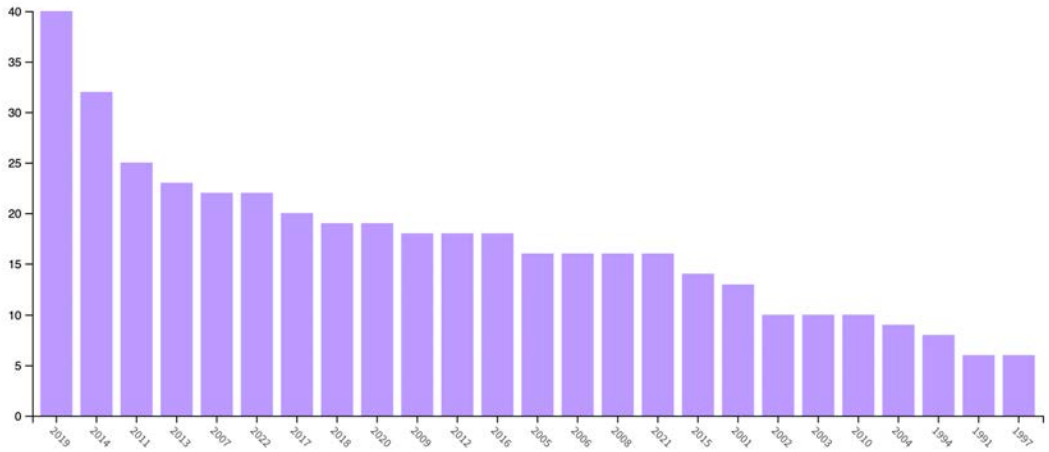

Fig. 1. The number of publications in 1991-2022.

Table 1. The top published countries

Country/Region	Record Count	% of 470
Turkey	141	30.000
USA	48	10.213
Iran	40	8.511
Peoples R China	34	7.234
Spain	32	6.809
Saudi Arabia	23	4.894
Argentina	21	4.468
India	18	3.830
Israel	11	2.340
Brazil	9	1.915
England	9	1.915
France	9	1.915
Greece	9	1.915
Tunisia	8	1.702
Australia	6	1.277
Egypt	6	1.277
Italy	6	1.277
Portugal	6	1.277
Germany	5	1.064
Peru	5	1.064
Lebanon	4	0.851
Macedonia	4	0.851
South Korea	4	0.851
Iraq	3	0.638
North Macedonia	3	0.638

Total 64 countries

slight decrease in the number of publications, with 4.68% of publications in 2022 (Fig. 1).

Table 1 presents the top published countries in osteoarticular brucellosis research. A total of 64 countries contributed to the research output. Turkey emerged as the leading country with 141 publications, accounting for 30% of the total records. The United States followed with 48 publications (10.213%), and Iran ranked third with 40 publications (8.511%). Other top publishing countries included China (7.234%), Spain (6.809%), Saudi Arabia (4.894%), Argentina (4.468%), India (3.830%), Israel (2.340%), Brazil, England, France, and Greece each with nine publications (1.915%), and Tunisia (1.702%). The remaining countries contributed fewer publications, with percentages ranging from 1.277% to 0.638%. This distribution of research output highlights the global interest in osteoarticular brucellosis and the significant contribution of countries with high brucellosis prevalence to the existing body of knowledge.

Table 2 showcases the top-ranked institutions contributing to research in osteoarticular brucellosis. A total of 619 organizations were involved in the publication of these studies. The University of Buenos Aires in Argentina led the list with 17 publications, representing 3.617% of the total records. Argentina's Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) was the second most prolific institution, with 11 publications (2.340%). Erciyes University in Turkey ranked third with ten publications (2.128%). Başkent University and Çukurova University, both from Turkey, followed with nine publications each (1.915%). Other leading institutions included Babol University of Medical Sciences in Iran, Hospital Carlos Haya in Spain, and Tehran University of Medical Sciences in Iran, each with eight publications (1.702%). Dicle University and Gaziantep University, located in Turkey, contributed seven publications each (1.489%). These findings highlight the significant role of various institutions in advancing research on osteoarticular brucellosis, with a strong representation of Turkish and Argentine institutions among the top contributors.

Table 3 displays the distribution of publications on osteoarticular brucellosis across various research areas. A total of 49 research areas were covered in the analysis, with the top 10 areas presented in the table. General Internal Medicine was the most represented research area with 109 publications (23.191%), followed closely by Infectious Diseases, accounting for 101 publications (21.489%). Rheumatology came in third with 67 publications (14.255%). Other significant research areas included Immunology and Microbiology, each with 51 publications (10.851%), Pediatrics with 39 publications (8.298%), Tropical Medicine with 24 publications (5.106%), Veterinary Sciences with 22 publications (4.681%), Orthopedics with 20 publications (4.255%), and Public Environmental Occupational Health with 19 publications (4.043%). These findings demonstrate the interdisci-

Table 2. **The top ranked institutions**

Institutions, Country	Record Count	% of 470
University of Buenos Aires	17	3.617
Consejo Nacional de Investıgacıones Cientificas Y Tecnicas Conicet	11	2.340
Erciyes University	10	2.128
Baskent University	9	1.915
Cukurova University	9	1.915
Babol University of Medical Sciences	8	1.702
Hospital Carlos Haya	8	1.702
Tehran University of Medical Sciences	8	1.702
Dicle University	7	1.489
Gaziantep University	7	1.489

Total 619 organizations

plinary nature of osteoarticular brucellosis research, emphasizing the involvement of various medical fields in understanding and addressing this condition.

Table 4 lists the top funding agencies supporting research in osteoarticular brucellosis. Out of 114 funding agencies identified, ten are shown in the table, while 387 records (82.340%) did not have data available for analysis. The Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) from Argentina was the leading funder with 16 publications (3.404%). The National Institutes of Health (NIH) in the United States and the United States Department of Health and Human Services both supported 13 publications each (2.766%). Argentina's Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) funded 12 publications (2.553%), and the National Natural Science Foundation of China (NSFC) supported nine publications (1.915%). Other notable funders included the University of Buenos Aires (1.277%), Brazil's Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (1.064%), the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) in Brazil (0.851%), the National Institute of Allergy and Infectious Diseases (NIAID) in the United States (0.851%), and the University of Missouri College of Veterinary Medicine and Research Board (0.851%). This highlights the critical role of various funding agencies in promoting and advancing osteoarticular brucellosis research worldwide.

Table 5 and fig. 2 summarizes citations, H-indexes, and the number of publications in osteoarticular brucellosis research across different periods. From 1991 to 2000, 46 publications received 1,621 citations and 1,583 without self-citations. The average number of citations per publication was 35.24, and the H-index for this period was 19. Between 2000 and 2009, the number of publications increased to 135, with 3,113 total citations, 2,939 citations without self-citations, and an average of 23.06 citations per publication. The H-index for this time span was 31.

In the following decade, 2010-2019, there were 219 publications with 2,738 total citations, 2,325 ci-

Table 3. **Research areas**

Research Area	Record Count	% of 470
General Internal Medicine	109	23.191
Infectious Diseases	101	21.489
Rheumatology	67	14.255
Immunology	51	10.851
Microbiology	51	10.851
Pediatrics	39	8.298
Tropical Medicine	24	5.106
Veterinary Sciences	22	4.681
Orthopedics	20	4.255
Public Environmental Occupational Health	19	4.043

Showing 10 out of 49 entries

Table 4. **Funding agencies**

Funding Agency	Record Count	% of 470
Agencia Nacional de Promoción Científica y Tecnológica	16	3.404
National Institutes of Health	13	2.766
United States Department of Health Human Services	13	2.766
Consejo Nacional de Investigaciones Cientificas Y Tecnicas Conicet	12	2.553
National Natural Science Foundation of China	9	1.915
University of Buenos Aires	6	1.277
Conselho Nacional de Desenvolvimento Cientifico E Tecnologico	5	1.064
Fundacao de Amparo a Pesquisa do Estado de Minas Gerais	4	0.851
National Institute of Allergy Infectious Diseases	4	0.851
University of Missouri College of Veterinary Medicine and Research Board	4	0.851

Showing 10 out of 114 entries; 387 record(s) (82.340%) do not contain data in the field being analyzed.

Table 5. **The summary of citations, H indexes, and the number of publications**

Time span	No. of publications	Total citations	Citations without self-citations	Citations average per	H-Index
1991-2000	46	1,621	1,583	35.24	19
2000- 2009	135	3,113	2,939	23.06	31
2010-2019	219	2,738	2,325	12.5	27
2019-2022	97	298	260	3.07	9

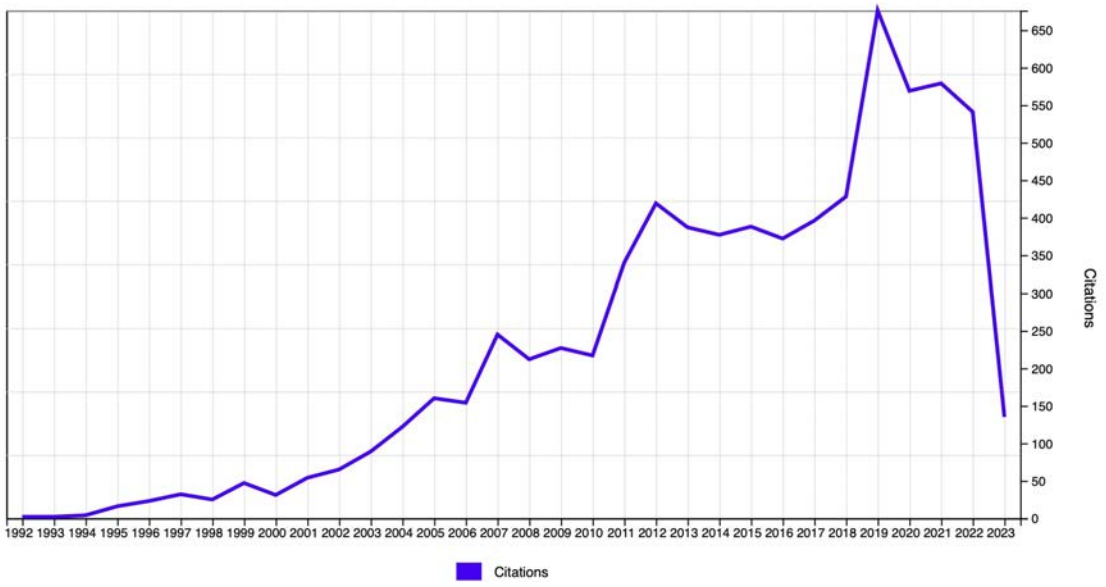

Fig. 2. **The number of citations over the years.**

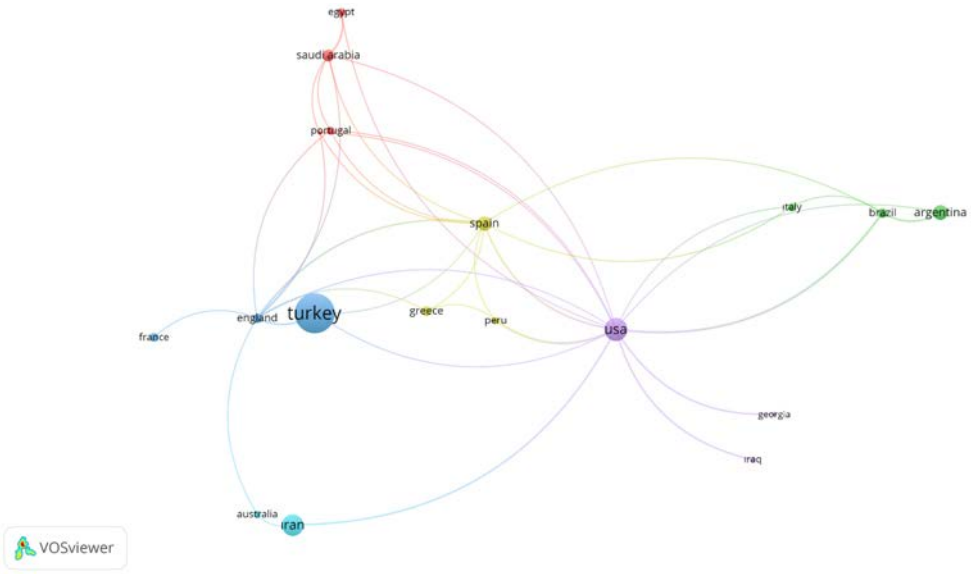

Fig. 3. **Co-authorship (Countries).**

tations without self-citations, and an average of 12.5 citations per publication. The H-index for this period was 27. From 2019 to 2022, 97 publications garnered 298 total citations and 260 citations without self-citations. The average number of citations per publication was 3.07, and the H-index was 9. This table illustrates the growth in osteoarticular brucellosis research over time and the impact of these publications as measured by citations and H-indexes. The mapping analysis of the documents is given in Figs. 3-5.

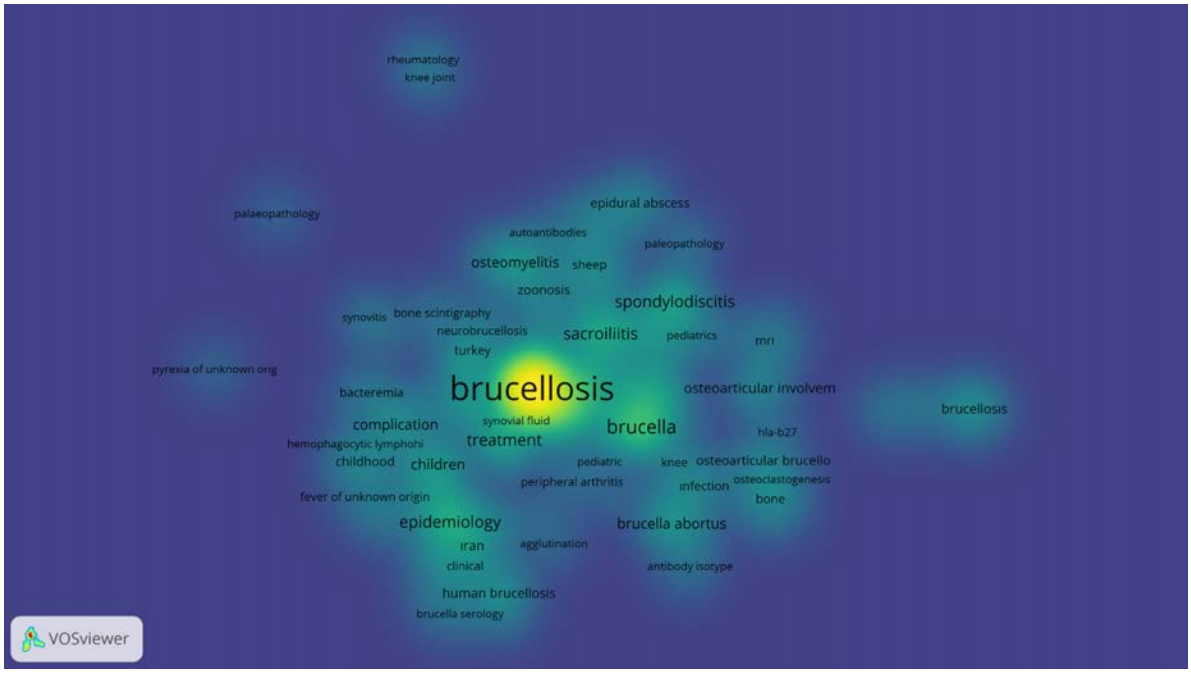

Fig. 3. **Keyword co-occurrence.**

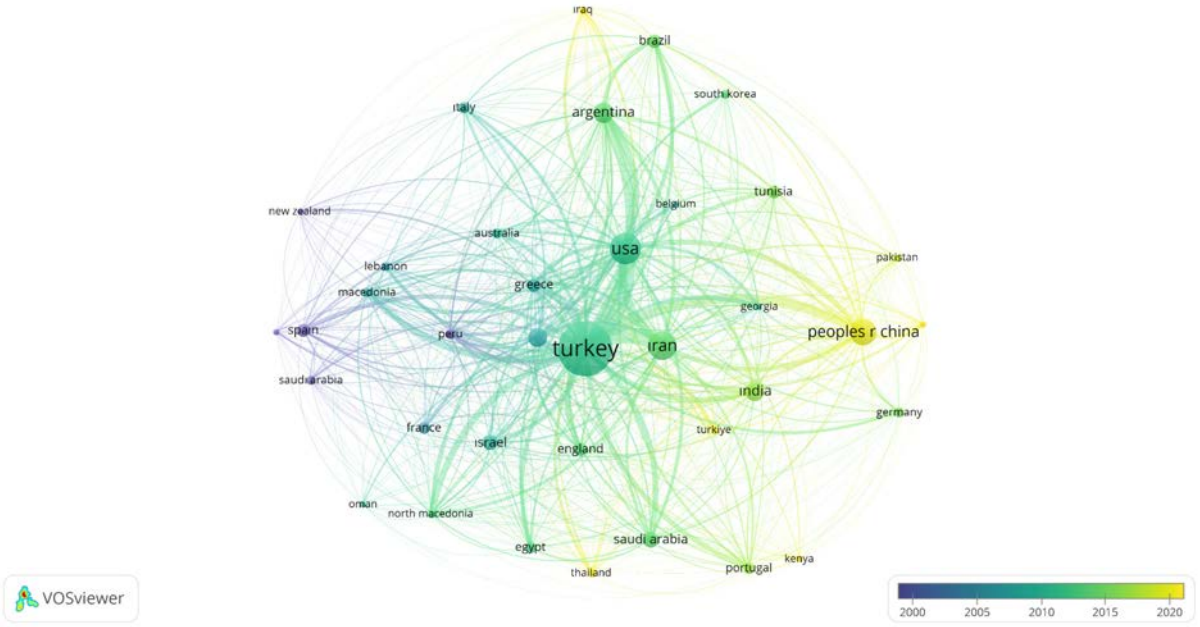

Fig. 5. **Bibliographic coupling of countries according to citations.**

DISCUSSION

Bibliometric research has become more and more known in the context of classification, knowledge and quality of work of different disciplines, especially within the medical literature in recent years [5, 6]. Researchers from numerous countries, including ours, have significantly contributed significantly to this area [7]. The scientific literature can be systematically evaluated by employing bibliometric analyses, offering valuable insights to researchers in the relevant fields (8). Some databases, such as Elsevier's Scopus database [9], Web of Science Core Collection (WoSCC) [10], and PubMed Medline [11] have used various bibliometric studies. In the current view, the WoSCC database was chosen because its comprehensive range of journal content and is suitable for extensive research [12].

The bibliometric analysis of the distribution of osteoarticular brucellosis from 1991 to 2022 shows several highlights of regional trends. Long-term interest in questioning outcomes is widespread, reflecting awareness of the importance of osteoarticular brucellosis as a zoonotic disease and its global impact on public health [1]. However, the slight decline in the number of publications in 2022 (4.68%) calls for renewed efforts in research and funding to address this disease effectively. The reason for this decrease in the number of publications may be the concentration of scientific research in this field due to the COVID-19 pandemic.

The main points of keyword co-occurrence analysis indicate that osteoarticular brucellosis research mainly focuses on proposed strategies, treatment-modalities and epidemiology. However, more research is needed on the principles of osteoarticular brucellosis and the development of new treatments.

The best of osteoarticular brucellosis research demonstrates collaborative research between important different disciplines, as evidenced by the combination of disparate materials such as internal medicine, infectious diseases, rheumatology, immunology, and microbiology. This collaboration provides a better understanding of disease etiology, pathogenesis, and clinical symptoms and illuminates advances in symptoms and treatment strategies [3].

The geographical distribution of studies investigating the occurrence of osteoarticular brucellosis have shown that countries with high brucellosis rates such as Turkey, United States, and Iran are responsible for the already existing knowledge. This finding fits well with the previous notion that these countries have a heavy burden of brucellosis and funding research to address this health proble [13].

The review also highlights the important role of different funding agencies in advancing and improving osteoarticular brucellosis research. Cash support is essential for us to better understand the disease and develop effective ways to prevent it. It is worth noting that Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT), National Institutes of Health (NIH) and the United States Department of Health and Human Services are the main funding agencies [14].

Limitations

The limitation of our study is that only one database was searched, which may lead to the exclusion of relevant scientific literature.

CONCLUSION

In conclusion, a bibliometric review of publications on osteoarticular brucellosis from 1991 to 2022 demonstrates the growth of the research literature, with the importance of collaboration and significant contributions to countries with high brucellosis rates. Continuing research and funding are required to address the challenges of osteoarticular brucellosis and improve public health outcomes.

Authors' Contribution

Study Conception: CS; Study Design: CS; Supervision: CS; Funding: CS; Materials: CS; Data Collection and/or Processing: CS; Statistical Analysis and/or Data Interpretation: CS; Literature Review: CS; Manuscript Preparation: CS and Critical Review: CS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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The relationship between social phobia and cognitive impairment in idiopathic generalized epilepsy patients: a cross-sectional study

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ABSTRACT

Objectives: Epilepsy, a neurological disorder affecting approximately 65 million people worldwide, frequently presents with various comorbidities, including cognitive impairment. The factors contributing to cognitive impairment are complex and multifaceted. This study aimed to investigate the influence of social phobia on cognitive function in patients with idiopathic generalized tonic-clonic epilepsy.

Methods: This prospective study recruited 87 adult idiopathic generalized tonic-clonic epilepsy patients diagnosed according to the International League Against Epilepsy 2017 classification. Differential diagnosis involved electroencephalography, magnetic resonance imaging, and neurological examinations. All participants were assessed for cognitive impairment, social phobia, depression, and anxiety using the Montreal Cognitive Assessment, Liebowitz Social Anxiety Scale, Beck Depression Inventory, and Beck Anxiety Inventory, respectively .

Results: A significant majority (73.6%) of participants reported social phobia. Compared to those without social phobia, the Montreal Cognitive Assessment total score was significantly lower in the social phobia group (P=0.002). Additionally, epilepsy duration was significantly longer in the social phobia group (P=0.03). Montreal Cognitive Assessment scores showed a negative correlation with Liebowitz Social Anxiety Scale-avoidance, Liebowitz Social Anxiety Scale-total, and age (P=0.003, P=0.005, and P<0.001, respectively).

Conclusion: This study suggests that individuals with idiopathic generalized tonic-clonic epilepsy experiencing social phobia may exhibit lower cognitive function compared to those without. This indicates that comorbid social phobia might negatively impact cognitive abilities in idiopathic generalized tonic-clonic epilepsy patients.

Keywords: Idiopathic generalized tonic-clonic epilepsy, social phobia, cognitive impairment, anxiety, depression

Epilepsy is a chronic neurological disease characterized by at least two unprovoked seizures occurring >24 hours apart and is a significant public health problem affecting 65 million people worldwide. The prevalence of active epilepsy ranges from 4 to 10 per 1000. The lifetime prevalence of epilepsy is 10.3 per 1000 in developing countries and 5.82 per 1000 in developed countries [1]. Epilepsy pa-

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tients often experience difficulties in their social and professional lives. Studies indicate that psychiatric comorbidities are common in these patients, reported at a rate of 19-71%. Comorbidities in epilepsy patients can sometimes be more burdensome than seizures, and the most common psychiatric comorbidities in epilepsy patients are mood disorders (24-74%), followed by anxiety disorders (10-25%), psychosis (2-7%) and personality disorders (1-2%) [2].

Social phobia, a marked fear or anxiety about one or more social situations in which an individual is subject to possible scrutiny by others, is a common disorder among anxiety disorders. Only a few studies evaluated social phobia in epilepsy patients [3, 4]. Moreover, social phobia is associated with an increased risk of cognitive impairment [5-7]. Cognitive impairment is a decline in cognitive abilities, such as memory, attention, and problem-solving that interferes with daily life. Cognitive impairment is a common problem in people with idiopathic generalized tonic-clonic seizures [8]. The severity of cognitive decline can vary from person to person. Studies have shown that up to 70% of people with generalized tonic-clonic seizures have some degree of cognitive impairment [8, 9].

There are only a limited number of studies exploring the connection between social phobia and generalized tonic-clonic seizures [6, 7]. Furthermore, to our knowledge, no research has yet examined the relationship between social phobia and cognitive impairment in this specific patient population. This study was designed to primarily investigate the connection between cognitive impairment and social phobia, depression, and anxiety in individuals with generalized tonic-clonic seizures. Additionally, we aimed to analyze the potential associations between cognitive impairment and factors such as age, gender, epilepsy duration, seizure frequency, and medication use.

METHODS

Study Overview

This prospective study, carried out between March and July 2023 in a neurology outpatient clinic of a tertiary hospital. Informed written consent was obtained from all patients.

Ethical Considerations

This study was approved by the Kastamonu University Ethics Committee (project number 2023-KAEK-22).

Study Population

The study included 87 adult epilepsy patients diagnosed with idiopathic generalized tonic-clonic epilepsy, according to The International League Against Epilepsy 2017 (ILAE), who applied to the Neurology Outpatient Clinic of a tertiary hospital. Patients diagnosed with a psychiatric disease or intellectual disability (n=14), those with neurological disease other than epilepsy (n=7), patients under the age of 18 (n=3), those with any severe and progressive organic disease (n=1), those with any structural lesion in the brain identified using magnetic resonance imaging (MRI) (n=5), those who had seizures in the last one month (n=9), patients with seizures other than generalized tonic-clonic seizures (JTKSs) (n=11), and patients over 65 years of age (n=9) were not included in the study. A neurologist examined all 87 patients (18-61 years) with epilepsy.

Study Procedure

The patients were asked questions about their age, gender, education level, personal and familial medical history, duration of epilepsy, age of onset of epilepsy, frequency of seizures, and drug use. Differential diagnosis was made using electroencephalography (EEG), MRI, and neurological examination. Seizure frequencies in the last month were recorded. Who received one of the first, second or third generation anti-seizure drugs were grouped as monotherapy and who received them together were grouped as polytherapy. Montreal Cognitive Assessment (MoCA) was applied to test the cognitive status of the patients, Liebowitz Social Phobia Scale (LSPS) was applied to detect the presence and degree of social phobia, and Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were applied to determine depression and anxiety states, respectively.

Study Assessment

MoCA: This assessment comprises 11 sections, including tracing tests, visual construction skills (cube and clock), naming, memory, attention, sentence repetition, verbal fluency, abstract thinking, delayed recall, and orientation. The maximum achievable score

on the test is 30. A total score of 21 and above is considered within normal limits [9]. Kaya *et al*. [10] conducted a validity and reliability study of the test in Turkish society.

LSPS: This instrument consists of two parts. The first part comprises 24 questions scored between 0 and 3 based on the severity of anxiety experienced in described situations. The second part consists of 48 questions, with 24 questions scored between 0 and 3 based on the severity of avoidance in the same situations. While the validity and reliability study did not specify a cut-off value, some studies suggested a cut-off value of 30 [11, 12]. In this study, the LSPS total score was used in statistical analysis, and groups were created as having or not having social phobia using the LSPS cut-off score.

BDI: This scale comprises a total of 21 questions, asking the patient to reflect on their condition in the last week [13]. In the validity and reliability study conducted on the Turkish population by Kapci *et al*. [14], scores of 0-9 indicate minimal depression, 10-16 indicate mild depression, 17-29 indicate moderate depression, and 30-63 indicate severe depression.

BAI: This scale consists of 21 questions with four options, asking the participant to consider the last week [15]. Ulusoy *et al*. [16] conducted a validity and reliability study in the Turkish population, where scores of 8-15 indicate mild anxiety, 1625 indicate moderate anxiety, and 26-63 indicate severe anxiety.

Sample Size Estimation

Using G*Power version 3.1.9.4 for sample size estimation, A prior power analysis was performed based on published study data; The effect size (correlation pH1) in the published study, in which cognitive functions in epilepsy patients were evaluated by MoCA score and correlation analysis with 70 participants [6], was 0.335. Significance criterion=α. 05 and power=.80, the minimum sample size required for a medium effect size is N=84 [for correlation analysis]. Therefore, the resulting sample size N=84 is sufficient to test the study hypothesis.

Statistical Analysis

Data analysis was conducted using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was employed to assess the normality of the data distribution. Descriptive statistics

Table 1. Sociodemographic and clinical characteristics of epilepsy patients

Variable	Data
Age (years)	34.06±11.86
Education (years)	9.01±3.07
Disease duration (years)	12.99±10.47
Number of seizures in the last year	2.73±3.75
Gender, n (%)	
Male	38 (43.7)
Female	49 (56.3)
Marital status, n (%)	
Single	42 (48.3)
Married	45 (51.7)
Place of residence, n (%)	
Rural	24 (27.6)
Urban	63 (72.4)
Smoking, n (%)	
Yes	14 (16.1)
No	73 (83.9)
Alcohol use, n (%)	
Yes	4 (4.6)
No	83 (95.4)
Anti-seizure use, n (%)	
Monotherapy	63 (72.4)
Polytherapy	24 (27.6)
MoCA (cut-off score 21) Cognitive impairment, n (%)	
Yes	40 (46)
No	47 (54)
LSPS (cut-off score 30) Social phobia, n (%)	
Yes	64 (73.6)
No	23 (26.4)
BAI (cut-off point 16) Anxiety, n (%)	
None or mild	59 (67.8)
Moderate or severe	28 (32.2)
BDI (cut-off point 17) Depression, n (%)	
None or mild	63 (72.4)
Moderate or severe	24 (27.6)

Data are shown as mean±standard deviation or n (%). MoCA=Montreal Cognitive Assessment Scale, LSPS=Liebowitz Social Phobia Scale, BDI=Beck Depression Inventory, BAI=Beck Anxiety Inventory,

presented the data, with frequencies and percentages for categorical variables. Continuous variables with normal distributions were expressed as mean±standard deviation, while those without normal distributions were presented as median (maximum-minimum).

For comparisons between numerical values, the Mann-Whitney U test was applied. Categorical values were compared using the Chi-square test. Correlation analysis involved Pearson's correlation coefficient for normally distributed values and Spearman's correlation coefficient for non-normally distributed values. A P-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 38 (43.7%) participants were male, 49 (56.3%) were female, 42 (48.3%) were single, and 45 (51.7%) were married. The mean age of the participants was 34.06±11.86 years, and the duration of education was 9.01±3.07 years. Of the 87 patients, 24 (27.6%) lived in rural areas, while 63 (72.4) lived in urban areas. The disease duration of epilepsy patients was 12.99±10.47 years, the number of seizures in the last year was 2.73±3.75, 63 (72.4%) individuals were receiving monotherapy, and 24 (27.6%) were receiving polytherapy as anti-seizure treatment. In the evaluation with the MoCA scale, cognitive impairment was detected in 40 (46%) participants. When evaluated according to the cut-off values of the scales (LSPS, BAI, BDI) 64 (73.6%) individuals had social phobia, 28 (32.2%) had significant anxiety and 24 (27.6%) had significant depressive symptoms (Table 1).

No significant differences were identified between the groups with and without social phobia concerning age, education, gender, and the number of seizures in the last year (P>0.05). However, it was observed that the group with social phobia had a significantly lower MoCA total score and a significantly longer disease duration compared to the group without social phobia (P=0.002 and P=0.030, respectively). When comparing groups receiving monotherapy and polytherapy, no significant differences were found in terms of age,

Table 2. Comparison of the group with and without social phobia

Variable	No Social Phobia Group	Social Phobia Group	P value
Age	30.78±13.74	35.23±10.99	**0.052****
Education (years)	12.00 (5.00-12.00)	8.00 (5.00-14.00)	0.414**
Gender, number (%)			0.338*
Male	12 (52.2)	26 (40.6)	
Female	11 (47.8)	38 (59.4)	
MoCA total	24.22±3.86	20.55±4.82	**0.002****
Disease duration (year)	5.50 (1.00-33.00)	10.50 (1.00-44.00)	**0.030****
Last year's seizure	0.00 (0.00-12.00)	1.50 (0.00-12.00)	0.260**
	Monotherapy group	**Polytherapy group**	
Age, mean ± SD	34.90±12.11	31.83±11.10	0.300**
Education (years)	8.00 (5.00-14.00)	8.00 (5.00-12.00)	0.503**
Gender, number (%)			0.473*
Male	29 (46)	9 (37.5)	
Female	34 (54)	15 (62.5)	
MoCA total	20.95±5.10	23.00±3.82	0.098**
Disease duration	9.00 (1.00-44.00)	18.50 (1.00-35.00)	0.240**
Last year's seizure	1.00 (0.00-12.00)	2.00 (0.00-12.00)	0.400**

Data are shown as mean±standard deviation or median (minimum-maximum or n (%). MoCA=Montreal Cognitive Assessment Scale, *Chi-square test, **Mann Whitney U test

Table 3. Comparison of MoCA total score with clinical features

	MoCA Total	
	R	P value
Age	−0.449	**<0.001***
Education	0.458	**<0.001****
Disease duration	−0.144	0.182**
Last year seizure	−0.033	0.763**
LSPS-avoidance	−0.317	**0.003***
LSPS-anxiety	−0.168	0.120**
LSPS-total	−0.296	**0.005****
BDI	0.005	0.966**
BAI	−0.154	0.154**

MoCA=Montreal Cognitive Assessment Scale, LSPS=Liebowitz Social Phobia Scale, BDI=Beck Depression Inventory, BAI=Beck Anxiety Inventory, *Pearson correlation analysis, **Spearman correlation analysis

education, gender, MoCA total score, disease duration, and the number of seizures in the last year (P>0.05) (Table 2).

When the relationship between the MoCA total score and the variables was evaluated, the MoCA total score was weakly negatively significant (r= −0.317, P=0.003; r= −0.296, P=0.005) with the LSPS-avoidance and LSPS-total scores and moderately negatively significant (r =−0.449, P<0.001) with age while there was a moderately positive significant (r=0.458, P<0.001) relationship with education (Table 3).

DISCUSSION

In our study, a substantial proportion of epilepsy patients (73.6%) exhibited social phobia. When comparing individuals with and without social phobia, no statistically significant differences were observed in age, education level, gender, or seizure frequency in the last year. However, the group with social phobia had a significantly lower MoCA total score compared to the group without social phobia. Additionally, a negative significant relationship was observed between the MoCA total score, LSPS-avoidance, and LSPS-total scores, as well as age. Conversely, there was a positive and meaningful relationship with education.

Cognitive impairment is a common complication of epilepsy, affecting up to 50% of patients, and is a result of various factors such as the patient's age, seizure frequency, and polytherapy [5]. The relationship between seizure frequency and cognitive decline in epilepsy is complex. Some studies have found a correlation between seizure frequency and cognitive decline, while others have not. Voltzenlogel *et al*. [17] found a correlation between seizure frequency and cognitive decline in refractory epilepsy patients. Black *et al*. [18] found that frequent seizures caused a significant decrease in cognitive functions in patients with temporal lobe epilepsy. In their research, Taylor *et al*. [19] identified seizure frequency as a crucial factor influencing cognitive abilities in untreated epileptic patients [19]. However, Piazzini *et al*. [20] found no correlation between seizure frequency and cognitive impairment in epilepsy patients. Our study found cognitive impairment in 46% of epilepsy patients, similar to the literature. However, we found no significant relationship between seizure frequency and cognitive decline. This result may be due to the low number of patients with frequent seizures in our cohort or to the fact that we exclude patients with brain structural lesions that may cause cognitive impairment [21].

Cognitive impairment is common in epilepsy patients receiving high-dose and multiple anti-seizure treatments [22]. It is primarily manifested in executive functions [23]. Most anti-seizure drugs (ASDs) have mental side effects such as inattention, insomnia, and dizziness [24]. The relationship between cognitive impairment and medication in epilepsy is complex. Some studies have found that polytherapy is associated with worse cognitive function, but others have not [24]. The higher incidence of cognitive impairment in patients receiving polytherapy may be due to resistant and frequent seizures [24]. Interestingly, our study found no significant difference in cognitive impairment between groups taking polytherapy and those on monotherapy. This could potentially be due to the younger average age of the polytherapy group.

Anxiety is a common comorbidity in epilepsy patients, with a reported prevalence of around 20% [25]. However, the relationship between anxiety and cogni-

tive function in epilepsy patients is complex and poorly understood. Some studies have found an association between anxiety and cognitive impairment. For example, Miller *et al*. [26] found that higher anxiety levels were associated with worse visual memory outcomes in epilepsy patients. Velissaris *et al*. [27] found that epilepsy patients with high anxiety levels had lower cognitive function scores. Our study found that anxiety levels were high (32.2%), but there was no significant relationship between anxiety and cognitive impairment.

Depression is a common comorbidity in epilepsy patients, with a reported prevalence of around 20-30% [28-32]. It has been associated with many factors, including seizure frequency, type of epilepsy, medication use, and occupational activity [23]. Our study revealed a prevalence of moderate-to-severe depression in 27.6% of epilepsy patients, consistent with the literature. However, we did not find a statistically significant link between depression symptoms and cognitive impairment.

The number of studies investigating social phobia in epilepsy patients is limited [3,4]. Moreover, to the best of our knowledge, no prior study has explored the specific interaction between social phobia and cognitive function in epilepsy patients. Kutlu *et al*. [4] showed that patients with epilepsy had significant levels of social phobia compared to healthy control groups. In a recent study, especially persistent seizures were related to social phobia in males [33]. A study conducted in China showed that social anxiety is independently associated with low quality of life [34]. In our study, social phobia symtoms were observed in 73.6% of the patients. Notably, individuals in the social phobia group demonstrated significantly lower overall scores on the MoCA compared to those without social phobia. This suggests a potential link between social anxiety and cognitive impairment in epilepsy patients. The underlying mechanisms responsible for the association between social phobia and cognitive impairment remain unclear. However, social phobia may lead to social isolation, a known risk factor for cognitive decline. Furthermore, social phobia may be associated with underlying cognitive deficits that hinder engagement in social activities. For instance, individuals with social phobia may experience difficulties with memory, attention, and executive functioning. These cognitive impairments can make it challenging to maintain social connections and engage in stimulating activities, further contributing to cognitive decline [7, 8].

Limitations

This study has some limitations. Considering the sample size was not very large, groups could not be formed according to individual drug use, and scale scores could not be compared. Our study is a cross-sectional measurement, and the type of data collection tools we used may be reflected in our findings; longitudinal studies are needed for more valid evidence. The patients' levels of anxiety, depression, and social phobia were measured using the BAI, BDI, and LSPS scales, respectively. The patients were unable to have a comprehensive psychological examination.

CONCLUSION

The group with social phobia exhibited a significantly lower MoCA total score, and the duration of the disease was significantly longer compared to the group without social phobia. In conclusion, the presence of comorbid social phobia in epilepsy patients appears to be linked to poorer cognitive functions. Offering social and psychological support to these patients regarding social phobia may prove beneficial in preserving cognitive functions.

Authors' Contribution

Study Conception: İK, Aİ; Study Design: İK, Aİ; Supervision: İK, Aİ; Funding: İK, Aİ; Materials: İK, Aİ; Data Collection and/or Processing: İK, Aİ; Statistical Analysis and/or Data Interpretation: İK; Literature Review: İK; Manuscript Preparation: İK, Aİ and Critical Review: İK, Aİ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2024;10(2):234-240 Review

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Occupational skin carcinogens

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ABSTRACT

Occupational skin cancer may manifest when employees are under exposure to one specific carcinogenic substance or more in the workplace. Workplaces often have higher concentrations of carcinogens compared to any other setting. The most common causes of skin cancer in the workplace are ultraviolet radiation, ionizing radiation, polycyclic aromatic hydrocarbons, and arsenic. However, there is only a limited number of studies on skin cancer from occupational exposure. Skin cancers that are considered mainly work-related are non-melanoma skin cancers. Their most common variants are basal cell carcinomas, squamous cell carcinomas, and actinic keratosis. Two factors that reduced the risk of occupational carcinogen exposure are as follows: a better understanding of skin cancer risk factors involved in industrial processes and better control of the use of ionizing radiation. However, the exposure risk to ultraviolet radiation at dangerous levels remains. Worse still, this risk is often not considered. Yet, the prevention and risk reduction for occupational skin cancer requires the elimination of the contact of all carcinogens present in the workplace with the employees' skin. Additionally, to encourage and facilitate the early recognition and management of premalignant and malignant skin lesions, training should be given to those working under higher skin cancer risk, and periodic examinations should be performed.

Keywords: Cancer, occupation, skin, ultraviolet radiation

Especially in the last 30 years, skin cancers have become a significant public health concern following a rapid increase in their occurrence. According to data from the World Health Organization (WHO), approximately 2-3 million people worldwide are diagnosed with non-melanoma skin cancer (NMSC), and 132,000 people are diagnosed with malignant melanoma in a year. Furthermore, one out of every three people diagnosed with cancer is diagnosed with skin cancer [1]. Its occurrence has increased by 600% since the 1940s [2]. In addition to being the most diagnosed type of cancer in the Americas, one in five people has the risk of developing skin neoplasm [1]. In Australia, which is one of the countries with the highest incidence rate, 80% of newly diagnosed cancers are skin cancers [3]. According to the Public Health Agency of Turkey (2017), the age-standardized rate of C43-other skin cancers and C44-cutaneous melanoma skin cancers per 100,000 men were 1.7 and 25.5, respectively; for 100,000 women, they were 1.2 and 16.7, respectively [4].

Although human skin is resistant to the damage of many substances, it is the most frequently damaged organ in working life. Occupational skin cancer may develop when employees are under exposure to one or more specific carcinogenic substances in the work-

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place. Workplaces often have higher concentrations of carcinogens than any other setting. Moreover, there is only a limited number of studies on skin cancers from occupational exposure. While the exact number of work-related skin cancers is unknown, most observers agree that it is a considerably large number [5]. People with fair skin are more prone to develop NMSC [6]. It originates mainly from work-related exposure. Its most prevalent forms are basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs), and actinic keratosis (AK). Until recently, AKs were considered precancerous due to their potential for SCC development. Currently, they are regarded as malignant intraepidermal neoplasms at an early stage [7]. Particularly for earlier stages of life, malignant melanoma results from intermittent ultraviolet radiation (UVR) exposure rather than cumulative sun exposure [8].

The list of skin carcinogens in humans with sufficient or limited evidence according to the International Agency for Research on Cancer (IARC) is listed in Table 1 [9].

Workers in the following jobs are at higher risk for occupational skin cancer: outdoor workers; coal tar workers; electrode production workers; dye industry workers; roof workers; workers in the production of arsenic-containing pesticides; workers in copper, lead, and zinc refining; uranium mine workers; and healthcare workers [10]. The most common causes of occupational skin cancer are UVR, polycyclic aromatic hydrocarbons (PAHs), arsenic, ionizing radiation, and trauma [5]. Chemicals carcinogenic to the skin were identified more than one hundred years ago, but they are not considered to contribute to the development of NMSC as much as UVR. Moreover, current studies propose that other potential factors (radon and air pollution) may also increase the risk of skin cancer [11, 12]. This manuscript discusses occupational skin carcinogens, such as UVR, ionizing radiation, arsenic compounds, and polycyclic aromatic hydrocarbons.

Table 1. Skin carcinogens with sufficient or limited evidence in humans

Skin cancer	Carcinogens with sufficient evidence in humans	Carcinogens with limited evidence in humans
Cutaneous malignant melanoma	Polychlorinated biphenyls	Oil refinery (occupational exposure)
	Sunlight	
	UVR-emitting tanning devices	
Non-melanomatous skin cancer	Arsenic and inorganic arsenic compounds	Creosotes
	Azothioprine	Human immunodeficiency virus type 1 (infection)
	Coal tar distillation	Human papillomavirus types 5 and 8 (in patients with epidermodysplasia verruciformis)
	Cyclosporine	Hydrochlorothiazide Merkel cell polyomavirus (MCV)
	Methoxsalen and UVA radiation	Nitrogen mustard
	Mineral oils, unprocessed or lightly processed	Oil refinery (occupational exposure)
	Shale oil	UVR emitting tanning devices
	Sunlight	
	Soot (e.g., chimney sweeps)	
	X-ray	
	Gamma radiation	

Ultraviolet Radiation and Ionizing Radiation

Exposure to UVR is usually through exposure to sunlight. Indeed, sunlight is a significant risk factor for occupational skin neoplasm development. Since 2012, the IARC and WHO have categorized UVR as "carcinogenic to humans" because it can result in both malignant melanoma and NMSC [13]. UVR causes mutations in the p53 tumor suppressor gene, and it may have a carcinogenic effect through this pathway. Among all employees, the ones working in an outdoor environment are under higher exposure to UVR from sunlight. There were studies investigating the frequency of skin neoplasms occurrence in outdoor employees. Recent European studies reveal that the risk of developing SCC and BCC in long-term outdoor employees is twice the frequency observed in the general population [14]. Nevertheless, skin cancer resulting from work-related exposure to UVR is not yet an occupational disease. According to the European Agency for Occupational Health and Safety, UVR is carcinogenic; about 14.5 million people working outdoors in 36 different employment sectors in the European Union are under UVR exposure for at least 75% of their working hours. This situation may further get worse by prolonged exposure to sunlight and the use of inappropriate sun protection equipment during working hours. Workers with the highest UVR exposure are in the agriculture, hunting, and construction industries. Other people with higher-risk occupations are farmers, forestry workers/gardeners, agricultural workers, garden and park workers, postmen/women, sorters, newspaper delivery workers, physical education trainers, and childminders [15]. In systematic meta-analysis studies, the risk of SCC and AK (i.e., intraepidermal SCC) development increased by 77%, and for BCC by 43%, compared to the general population [16, 17]. In a meta-analysis of 23 scientific articles, Bauer *et al*. [18] reported that outdoor employees are at a significantly higher risk for BCC (p = 0.014). A multi-center European case-control study compared the risk of occurrence of BCC, SCC, melanoma, and AK among 1416 outdoor and 1863 indoor employees. They found that 37.7% of outdoor employees versus 28.6% of indoor employees were diagnosed with skin cancers more than twice throughout their lives. The incidence of AK increased 1.55 times in outdoor employees and 2.58 times in agricultural and construction employees. On the other hand, for SCC, it is 1.32 times higher for outdoor employees and 2.77 times higher for agricultural and construction employees. For BCC, it is 1.53 times higher for outdoor employees and 1.83 times higher for agricultural and construction workers. The risk of skin cancer and AK was significantly higher for employees working outdoors for ≥ 5 years [19]. A cohort study based on the Norwegian Cancer Registry also asserts that exposure to UVR is a significant factor in having a higher risk of skin cancer (cutaneous melanoma and NMSC) among North Sea offshore employees [20]. The EPIDERM study covering the period from 1996 to 2012 in the United Kingdom revealed that 99% of described cases of occupational skin neoplasia resulted from sun/sunlight/ultraviolet radiation exposure [21]. In welders, UVR from the welding process is a potential factor in NMSC development [22]. According to recent studies, outdoor workers are under UVR exposure at an alarming rate, and the daily limit set by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) was exceeded. This situation highlights the need for national and European health executives to take preventive measures [23].

The fact that ionizing radiation has the potential to cause SCC and premalignant changes are well-known since the experience of the first scholars to use X-rays and radiation devices. The first proof of the carcinogenic potential of ionizing radiation is in a case report in 1902 describing the occurrence of NMSC in the hands of radiation employees [24]. Since then, high incidences of skin cancer related to radiation exposure have been reported among various groups, including atomic bomb survivors, uranium miners, radiologists, interventional cardiologists, and individuals treated with radiation for childhood tinea capitis and malignant tumors. Nearly all of these reports suggest that exposure to radiation increases the incidence of basal cell carcinoma rather than melanoma or SCC. The mechanism behind the different effects of basal cells and squamous cells on radiation-mediated malignant transformation has not been clarified yet [25, 26]. Exposure to ionizing radiation devices is now sufficiently controlled and monitored. That's why skin cancer diagnosis is not expected in X-ray workers as frequently as before. However, a recent study highlighted that the risk of malignant melanoma is higher among radiological technologists who worked before 1950 and those who did not wear lead aprons, which are protective

against this radiation [27]. Wang *et al*. observed 27,011 X-ray employees (radiologists and technicians) in China and described that the relative risk for all cancers among X-ray workers was 4.1 times greater than among doctors working in the same hospitals. The highest relative risk for skin cancer was in those working for more than 15 years [28, 29].

A review by Wakeford [30] reported skin cancers associated with occupational ionizing radiation exposure in aircrew, uranium miners, nuclear weapon test participants, and employees from the nuclear industry. Air crews are under a greater degree of cosmic radiation exposure because of the reduced shielding of the atmosphere at higher altitudes. In another article, working as a pilot for more than 20 years was a risk factor for NMSC, as it increased exposure to ionizing radiation, especially for pilots with longer flight times at high altitudes [25]. A comprehensive review of studies about aircrews over the last 20 years reported a higher risk of melanoma [31]. A higher risk for skin cancer in pilots may result from exposure to excessive UVA radiation during flight operations. While most UVB radiation can be filtered by plastic and glass window protection, up to 54% of UVA radiation can enter planes and UVA radiation is 2 times higher at 9,000 meters compared to the ground [32]. Recently, some researchers have described a high prevalence of malignant melanoma among airline pilots and flight attendants exposed to cosmic radiation. However, some researchers argued that this is due to their lifestyle (e.g., sun exposure from sunbathing) rather than their relatively higher exposure to cosmic radiation [33, 34].

Another carcinogenic radiation is alpha particles. Hard rock miners (uranium, iron, tin, and gold) work in radon-rich environments. Yet, the risk of NMSC in radon-rich environments is not associated with inhalation of radon, but with contamination by the radon products composed of Po-218 and Po-214 on the epidermis exposed to alpha particles. Mechanistic studies of radon-associated carcinogenesis show that alpha particles produce complex biological responses. They involve mutations, chromosomal abnormalities, generation of reactive oxygen species, modification of the cell cycle, changes in cytokines, and carcinogenesis [35, 36]. Although epidemiological studies suggest a relationship between radon exposure and skin neoplasm risk among uranium miners, this relationship is not well-established [37]. The only research with a clear association between alpha radiation and skin cancer was in 1978, which was related to Czech uranium miners. A follow-up study with the same cohort by Sevcová *et al*. [38] described a significantly higher incidence of BCC with a 1-year attributable risk per 10,000 employees at the 1 Sv dose.

Arsenic and Inorganic Arsenic Compounds

Arsenic is a metalloid present in land, rocks, and water. Arsenic has been recognized as a group "A" carcinogen by the US Environmental Protection Agency (EPA) (corresponding to the sufficient evidence for cancer effect) and a group "I" carcinogen by the IARC that can induce cutaneous SCC, BCC, bladder, kidney, and lung cancers. Arsenic is a potent mutagen, as it causes a wide range of chromosomal mutations and acts as a carcinogen only with UVR. Arsenic suppresses DNA repair by inhibiting the PARP1 enzyme. Arsenic exposure increases the vulnerability of keratinocytes and melanocytes to UVR impairment. The cocarcinogenic consequences of UVR and arsenic may partially explain the higher risk of melanoma and keratinocyte carcinoma after arsenic exposure [39]. Prolonged exposure usually results in precancerous arsenic keratosis. However, carcinoma in situ (Bowen's disease and AK) and invasive BCC or SCC have also been detected [40]. Arsenic-related skin tumors occur after ingestion, injection, inhalation, and skin contact with arsenic. Among them, the most common exposure route is arsenic in drinking water. Detailed studies conducted in Taiwan revealed that using well water with a high arsenic concentration caused skin cancer in a dose-response correlated manner. An estimated 1.5 million workers in the United States are under inorganic arsenic exposure. They are from industries such as copper and lead smelting, the metallurgical industry, and pesticide production and use. Skin tumors attributable to occupational arsenic exposure were rare. The same conclusion was reached by studies on arsenic in pesticides as a possible skin neoplasm risk for farmers. Furthermore, some arsenic-induced skin cancer cases of agricultural workers might be from the carcinogenic effects of sunlight and other substances, such as tar [5, 41].

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs occur as a result of the incomplete combustion of organic compounds of both natural and human

origin. It naturally occurs due to forest fires or volcanic eruptions. Human-induced formations originate from industrial resources, motor vehicles, and cigarettes [42]. Industrial procedures, such as the pyrolysis or burning of coal, and the manufacture and use of coal tar and coal-derived goods, are the most significant sources of work-related exposure to PAHs [43]. Exposure is mostly by inhalation and skin contact. St. Percivall Pott, who was working as a surgeon at Bartholomew's Hospital, reported the relationship between PAHs and cancer for the first time. He observed that chimney cleaning workers had testicular cancer due to the exposure of their skin to soot. Then, 100 years later, Volkmann and Bell confirmed Pott's observation by detecting testicular skin cancer in people working in the paraffin industry in Germany and Scotland [42]. However, it was not until the 1940s that a carcinogenic PAH, benzo[a]pyrene, was shown to be a soot component. Several PAH types or their mixtures can increase the likelihood of cancer, and the carcinogenic effects of PAHs vary with the type or dose of PAHs. Most processes generate several different types of PAHs simultaneously. Among the PAHs, benzo[a]pyrene is the best-known carcinogen. Some professions are at higher exposure to PAHs that are human carcinogens (Group 1) by the IARC. These include coal gasification, coke production, coal tar distillation, chimney sweeping, asphalting, and coal tar roofing; jobs including mineral oils, petroleum oil manufacturing, and aluminum manufacturing [44]. There are several types of PAH in coal tar, bitumen, asphalt, soot, creosotes, anthracenes, paraffin waxes, and lubricating and cutting oils. There is an association between exposure to unprocessed or lightly processed mineral oil containing PAHs and skin and scrotal cancers in wax press workers, metal workers, and machine operators. The latent time between exposure to PAHs and skin neoplasms ranges from 20 (coal tar) to 50 years or more (mineral oil) [5]. In a cohort study found an association between exposure to crude oil or benzene and the risk of skin cancer on the hands and arms of offshore workers [45].

CONCLUSION

While UVR exposure is the most significant risk factor for occupational skin neoplasm development, other non-negligible carcinogens are polycyclic aromatic hydrocarbons, arsenic, and ionizing radiation exposure. The following jobs are at higher risk for occupational skin cancer: outdoor works, coal tar works, electrode production, dye industry, roof works, production of arsenic-containing pesticides, copper, lead, zinc refining, uranium mines, and healthcare works. A better understanding of skin cancer risk factors in industrial processes, cautious use of ionizing radiation, and taking necessary precautions, have resulted in a reduced risk of exposure to a chemical- and radiation-based carcinogens. However, the risk of exposure to UVR remains unsolved. Except in countries where skin cancer is a common public health problem (such as Australia), this risk is often overlooked as a predisposing factor for skin cancer.

The employees' skin contact with carcinogens in the workplace should be prevented to eliminate occupational skin cancer. For those working outdoors, taking protective measures is recommended. These are covering exposed skin with protective equipment (hat, long pants, long-sleeved shirt, sunglasses), and using sunscreen creams. Moreover, training should be organized, and periodic health examinations should be performed to support and facilitate the early recognition and management of premalignant and malignant skin diseases in those working at higher risk.

Authors' Contribution

Study Conception: SK, NG; Study Design: SK, NG; Supervision: SK, NG; Funding: SK, NG; Materials: SK, NG; Data Collection and/or Processing: SK, NG; Statistical Analysis and/or Data Interpretation: SK, NG; Literature Review: SK, NG; Manuscript Preparation: SK, NG and Critical Review: SK, NG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2024;10(2):241-244 Case Report

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Secondary iatrogenic duedonum perforation: a rare complication

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ABSTRACT

The incidence of perforations resulting from Endoscopic Retrograde Cholangiography (ERCP) is observed to be less than 1%. In this case report, we aim to present our unique experience as a mechanism, which is even more uncommon. A 68-year-old male with an ASA score of 2 was prediagnosed with a distal common bile duct tumor. ERCP was performed for therapeutic and diagnostic purposes and a 9-F 10 cm plastic stent was placed to relieve obstruction. The patient, who had the sudden onset of abdominal pain within the initial 24-hour period following the procedure, underwent surgical intervention subsequent to a computed tomography assessment. In the third portion of the duodenum, an approximately 4 mm perforation originating from the stent was observed during the examination. It was repaired with a 3.0 prolene suture, followed by omentopexy. He was discharged uneventfully on the eighth day. Although duodenal perforation due to the placement of a plastic biliary stent with ERCP is a very uncommon complication, the patient's clinical and imaging findings are essential for treatment planning.

Keywords: Endoscopic retrograde cholangiography, biliary stent, duedonum, perforation, complication

Since 1968, Endoscopic Retrograde Cholangiopancreaticography (ERCP) has been widely adopted in the diagnosis and treatment of pancreatic and biliary tract pathologies [1, 2]. ERCP is performed for a variety of reasons, including suspected biliary obstruction, pancreatic duct and biliary tract diseases, imaging studies revealing a pancreatic mass, idiopathic pancreatitis, benign or malignant stenosis, fistula, and postoperative biliary fistula [3].

While ERCP is generally considered a safe procedure, it is not devoid of potential complications. The most frequently observed post-procedural complications include bleeding and pancreatitis. However, the occurrence of perforations, although less common at a rate of less than 1%, is a significant concern. The majority of these perforations are attributed to therapeutic interventions such as sphincterotomy, dilatation of strictures, or complications related to stenting [4, 5].

In this case report, we will assess our management of duodenal perforation secondary to stent, which is an extremely uncommon complication of ERCP.

CASE PRESENTATION

A 68-year-old male with an ASA score of 2, a body mass index of 25.42, and the Eastern Cooperative Oncology Group score of 1 was prediagnosed with mechanical icterus and a distal common bile duct tumor. He was admitted after granting permission for addi-

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tional examination and treatment, as well as data sharing for academic purposes.

ERCP was performed for therapeutic and diagnostic purposes on the distal stenosis, and a 9-F 10 cm plastic stent was placed to relieve obstruction. There were no complications during the procedure. 24 hours after the procedure, the patient's vital signs were as follows: blood pressure 100/70 mm Hg, hearth rate 128 bpm, body temperature 36.1 °C, blood oxygen level 92, and respiratory rate 16 breaths per minute. The physical examination revealed defense in all four quadrants and rebound in the bilateral lower quadrants. White blood cell count was 19.74 109/L, hemoglobin level was 9.6 g/mL, alanine aminotransferase level was 122 U/L, aspartate aminotransferase level was 164 U/L, and total bilirubin level was 3.68 g/mL. The remaining laboratory parameters were all normal. Intra-abdominal lower quadrants exhibited a hyperdense appearance and free fluid densities thought to be due to the contrast agent on abdominal computed tomography with oral and intravenous contrast. When contrast material extralumination (Figs. 1 and 2) was observed, the decision to perform surgery was made.

In the third portion of the duodenum, an approximately 4 mm perforation originating from the stent was observed during the examination. It was repaired with a 3.0 prolene suture, followed by omentopexy. (Fig. 3) After surgery, the patient was transferred to the intensive care unit as an extubated patient, and on the first postoperative day, respiratory complications were treated medically. (Clavien-dindo type 2). On the second day following the surgical procedure, a percutaneous biliary drainage catheter was utilized in order to establish biliary drainage for the patient. This intervention became necessary due to the occurrence of perforation caused by the stent, which eventually led to its removal. Patient monitored with nasogastric tube in the early postoperative period, whose oral intake was resumed on the fifth postoperative day, was discharged without incident on the eighth day.

DISCUSSION

The prevalence of duodenal perforation caused by ERCP ranges from 0.09 to 1.67 percent. [5-7] If it is observed during the procedure, it may be preferred to close it with a clip; however, the patient's clinic may prefer surgical intervention after the procedure [5, 8]. In our patient, the perforation developed after the procedure, and based on the patient's physical examination and vital signs, surgical intervention was preferred.

Perforations caused by ERCP are classified as type 1 lateral or medial duodenal wall perforation, type 2 injury around the ampulla vatery, type 3 distal bile duct injury, and type 4 only free air.[4, 9] Type 1 perforations are typically treated surgically, whereas types 3 and 4 are typically managed conservatively. There is no agreement regarding type 2 perforations [10, 11]. We think that our patient had type 1 perforation, but it was caused by stent migration rather than endoscope manipulations.

Migration is observed in 6% of ERCP stent applications, the duodenum is most commonly affected, and perforation is observed in less than 1% of cases [5, 12]. Ida Bagus [5] surgically managed the late-term 5 mm perforation of a patient who had a plastic stent

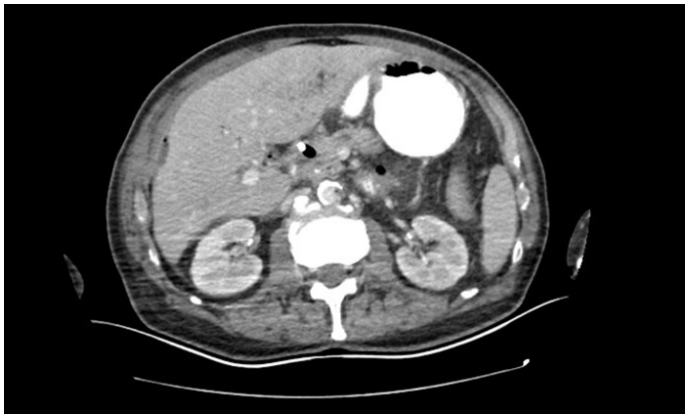

Fig. 1. Preduodenal free air densities.

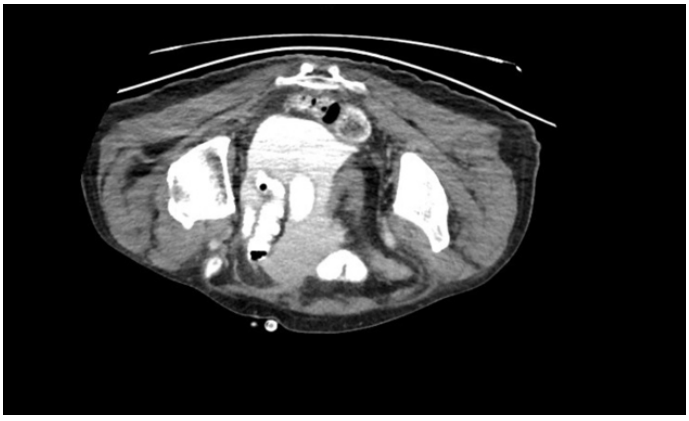

Fig. 2. Contrast material extralumination.

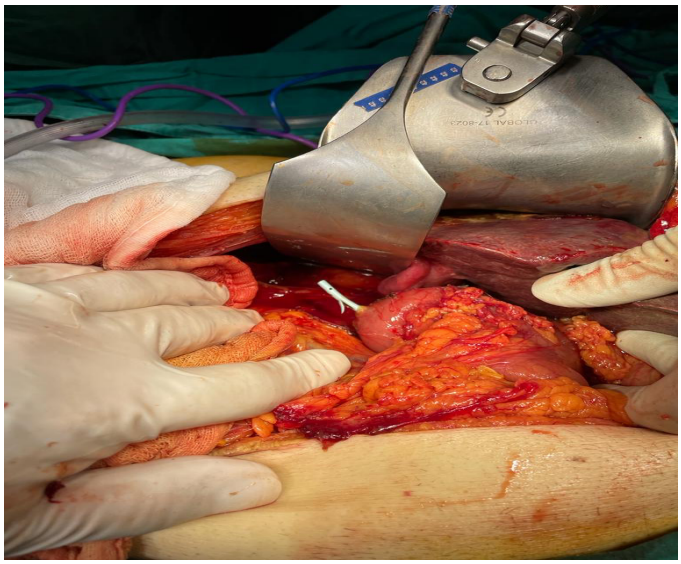

Fig. 3. View of perforated duodenum caused by stent.

placed with ERCP due to malignant biliary obstruction, similar to our experience in the literature. His surgery included primary duodenal closure, cholecystoenteric bypass, pyloric exclusion, gastroentorostomy, and braun anastomosis [5]. We suppose that the difference with our surgical approach is due to the fact that their patients were operated at a later period and we applied the principle of damage control surgery based on the hemodynamic status of our patient.

Benign biliary stenosis, long stent and proximal biliary stricture are considered as risk factors for ERCP stent migration [13, 14]. For stent migration risk factor analysis in Yuan et al.'s case series [12], etiology, stricture location, stent diameter, stent length, how far the stent length extends beyond the proximal end of the biliary stenosis, how far the stent is from the papilla, the distal end of the stent, and the body end of the stent were considered. The angle with respect to the center was measured. As risk factors for stent migration into the duodenum, benign biliary stenosis and placement of the stent with a length >2 cm from the proximal end of the biliary stenosis were evaluated [12]. For the distal common bile duct stenosis in our case report, a plastic stent with a diameter of 3.3 mm, a length of 9 cm, a length of >2 cm outside the papilla, and an angle of >30o was used. Contrary to published data, perforation has developed in malignant stenosis, and as emphasized by Yuan et al. [12], the stent is >2 cm above the stenosis' proximal end.

For successful outcomes in duodenal perforations caused by ERCP, a prompt diagnosis and effective treatment are crucial [5]. In our case, the diagnosis was made within 12 hours, and the patient was successfully discharged.

CONCLUSION

In conclusion, duodenal perforation caused by ERCP is a rare but potentially serious complication. The management of such perforations depends on several factors, including the type of perforation and the patient's clinical condition. Stent migration is a known risk factor for duodenal perforation, occurring in about 6% of ERCP stent applications, although perforation is relatively rare in these cases. Risk factors for stent migration include benign biliary stenosis, long stent length, and proximal biliary strictures. Prompt diagnosis and effective treatment are essential for successful outcomes in duodenal perforations caused by ERCP. In the case discussed here, the diagnosis was made within 12 hours, and surgical intervention was successfully performed based on the patient's condition. It is important for healthcare providers to be vigilant and consider risk factors when performing ERCP procedures, taking appropriate measures to minimize the risk of complications such as stent migration and duodenal perforation.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying pictures or data.

Authors' Contribution

Study Conception: OFA; Study Design: AÖ; Supervision: İY; Funding: N/A; Materials: AÖ; Data Collection and/or Processing: AÖ; Statistical Analysis and/or Data Interpretation: OFA; Literature Review: OFA; Manuscript Preparation: AÖ and Critical Review: İY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2024;10(2):245-248 Case Report

DOI: https://doi.org/10.18621/eurj.1399415 *Cardiovascular Surgery*

Surgical excision of the right ventricular hydatid cyst: a case report

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ABSTRACT

Hydatid cyst is described as an endemic situation predominantly observed in different undeveloped regions of the world which is caused by Echinococcus granulosus tapeworm. This disease usually affects the lungs or liver. Cardiac location is reported in less than 2 % to 0.5% of patients in all cases and as in our case the intraventricular location is seen seldomly. A 38-year-old female patient with diagnosed systemic hydatid cyst disease was consulted with chest pain, palpitation, and shortness of breath. Transthoracic echocardiography and cardiac computerized tomography imaging showed the location of the cardiac hydatid cyst was the right ventricle. She underwent elective surgery swiftly and was discharged uneventfully.

Keywords: Cardiac hydatid cyst, right ventricle, surgical excision

Cardiac Hydatid Cyst (CHC) is an endemically seen disease which is caused by Echinococcus granulosus tapeworm. Lungs and liver are the most seen localizations when compared to cardiac involvement (2% to 0.5%) CHC is a well-known disease that has been reported for a long period [1]. Right ventricle localization may result with severe arrhythmias, infectious metastasis, multi-organ insufficiencies, and sudden death. Diagnostic tools are transthoracic echocardiography, computerized tomography (CT), and/or cardiac magnetic resonance imaging. The treatment method for cardiac CHC is surgery [2].

CASE PRESENTATION

A 38-year-old female patient with CHC was consulted to our department for surgery due to worsening complaints of chest pain, shortness of breath, and palpitation. She was living in a rural area. CT Images showed pulmonary hydatid cyst disease in multiple localizations besides CHC large as 8×8×8 cm (Fig. 1A). There were no signs of further disease in the liver and cranium. A transthoracic echocardiography also supported the diagnosis by revealing CHC in the right ventricle as 8×8 cm in diameter (Fig. 1B). On her physical examination, a 4/6 systolic murmur was auscultated on the left chest precordial area. With a sinus rhythm electrocardiogram showed a rate of regular 90 beats and the routine laboratory tests were within normal limits except for a raised eosinophil count. Her medical history recorded neither a prior surgery nor serious diseases. We discussed the diagnostic images and the clinical conditions by radiological presentation with radiologists, preoperatively. Cystic mass with

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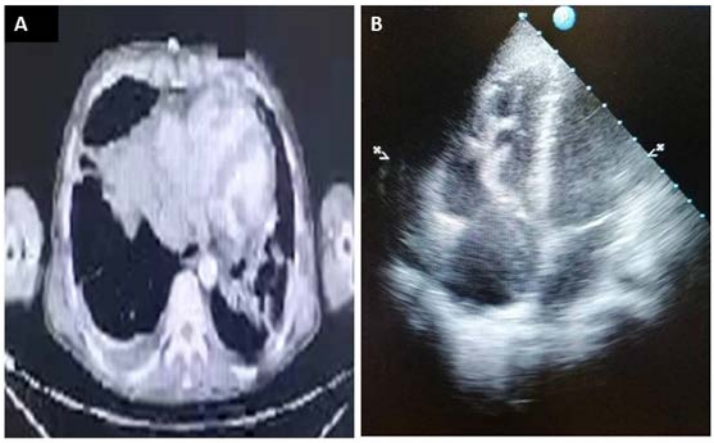

Fig. 1. (A) Computed tomographic images of cardiac cydatid cyst, (B) Transthoracic echocardiography images of cardiac hydatid cyst.

thin and regular walls was reported as almost filling the right ventricle chamber.

After general anesthesia, a median sternotomy was performed. After opening the pericardium, the structure of the cyst was palpable over the right ventricle (Fig. 2A). Conventional cardiopulmonary bypass and cardiac arrest were applied via aorta-bicaval cannulation and antegrade cardioplegia. The polyvinyl-iodine-soaked towels were placed into the pericardial area to avoid further local contamination. The cardiac ventriculotomy incision was applied parallel to the interventricular septum and left anterior descending coronary artery (Fig. 2B). The cyst was reached by performing some blunt dissection on both sides. CHC

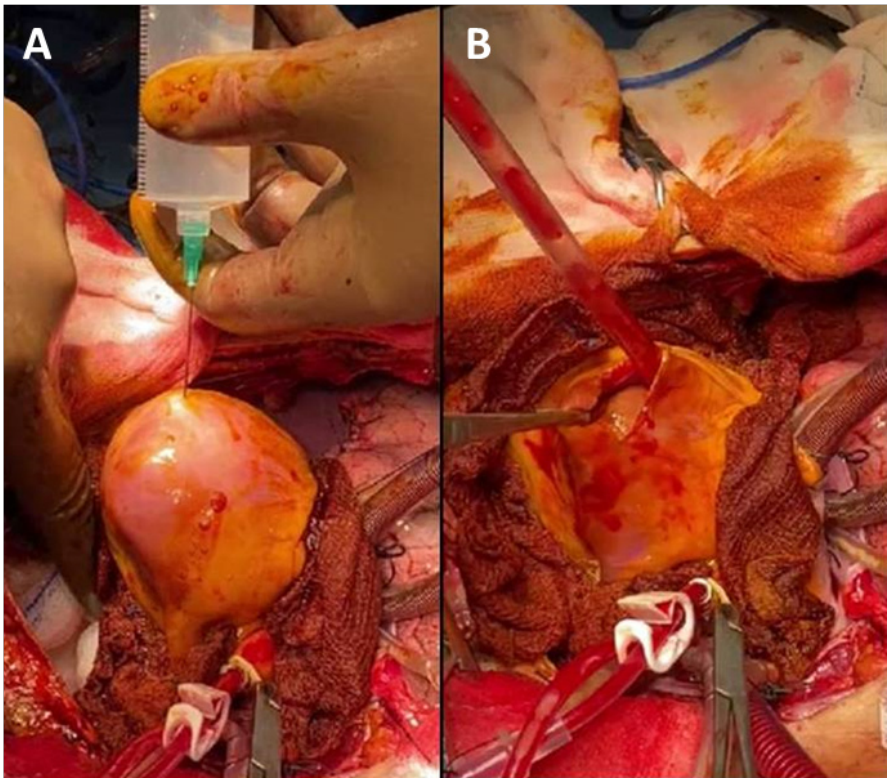

Fig. 2. (A) Cardiac hydatid cyst palpable in the right ventricule, (B) Right ventriculotomy incision.

opened via a direct approach. The cyst content was aspirated almost totally by a syringe with hypertonic NaCl solution and replaced with adequate amounts of polyvinyl iodine, oppositely. The germinal cyst membranes were removed with utmost care (Fig. 3A). Afterwards, the cavity was washed with hypertonic and iodinated solutions again, after a total removal of the cyst. The right ventriculotomy incision was closed by cappitonage technique, and the area was secured with a fibrin sealant agent (Fig. 3B). Rest of the surgery was achieved conventionally without any complication. Then, the patient was transferred to the cardiovascular surgery intensive care unit. The postoperative period and necessary specific hydatid cyst medical treatment continued with a multi-disciplinary approach with the infectious diseases department. She was discharged on postoperative day eleven with albendazole treatment aside from our cardiac postoperative medical protocol.

DISCUSSION

Cardiac echinococcosis is rare. Among all cases, it is observed by a rate of lower than 2%. Parasites may present themselves by the larval stages in any organ as in the pleural cavity, pulmonary areas, intra-cranially, or abdominal cavity. The parasite larvae may gain access to blood and/or portal circulation after it is taken by contaminated food as a primary source [3].

Diagnosis is an indication for surgery for CHC cases. Severe and life-threatening complications may occur by cyst rupture. Several medical studies report that distally embolism to the brain and other visceral areas may have relevant complications such as epilepsy and internal organ acute insufficiencies that lead to death are well known to occur. For these reasons and cardiac tamponade, cardiac vulvar dysfunctions, acute carotid vessel occlusion, and pulmonary risks due to CHC, surgery should not be delayed.

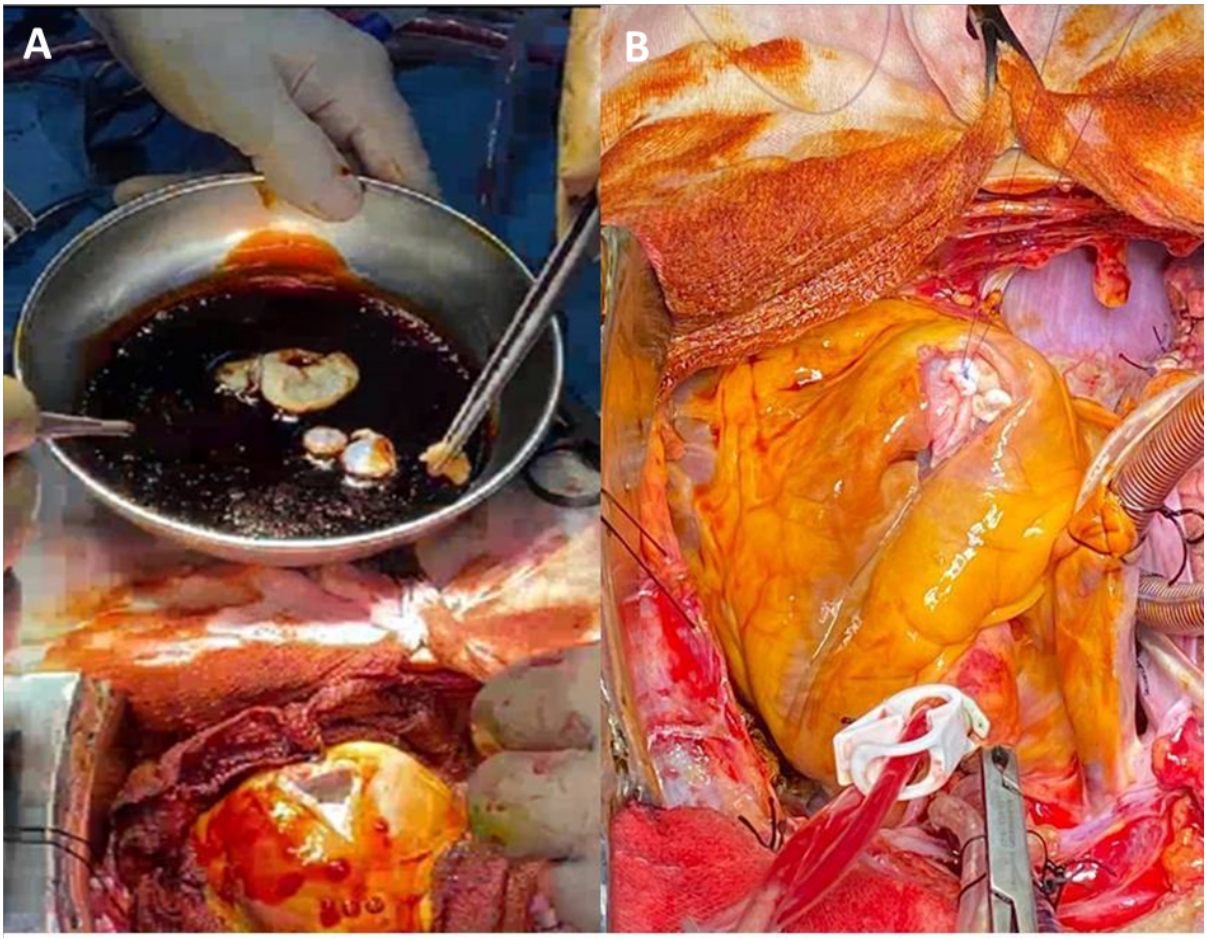

Fig. 3. (A) Germinal membrane removal and excision of cardiac hydatid cyst, (B) Right ventriculotomy closure.

Furthermore, a differential diagnosis of cardiac tumors and myxomas should always be excluded before CHC surgery [4, 5].

In our opinion, the majority of the symptoms of this patient may be due to rhythm irregularities, which may be associated with hemodynamic changes induced by this large hydatic cyst.

CONCLUSION

CHC is a rare medical condition and may present with various clinical observations. Although dyspnea, palpitations, shortness of breath with exertion, and heart murmur primarily suggest heart valve disease, the cause of this whole picture may also be a hydatid cyst. After a clinical suspicion, definite diagnosis is possible by CT and echocardiography. Early diagnosis should lead to a quick surgical treatment. Preoperative prolonged medical treatment may result in mortality. Accordingly, diagnosis is an indication without delay for surgery.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying pictures or data.

Authors' Contribution

Study Conception: MA, MY, ST, CM; Study Design: MA, MY, ST, CM; Supervision: MA, MY, ST, CM; Funding: N/A; Materials: MA, MY; Data Collection and/or Processing: MA, MY, ST, CM; Statistical Analysis and/or Data Interpretation: MA, MY, ST, CM; Literature Review: ST, CM; Manuscript Preparation: ST and Critical Review: MA, MY, ST, CM.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The European Research Journal 2024;10(2):249-253 Case Series

DOI: https://doi.org/10.18621/eurj.1208264 *Chest Diseases*

Methemoglobinemia after local anesthesia with prilocaine in adults: four case reports

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ABSTRACT

Methemoglobinemia is a serious hematological disease characterized by the incapability of sufficient oxygen delivery to tissues and cyanosis when iron within hemoglobin in ferrous form (Fe+2) is oxidized to ferric form (Fe+3). Methemoglobinemia may be congenital or acquired. While prilocaine-induced methemoglobinemia can be seen in newborns and early pediatric ages, it is a rare condition in adults. We aimed to investigate prilocaine-induced adult methemoglobinemia with four cases.

Keywords: Adult, methemoglobinemia, prilocaine, cyanosis

Hemoglobin (Hb) is a molecule that carries oxygen from respiratory organs to the rest of the body. Hb binds to iron in a ferrous (Fe2+) oxidation state under normal conditions. However, the existence of oxidative stress is known to transform iron into ferric iron (Fe3+). Upon oxidation, hemoglobin or methemoglobin (MetHb) cannot bind to oxygen molecules. In methemoglobinemia, the Hb is unable to release oxygen effectively to body tissues [1].

There are three common causes of methemoglobinemia, including hemoglobinopathies, hereditary enzyme deficiencies (NADH MetHb reductase), and exposure to drugs. Interestingly, hemoglobinopathies and hereditary enzyme deficiencies (NADH MetHb reductase) are the least common causes, whereas exposure to drugs is the most common [2].

Nitrite, nitrate, aniline, and benzene compounds and drugs such as sulfonamides, dapsone, phenacetin, primaquine, and benzocaine are important drugs that cause methemoglobinemia. Prilocaine, an amide compound frequently used as a local anesthetic, may also cause methemoglobinemia [2].

Gray-blue central cyanosis unresponsive to oxygen therapy is a valuable clinical finding. Peripheral cyanosis becomes prominent when blood methemoglobin levels exceed 10%, and tissue hypoxia and diffuse cyanosis are seen in cases with methemoglobin levels ≥35%. When methemoglobin levels approach 70%, the patient falls into a coma and may be mortal if left untreated [3].

We aimed to investigate prilocaine-induced adult methemoglobinemia with four cases.

CASE PRESENTATIONS

CASE 1

A 71-year-old male patient with a body weight of 78 kg and a nephrostomy diagnosed with metastatic bladder cancer was admitted to the urology clinic for bi-

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lateral nephrostomy revision. We consulted the patient who developed local anesthesia with 80 mg of prilocaine and developed low saturation and cyanosis during the procedure. SpO_2 was 75% in room air and 78% with oxygen support, heart rate was 85 beats/min rhythmic, respiratory rate was 17/minute, and arterial blood pressure was measured as 130/75 mmHg. In the physical examination of the patient, his lips and fingertips were slightly cyanotic, and he did not have any respiratory complaints. In the respiratory examination, bilateral breath sounds were heard as decreased at the base of the lung. Electrocardiogram (ECG) was normal sinus rhythm.

In laboratory tests; hemoglobin 8.6 g/dL, hematocrit 26%, MCV 85.0 fL, leukocytes 3200/µL, platelets 261000/µL, pH 7.46, PaO_2 133 mmHg, FO_2Hb 77%, pCO_2 35.7 mmHg, HCO_3act 25.2 mmol/L, MetHb: 20.7% in the blood gas taken by nasal cannula with 5 L/min oxygen support. Similar to the previous ones, bilateral costophrenic sinuses were observed to be closed in the chest X-ray, and there was no other pathology. Thereupon, the patient was evaluated as methemoglobinemia due to local anesthesia. It was detected that methemoglobinemia developed for the first time in a patient who had previously undergone interventional procedures under local anesthesia.

The patient, whose vital signs were stable and asymptomatic, was monitored and followed up with nasal oxygen support. MetHb 11.7%, FO_2Hb 77% in blood gas taken 6 hours later; MetHb %3.0, FO_2Hb 93% in blood gas taken at 12th hour; MetHb was 0.9% and FO_2Hb was 95.8% in the blood gas taken at the 24th hour. In the patient who did not develop any complications during the follow-up, his treatment and follow-up were terminated with only oxygen support, without the need for methylene blue.

CASE 2

A 54-year-old male patient with a body weight of 65 kg, hospitalized in the general surgery ward, was consulted with cyanosis and low saturation unresponsive to oxygen. In the patient with rectal carcinoma and nephrolithiasis, it was learned that cyanosis developed during nephrostomy insertion with 60 mg prilocaine under local anesthesia. In the first physical evaluation of the patient; the general condition was good, he was conscious, oriented, and cooperative, arterial blood pressure was 140/80 mmHg, heart rate was 89 beats/minute rhythmic, and respiratory rate was 18/minute. In the patient whose SpO_2 was 75% measured by pulse oximetry in room air; There was cyanosis in the lips and fingers, both hemithorax were equally involved in breathing, and heart sounds were normal. The patient had no active respiratory complaints. With 4 L/min oxygen support with a nasal cannula, the SpO_2 was 80%. Other system examinations were normal and the patient's ECG was sinus rhythm.

In laboratory tests; hemoglobin 9.42 g/dL, hematocrit 29.2%, MCV 81.0 fL, leukocytes 15880/µL, platelets 506000/µL. Blood gas taken with a nasal cannula with 4 L/min oxygen support revealed pH 7.39, PaO_2 115, FO_2Hb 78%, pCO_2 21 mmHg, HCO_3act 16 mmol/L, MetHb 25.8%. No pathology was detected in the chest X-ray.

Since the general condition was good and he had no symptoms, the patient was monitored and followed up with oxygen support via nasal cannula. After 1 hour, his cyanosis was resolved and he was followed up with oxygen support. MetHb was 8% and FO_2Hb was 88% in the blood gas taken 6 hours later. At the 24th hour after diagnosis, MetHb was 0.2% and FO_2Hb was 96.4% in blood gas. In the patient who did not develop any complications during the follow-up, his treatment and follow-up were terminated with only oxygen support, without the need for methylene blue.

CASE 3

An 81-year-old male patient with a body weight of 72 kg diagnosed with bladder cancer in the urology clinic underwent a nephrostomy revision with 60 mg of prilocaine under local anesthesia. The patient who developed desaturation during the procedure was consulted with us. In the evaluation of the patient; Her general condition was good, she was conscious, oriented, and cooperative, her arterial blood pressure was 120/70 mmHg, her pulse rate was 82/min, rhythmic, and her respiratory rate was 17/min. He had mild cyanosis of his lips. Respiratory examination and heart sounds were normal in the patient, whose SpO_2 was 82%, measured with pulse oximetry in room air. The patient had no active respiratory complaints. SpO_2 was 88% with 5 L/min oxygen support with a nasal cannula. Respiratory and other system examinations were normal, and ECG was sinus rhythm.

In laboratory tests; hemoglobin 9.7 g/dL, hemat-

ocrit 31.2%, MCV 91.0 fL, leukocytes 13080/µL, and platelets 274000/µL. Blood gas taken with a nasal cannula 5 L/min oxygen support revealed pH 7.45, PaO_2 126, FO_2Hb 88%, pCO_2 36 mmHg, HCO_3act 21 mmol/L, MetHb 9.2%. No pathology was detected in the chest X-ray.

The patient was in good general condition and asymptomatic, and he was followed up with nasal cannula oxygen support. MetHb was found to be 1.4% and FO_2Hb 95% in the blood gas taken 6 hours later. The follow-up of the patient, whose methemoglobin level was within the normal range and had no symptoms, was terminated.

CASE 4

A biopsy was planned for a 30-year-old female patient with a body weight of 58 kg due to a mass in the anterior mediastinum. A needle aspiration biopsy was performed from the mass under local anesthesia with 60 mg of prilocaine. The patient, who became desaturated and cyanotic during the procedure, was admitted to the clinic. The general condition of the patient was good, conscious, oriented and cooperative, arterial blood pressure was 110/75 mmHg, heart rate was 76 beats/minute rhythmic, and respiratory rate was 18/minute. His lips had a cyanotic appearance. In the respiratory examination of the patient, whose SpO_2 was 75%, measured by pulse oximetry in room air, respiratory sounds were decreased in the lower zones and heart sounds were deep. His ECG was in sinus rhythm and wave amplitudes were decreased.

In laboratory tests; hemoglobin: 9.7 g/dL, hematocrit 36.3%, MCV 92.0 fL, leukocytes 5300/µL, platelets 84000/µL. In the blood gas taken under the support of 6lt/min oxygen with mask, pH 7.46, PaO_2 120, FO_2Hb 76%, pCO_2 37 mmHg, HCO_3act 25 mmol/L, MetHb 10.2%. In the chest X-ray, the cardiothoracic ratio increased in favor of the heart and bilateral costophrenic sinuses. Watched off. In the echocardiography of the patient, pericardial effusion was present and the same amount of fluid was present as in the previous evaluations. There was no increase in the amount of pleural effusion compared to previous imaging.

The patient, who did not show any change compared to the previous ones and was clinically stable, was evaluated as methemoglobinemia and was monitored and followed up with oxygen support with a nasal cannula. MetHb was 5.3%, FO_2Hb 90%; MetHb was 0.8% and FO_2Hb was 96.4% in the blood gas taken at the 24th hour. The follow-up of the patient, whose methemoglobin level was within the normal range and had no symptoms, was terminated. The pathological diagnosis of the patient was concluded as "High-Grade Large B Cell Lymphoma".

DISCUSSION

Prilocaine, an amide compound frequently used as a local anesthetic, may also cause methemoglobinemia [3].

When the literature is examined, prilocaine-induced methemoglobinemia cases are frequently seen in newborns and early pediatric ages. It is a rare condition in adults. As a local anesthetic drug, the therapeutic dose of prilocaine has been reported as 1-2 mg/kg. Cyanosis is generally not observed in cases of methemoglobinemia occurring at therapeutic doses. The maximum safe dose of prilocaine is 8 mg/kg [2]. However, there are cases that develop methemoglobinemia in the administration of a lower than the safe dose [4].

There are few adult cases reported in our country. A case of methemoglobinemia due to prilocaine applied before epilation, and a case of methemoglobinemia developed with prilocaine before subclavian artery thromboendarterectomy draws attention [5, 6]. Apart from this, the majority of the cases reported from in country are pediatric patients [7-11].

There are adult cases reported in the literature, who were administered local anesthesia with prilocaine before liposuction, local anesthesia with prilocaine before intracardiac defibrillator implantation, and developed methemoglobinemia [12-14].

Gray-blue central cyanosis unresponsive to oxygen therapy is a valuable clinical finding. In mild cases, clinical signs and symptoms may not be observed; however, in severe cases, cyanosis, tachypnea, hypotension, tachycardia, and confusion may occur. Advanced cases can be fatal [5]. Additional comorbidities in which oxygenation is compromised, such as anemia, lung diseases, infection, and hemoglobinopathies can cause severe symptoms even at lower methemoglobin levels [15].

In cases with methemoglobinemia, varying degrees of cyanosis associated with blood methemoglo-

bin levels may be observed. The level of methemoglobin in the blood is below 1% under normal conditions. Peripheral cyanosis becomes prominent when blood methemoglobin levels exceed 10%, and tissue hypoxia and diffuse cyanosis are seen in cases with methemoglobin levels ≥35%. When methemoglobin levels approach 70%, the patient falls into a coma and may be mortal if left untreated [3, 16].

The gold standard in diagnosis is the demonstration of high or normal partial oxygen pressure and high methemoglobin level in blood gas analysis. The discrepancy between pulse oximetry and partial oxygen pressure is due to the presence of methemoglobin in the blood [15].

The recommended first-line treatment for drug-induced methemoglobinemia is methylene blue infusion. Even if patients with methemoglobin levels above 30% are asymptomatic, treatment should be considered when the methemoglobin level is 20% in a symptomatic patient [17]. Methylene blue therapy is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency as it results in hemolysis and, paradoxically, methemoglobinemia, in these patients ascorbic acid can be given [17]. Methylene blue is given as 1-2 mg/kg intravenously over 3-10 minutes. If the methemoglobin level is greater than 50% or the clinical condition worsens, a higher initial dose of methylene blue (2 mg/kg) may be given. The dose may be repeated if symptoms do not improve or if elevated methemoglobin levels persist [18]. Hyperbaric oxygen therapy and exchange transfusion can be tried in cases with methemoglobin levels above 70% [19].

What was remarkable in our cases was that all four cases had an underlying malignancy and concomitant anemia. In addition, prilocaine was administered to these patients at a therapeutic dose without exceeding the safe dose recommended in the literature, but methemoglobinemia developed and cyanosis was observed.

CONCLUSION

Methemoglobinemia due to prilocaine, which is used as a local anesthetic in minimally invasive surgical procedures, is very rare and is fatal if not taken care of. In the case of blue-gray cyanosis unresponsive to oxygen therapy in the clinic after the use of local anesthetics, methemoblobinemia should be considered first and methylene blue should be considered in the treatment in appropriate cases together with oxygen therapy. All four of our patients were followed closely with only oxygen support and their follow-ups were terminated without any complications.

Authors' Contribution

Study Conception: MY; Study Design: MY, LCM; Supervision: LCM; Funding: N/A; Materials: MY, Aİ; Data Collection and/or Processing: MY, Aİ; Statistical Analysis and/or Data Interpretation: MY, Aİ; Literature Review: MY; Manuscript Preparation: MY and Critical Review: MY.

Informed Consent

Written informed consent was obtained from the patients for publication of this case series and any accompanying images or data.

Conflict of interest

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