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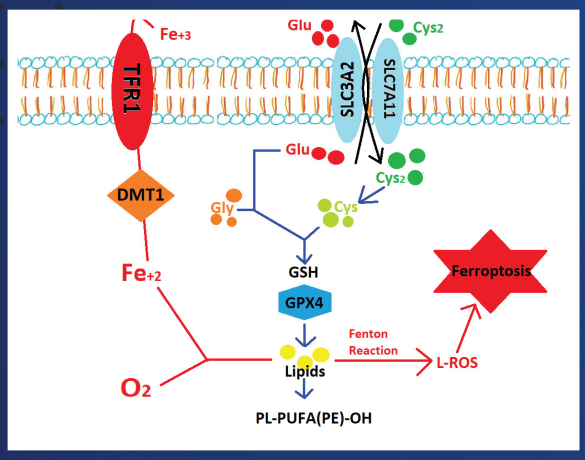

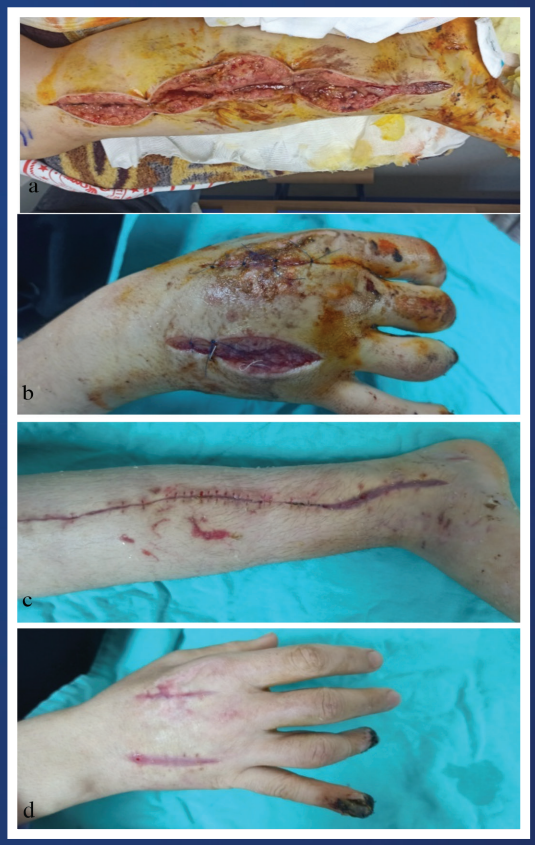

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REVIEW / DERLEME

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Assessment of Ferroptotic Cell Death and Related Treatment Targets in Neuroblastoma

Nöroblastomda Ferroptotik Hücre Ölümü ve İlişkili Tedavi Hedeflerinin Değerlendirilmesi

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Abstract

Ferroptosis is defined as an iron-dependent, non-apoptotic programed cell death modality that occurs due to an imbalance of intracellular redox hemostasis. Recently, ferroptosis has attracted attention in cancer research and has been shown to play a role in numerous oncogenic pathways. Studies have revealed that increased levels of intracellular reactive oxygen species play critical roles in oncogenic processes such as tumorigenesis, angiogenesis, invasion, metastasis, and chemoresistance because of their role in ferroptotic cell death. Neuroblastoma is the most common extracranial solid tumor in children and represents 8-10% of all pediatric cancers and 1/3 of all malign diseases of infancy. As seen in all types of cancers, the development of chemoresistance seriously affects the success of neuroblastoma treatment. Tolerance to chemotherapy in neuroblastoma was associated with the induction of exogenous defense genes and reduction of ferroptosis susceptibility biomarkers. Therefore, ferroptosis is a potential druggable driver in cancer treatment. In this review, studies associated with ferroptosis and neuroblastoma to date were reviewed and literature data were assessed in terms of ferroptotic mechanisms in neuroblastoma and potential treatment targets.

Keywords: Ferroptosis, neuroblastoma, treatment targets

Öz

Ferroptoz, hücre içi redoks hemostazındaki dengesizlik nedeniyle ortaya çıkan, demire bağımlı, apoptotik olmayan, programlanmış bir hücre ölümü şekli olarak tanımlanır. Son zamanlarda ferroptoz kanser araştırmalarında dikkat çekmiş ve birçok onkojenik yolda rol oynadığı gösterilmiştir. Çalışmalar, artan hücre içi reaktif oksijen türlerinin seviyelerinin, ferroptotik hücre ölümündeki rolü nedeniyle tümör oluşumu, anjiyogenez, invazyon, metastaz ve kemorezistans gibi onkojenik süreçlerde kritik rollere sahip olduğunu ortaya çıkarmıştır. Nöroblastom çocuklarda en sık görülen ekstrakraniyal solid tümördür ve tüm pediyatrik kanserlerin %8-10'unu, bebeklik çağının malign hastalıklarının ise 1/3'ünü oluşturur. Tüm kanser türlerinde görüldüğü gibi nöroblastomda da kemorezistansın gelişmesi tedavi başarısını ciddi şekilde etkilemektedir. Nöroblastomda kemoterapiye toleransın, ekzojen savunma genlerinin indüksiyonu ve ferroptoz duyarlılığı biyobelirteçlerinin azalmasıyla ilişkili olduğu belirtilmiştir. Bu nedenle, ferroptozun kanser tedavisinde ilaçla hedeflenebilir bir etken olması muhtemeldir. Bu derlemede ferroptoz ve nöroblastom ile ilgili bugüne kadar yapılan çalışmalar gözden geçirilmiş ve literatür verileri nöroblastomdaki ferroptotik mekanizmalar ve potansiyel tedavi hedefleri açısından değerlendirilmiştir.

Anahtar Kelimeler: Ferroptoz, nöroblastom, tedavi hedefleri

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Introduction

Ferroptosis is defined as an iron-dependent, non-apoptotic programed cell death modality. Ferroptosis occurs when the cellular levels of lipid reactive oxygen species (ROS) outweigh the glutathione peroxidase (GPX4) activity. As a result, cellular redox hemostasis is disrupted and cell death occurs[1]. Neuroblastoma (NB) is the most common extracranial solid tumor in children. The aim of this review was to address the mechanisms of action of ferroptosis suggested so far and to discuss ferroptosis-associated potential treatment targets in NB.

Molecular Mechanism of Ferroptosis

The fingerprint characteristic of ferroptosis is the generation of ROS, mostly due to an imbalance in iron metabolism[2]. Circulated iron (Fe^{3+}) uptake is processed by its attachment to transferrin (TF) and the transferrin receptor (TFR1). Iron Fe^{2+} is formed by the deoxidation of Fe^{3+} by a reaction catalyzed by the six-transmembrane epithelial antigen of prostate 3 (STEAP 3). Iron Fe^{2+} is readily soluble and has a high electron transfer capacity; therefore, it is taken up to the labile iron pool (LIP). The LIP repertoire comprises circulated iron uptake and ferritinophagy (ferritin degradation). Excessive LIP formation may initiate the Fenton reaction, which generates ROS because of the interaction between hydrogen peroxide (H_2O_2) and iron Fe^{2+}[3]. Research has suggested that iron overload resulting from increased iron intake and/or reduced iron storage finally leads to ferroptosis. This was demonstrated in a study in which ferroptosis-sensitive cells with RAS mutation showed increased TFR1 expression and decreased ferritin light and heavy chain 1 (FTL-FTH1) expression compared with ferroptosis-insensitive cells without RAS mutation[4].

Inhibition of antiporter system Xc^- or inactivation of enzyme GPX4 are responsible for ferroptosis initiation. System Xc^- mediates the importation of extracellular cystine (Cys2) accompanied by the exportation of intracellular glutamic acid (Glu)[5]. These amino acids (Cys2 and Glu) together with glycine (Gly) are essential for the generation of the major intracellular antioxidant glutathione (GSH), which reacts with the enzyme GPX. Intracellular cysteine levels are also increased by the transsulfuration of methionine (Met). Another mechanism contributing to cysteine levels in cells is the transporter system alanine/serine/cysteine (ASC), which mediates cysteine uptake[3]. Enzymes such as lysophosphatidylcholine acyltransferase 3 (LPCAT3), acyl-CoA synthetase long-chain family member 4 (ACSL4), and lipoxygenase (LOXs) mediate the reaction chain of phosphatidylethanolamine [(PE)-PUFAs-OOH] formation from free polyunsaturated fatty acids (PUFAs) via peroxidation[6].

Under physiological conditions, membrane lipid metabolism is mediated by the enzyme GPX4 and GSH availability. A recent study suggested that the breakdown of membrane lipids may be mediated by the key reductase GPX4[7]. The ferroptosis-initiating step is the inactivation of GPX4, followed by the importation of Iron (Fe) via TRF1. Subsequently, divalent metal ion transporter 1 transfers the ferrous ions to the cytosol. However, under ferroptotic conditions, membrane lipids are oxidized to Lipid-ROS (L-ROS) by the Fenton reaction directly bypassing the GPX4 pathway. The Fenton reaction, which is carried out with electrons from ferrous ions, is induced by cysteine deprivation or excessive numbers of intracellular ferrous ions. The Fenton reaction is one of the major pathways of ferroptosis. The Fenton reaction is responsible for cellular damage by oxidation of cellular substrates by hydrogen peroxide and iron. Low oxygen levels trigger L-ROS to attack vital intracellular molecules, especially DNA and RNA, resulting in imbalanced cellular homeostasis, and finally, cellular death occurs (Figure 1)[8].

Ferroptosis and Cancer

Ferroptosis was first discovered in RAS-expressing cancer cells with a small molecule called erastin, which had a lethal effect in an iron-dependent manner, unlike other cell death modalities described before. Ras-selective small molecule 3 (RSL3) was found to induce this type of cell death, and these small molecules were defined as ferroptosis-inducing agents. Following these findings, the research groups focused on the relationship between ferroptosis and Ras oncoprotein. It was observed that cell lines with WT Ras oncoprotein (fibrosarcoma and kidney tubule cells) were sensitive to erastin, whereas cells with Ras mutation (rhabdomyosarcoma cells) were resistant to RSL3 and erastin[9].

Studies have suggested that ferroptosis may represent an adaptive mechanism essential for the eradication of malignant cells. This phenomenon was clarified by studies on the well-known tumor suppressor protein p53 (TP53). Mutated $TP53^{3KR}$ was no longer capable of inducing apoptosis, senescence, and cell cycle arrest, thus losing the ability to inhibit malignant transformation. However, $TP53^{3KR}$ could still induce ferroptosis, which is promising for tumorigenesis inhibition (Figure 2)[10].

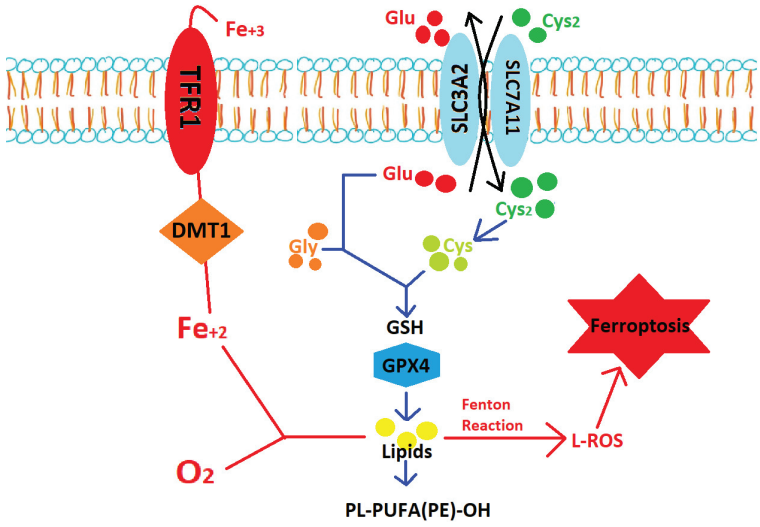

Figure 1. Normal cellular lipid metabolism and mechanism of ferroptosis. Under physiological conditions, membrane lipid metabolism is mediated by the enzyme GPX4 and the availability of GSH (blue arrows). However, under ferroptotic conditions, membrane lipids are oxidized to L-ROS by Fenton reaction directly bypassing the GPX4 pathway and as a result, ferroptosis occurs (red arrows)

Cys: Cysteine, Cys2: Cystine, DMT1: Divalent metal (Ion) transporter 1, Glu: Glutamine, Gly: Glycine, GPX4: Glutathione peroxidase 4, GSH: Glutathione, JNK: SLC7A11: Solute carrier family 7 member 11, SLC7A11: solute carrier family 3 member 2, L-ROS: Şipid-reactive oxygen species, PL-PUFA-OH: Phospholipid polyunsaturated fatty acid alcohols, TFR1: Transferrin receptor 1

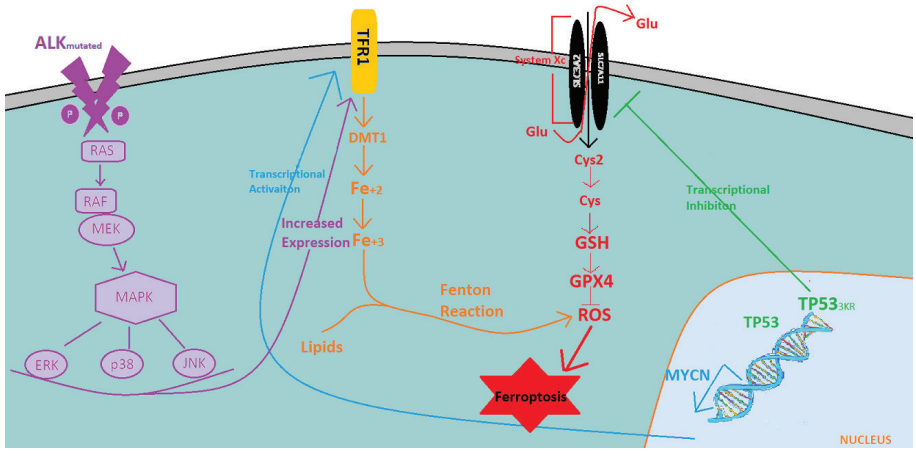

Figure 2. Involved mechanisms in neuroblastoma and their association with ferroptosis. Amplified MYCN in NB causes intracellular higher levels of iron and ROS accumulation via increasing TFR1 expression by transcriptional activation (blue arrows). Mutated TP53 (TP533KR) in NB supports ROS generation by blocking GPX4 enzyme activity by limiting GSH synthesis via the inhibition of SLC7A11 expression and therefore limiting the import of cystine through system Xc antiporter (green arrows). RAS-RAF-MAPK pathway is one of the downstream pathways of ALK in neuroblastoma. MAPK family members, ERK, p38, and JNK, cause ferroptosis by increasing TFR1 expression in RAS mutated NB cells (purple arrows)

ALK: Anaplastic lymphoma kinase, Cys: Cysteine, Cys2: Cystine, DMT1: Divalent metal (Ion) transporter 1, ERK: Extracellular signal-regulated kinases, Glu: Glutamine, GPX4: Glutathione peroxidase 4, GSH: glutathione; JNK: C-jun n-terminal kinase, MAPK: Mitogen-activated protein kinase, MEK: Mitogen-activated ERK-activating kinase, NB: Neuroblastoma, RAF: Rapidly accelerated fibrosarcoma; RAS: Rat sarcoma virus, SLC7A11: Solute carrier family 7 member 11, ROS: Reactive oxygen species, TFR1: Transferrin receptor 1, TP53: Tumor protein 53

The vulnerability of cancer cells to ferroptosis may be due to the activation of the Ras-MEK (mitogen-activated protein kinase) signaling pathway because the Ras-MEK pathway promotes iron excess in malignant cells by regulating the levels of TRF1 and ferritin expression. Upregulation of the Ras-MEK pathway can advance ROS generation by inhibiting cellular cysteine import or voltage-dependent anion channel 2/3 (VDAC 2/3), thus sensitizing cancer cells to ferroptosis[11].

Recently, ferroptosis has attracted attention in cancer research and has been shown to play a role in numerous oncogenic pathways. Ferroptosis has been suggested to be a target in processes such as tumorigenesis, angiogenesis, invasion, and metastasis. In addition, it was hypothesized that ferroptosis can contribute to combat chemoresistance and increase the effectiveness of cancer immunotherapy[12,13].

Based on the strong relationship between ROS and cell death, strategies that increase ROS generation or downregulate oxidative defense mechanisms have become the main focus of cancer treatment research. These strategies were strengthened by the study of Galadari et al.[12], which revealed that cancer cells have higher levels of ROS than healthy cells. High levels of intracellular ROS catalyze tumorigenesis by damaging or modifying cellular proteins, DNA, and lipids[14]; support angiogenesis by modifying vascular endothelial growth factors or by regulating tubular formation, migration, and proliferation[15]; contribute to invasion and metastasis by modulating signal cascades and the cellular skeleton[16]; and play a role in chemoresistance[17]. Ferroptotic cell death becomes prominent because of the same strong relationship in all these tumor-promoting cellular processes that occur because of high levels of ROS in cancer cells. Therefore, two different approaches have emerged to target cancer treatment options; one of these is to decrease cellular ROS levels and the other is to increase intracellular ROS levels to a toxic state and trigger ferroptosis[18].

NB is the most common extracranial solid tumor in children and represents 8-10% of all pediatric cancers and 1/3 of all malign diseases of infancy. The overall 5-year survival rate in low- and moderate-risk groups is over 90%, whereas it is lower than 50% in the high-risk group, which represents approximately half of all patients[19].

The most common genetic and epigenetic changes in NB are the expression alterations of MYCN, ALK (anaplastic lymphoma kinase), *PHOX2B* (paired-like homeobox 2b), *ATRX* (alpha-thalassemia/mental retardation, X-linked), *TERT* (telomerase reverse transcriptase), TP53, Histone deacetylase (*HDAC*), Lysine methyltransferase (*KMTs*), and histone lysine demethylase (*KDM*) genes[20]. Among these, MYCN amplification and 17q chromosome gain are the most well-known. In addition, 1p and 11q chromosome deletions and hyperploidy are frequently detected[21]. MYCN amplification and 1p and 11q deletions are related to poor prognosis, whereas hyperploidy is associated with a favorable prognosis[22]. In addition, ALK was defined as an oncogene associated with familial and sporadic NB[23].

As seen in all types of cancers, the development of chemoresistance seriously affects the success of treatment in NB. O-6-methylguanine-DNA-methyltransferase, which is a DNA methyltransferase that interacts with the Wnt/B-catenin signaling pathway, is upregulated in NB and is associated with chemoresistance[24]. Increased levels of HDAC8 (histone deacetylase 8) in NB cells were proposed to contribute to chemoresistance by suppressing the expression of miR-137 and triggering the expression of the multidrug resistance protein 1 (*MDR1*) gene[25]. MiR-17-92 cluster members are upregulated in NB cells and patients with MYCN amplification by the regulation of p21 (a cyclin-dependent kinase inhibitor 1A, a cell cycle regulator) and BIM (bcl-2-like protein 11, an apoptotic regulator)[26]. MYCN plays a critical role in resistance to platin-based molecules by inhibiting apoptosis via deregulating PPARG coactivator 1 alpha (*PPARGC1A*) and mitochondrial transcription factor A (*TFAM*) genes[27].

To overcome chemoresistance in NB, it is necessary to focus on other cell death modalities. Recent studies have shown that stimulation of ferroptosis in cancer cells can be a novel cancer treatment strategy[28] and have aimed to accelerate the clinical application of ferroptosis targeting[29]. To date, various strategies have been developed to induce ferroptosis in NB[30]. The aim of this review is to provide an overview of the ferroptotic mechanisms in NB and potential treatment approaches that can be developed via these mechanisms.

Method

In this review, all data present in "PubMed" database between 2002 and 2021 years were assessed and analyzed in terms of ferroptosis and related treatment approaches. A comprehensive search of peer-reviewed journals but no conference papers or reports was completed based on a wide range of keywords such as "ferroptosis", "GPX4", "GSH" and "NB". Original research articles assessing the role of ferroptosis in NB were reviewed and included in this review.

Results

Studies on the modulation of ferroptotic machinery in NB are summarized in Table 1 and detailed explanations are given below.

Buthionine sulphoximine (BSO) was identified as a glutathione synthesis inhibitor that sensitizes NB cells to melphalan by inducing ferroptotoic cell death. In this study, a panel of 20 different NB cell lines was tested. Most of these cell lines, including post-autologous hematopoietic stem cell transplantation cell lines, which are severely resistant to myeloablative melphalan levels and lack p53 function, became sensitive to clinically achievable levels of melphalan and BSO when combined[31].

Overexpression of mitochondrial ferritin in SHSY-SY NB cells increased the cells' resistance to oxidative stress and protected them from ferroptosis[32]. In a transgenic *drosophila* NB model, overexpression of mitochondrial ferritin suppressed erastin-induced ferroptosis[33].

Silencing of the iron export protein; FPN in SH-SY5Y human NB cells accelerated erastin-induced ferroptosis by increasing lipid ROS accumulation[34]. Therefore, ferroportin inhibitors can be used as chemosensitizer in neuroblastoma. Similarly, in another study, HDAC inhibitors were identified as a new class of chemotherapeutics because they minimize neuronal toxicity and contribute to tumor suppression by inducing ferroptosis[35].

A different study performed with SHSY-5Y NB cells reported that isoflurane triggers ferroptosis via the inhibition of cystine/glutamate antiporter activity by the formation of the Beclin1-Solute Carrier Family 7 Member 11 (SLC7A11) complex[36].

Ferroptosis has also been reported to be effective in refractory, high-risk NB. Withaferin-A (WA) was shown to be effective in NB by inducing both canonical and non-canonical ferroptotic pathways. On the one hand, WA induced the canonical ferroptotic pathway by reducing GPX4 protein levels and activity. On the other hand, WA induced a non-canonical ferroptotic pathway by increasing the labile Fe (II) pool via overactivation of heme oxygenase 1 (HMOX1) as a result of direct targeting of kelch-like ECH-related protein 1 (KEAP1). This bidirectional mechanism of WA, when compared with etoposide and cisplatin, was shown to be significantly more effective in killing a heterogeneous panel of high-risk NB cell lines and in reducing tumor growth and relapse in NB xenografts[37]. At the same time, Withaferin a nanoparticles (NP) were engineered and these NPs were reported to decrease tumor growth because they caused a better accumulation of the molecule in the tumor site via nanotargeting by systemic administration[37].

MYCN amplification constitutes a 20-25% portion of NB cases and a major percentage of pediatric cancer-related deaths. Amplified MYCN remodels the cell by the expression of key receptors and increases iron influx by the increased expression of TFRC1 (Figure 2). Accumulated iron causes ROS formation, and MYCN-amplified NB cells become more dependent on the Xc-cysteine/glutamate antiporter system for ROS detoxification. This dependency causes significant sensitivity to the targeting of the Xc-cystine/GSH pathway by ferroptosis inducers. Therefore, agents that target GPX4 or TFRC are potential strategies for treating MYCN-amplified NB[38]. FDA-approved molecules for rheumatoid arthritis, sulphasalazine, and auranofin can be tested for NB treatment. In MYCN-amplified patient-derived xenograft models, these two molecules stopped tumor growth and induced ferroptosis[39]. In another study performed with sulphasalazine, cancer stem cells (CSCs) were isolated from both etoposide-resistant and etoposide-sensitive NB cells, and CSCs were treated with etoposide alone or in combination with sulphasalazine or C2-4 (a PKC-α inhibitor). The combination of etoposide with sulfasalazine or C2-4 prevents the spread of cancer stem cells by avoiding epithelial-mesenchymal transition (EMT) and decreasing intracellular GSH levels. The results of this study indicate that these effects are caused by the downregulation of GPX4 and the triggering of ferroptosis by lipid peroxidation[40]. In another study, sulphasalazine was applied to a panel of MYCN-amplified and non-amplified NB cell lines, and it was shown that sulphasalazine exerts anti-tumor effects by triggering ferroptotic cell death rather than apoptosis[41].

Another study reported that MYCN sensitizes NB cells to ferroptosis when the intracellular cysteine availability required for glutathione synthesis is limited. A high MYCN state in NB cells causes lipid peroxidation and triggers ferroptosis via an acute intracellular cysteine decrease. These results can explain the spontaneous regression observed in NB patients[42].

Conclusion

Agents that inhibit GPX4 and GSH-mediated detoxification directly or indirectly and cause an increase in intracellular iron accumulation are potential treatment options for ferroptotic cell death in NB. These findings indicate that targeting ferroptosis in treatment-resistant or MYCN-

Table 1. Studies on the modulation of ferroptotic machinery in neuroblastoma

Tested agent/factor/ cellular state	Model	Cell line/experimental model	Outcome/ferroptotic mechanism affected	Reference
Buthionine sulfoximine (BSO)	*In vitro*	Post-AHSCT (CHLA-51, CHLA-79, CHLA-90, CHLA-134, and CHLA-136) ve pre-AHSCT (SMS-KAN, SMS-KANR, SMS-KCN, SMS-KCNR, SK-N-BE(1), SK-N-DZ, SMS-LHN, LA-N-5, LA-N-6, SK-N-RA, SK-N-FI, LA-N-1, SK-N-SH, SK-N-AS and SMS-MSN) cell lines	Inhibition of GSH synthesis	(31)
Overexpression of mitochondrial ferritin	*In vitro*	SHSY-5Y cell line	Increased resistance against oxidative stress	(32)
Overexpression of mitochondrial ferritin	*In vitro*	Transgenic *drosophila* NB model	Suppression of ferroptosis	(33)
Silencing of Fe export protein (FPN)	*In vitro*	SH-SY5Y cell line	Accelerated ferroptosis by increasing iron-dependent lipid ROS accumulation	(34)
HDAC inhibitors	*In vitro*	SH-SY5Y cell line	Xc^- cystine transport inhibition (Ferroptosis induction effect in neuroblastoma cells while ferroptosis inhibition effect in neuronal cells)	(35)
Isoflurane	*In vitro*	SHSY-5Y cell line	Beclin1-SLC7A11 complex formation and inhibition cystine-glutamate antiporter	(36)
Withaferin-A	*In vitro*	IMR-32, SK-N-SH, Kelly, NB69, and CHP-134, NLF, SH-EP, SH-SY5Y, SK-N-AS, SK-N-BE(2) C, and SK-N-DZ NB cell lines	Induction of canonical (GPX4) and non-canonical (KEAP1, HMOX) ferroptosis	(37)
Withaferin-A and withaferin-A NP	*In vivo*	BALB/c nude mice NB xenograft model	Decreased GPX4 activity and induction of ferroptosis Inhibition of tumor growth	(38)
Sulphasalazine and auranofin	*In vivo*	Patient-derived xenograft (PDX) NB model	Induction of ferroptosis by targeting the Xc-cystine/GSH pathway	(39)
Sulphasalazine	*In vivo*	HTLA-230/HTLA-ER NB CSC	Decrease of intracellular GSH levels, Switch from oxidative phosphorylation to aerobic glycolysis, Downregulation of GPX4 activity, Induction of ferroptosis by lipid peroxidation	(40)
C2-4 (PKCα inhibitor)	*In vitro*	HTLA-230/HTLA-ER CSC	Decrease of intracellular GSH levels, Switch from oxidative phosphorylation to aerobic glycolysis, Downregulation of GPX4 activity, Induction of ferroptosis by lipid peroxidation	(41)
Sulphasalazine	*In vitro*	LAN5, KELLY, LAN1, SKNSH, CHP134, CHP212, IMR32, SKNAS, SKNBE, SKNFI, SMSKAN, SMSKANR, SMSKCN, SMSKCNR, MYCN2, SHEP21N NB cell lines	Sensitivity to ferroptosis by ROS formation	(41)

AHSCT: Autologous hematopoietic stem cell transplantation, BSO: Buthionine sulphoximine, CSC: Cancer stem cells, FPN: Ferroportin, GPX4: Glutathione peroxidase 4, GSH: Glutathione, HDAC: Histone deacetylase, HMOX: Heme oxygenase, KEAP1: Kelch-like ECH-related protein 1, NB: Neuroblastoma, NP: Nanoparticle, ROS: Reactive oxygen species, SAS: Sulphasalazine, SLC7A11: Solute carrier family 7 member 11

amplified NB can be evaluated as a potential treatment approach.

Ethics

Authorship Contributions

Concept: G.S., Z.A., N.O., Design: G.S., Z.A., N.O., Data Collection or Processing: G.S., Literature Search: G.S., Writing: G.S., Z.A.

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REVIEW / DERLEME

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Hyperbaric Oxygen Therapy in Crush Injuries and Compartment Syndrome

Crush Yaralanmalar ve Kompartman Sendromunda Hiperbarik Oksijen Tedavisi

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Abstract

Hyperbaric oxygen (HBO) therapy is a medical treatment method based on breathing 100% oxygen from a mask, hood placed over the head, endotracheal tube, or space at pressures higher than (1 atmosphere absolute =760 mmHg) in completely closed single or multi-person hyperbaric chambers. The most common emergencies in which HBO therapy is used are carbon monoxide poisoning and decompression sickness. However, acute traumatic ischemias such as crush injury and compartment syndrome that cause tissue hypoxia are among the indications for effective HBO therapy. This review aims to share general information about HBO therapy and its use in crush injury and compartment syndromes. Thus, the role of HBO therapy in reducing morbidity and mortality when used together with necessary surgical and medical treatments has been emphasized.

Keywords: Hyperbaric oxygen therapy, crush injury, compartment syndrome, fasciotomy, amputation

Öz

Hiperbarik oksijen (HBO) tedavisi, tamamen kapalı tek ya da çok kişilik basınç odalarında, (1 atmosphere absolute =760 mmHg) daha yüksek basınçlarda, maske, başlık, endotrakeal tüp ya da ortamdan %100 oksijen solutulması esasına dayalı medikal bir tedavi yöntemidir. HBO tedavisinin en sık kullanıldığı durumlar karbonmonoksit zehirlenmesi ve dekompresyon hastalığıdır. Bununla birlikre crush yaralanma ve kompartman sendromu gibi doku hipoksisine neden olan akut travmatik iskemiler de HBO tedavisinin etkin olarak kullanıldığı durumlar arasındadır. Bu derlemede HBO tedavisi hakkında genel bilgilerin ve crush yaralanması ve kompartman sendromlarında kullanımına ait bilgilerin paylaşılması amaçlanmıştır. Bu sayede HBO tedavisinin gerekli cerrahi ve medikal tedavilerle birlikte kullanıldığında morbidite ve mortaliteyi azaltmadaki rolü vurgulanmıştır.

Anahtar Kelimeler: Hiperbarik oksijen tedavisi, crush yaralanma, kompartman sendromu, fasiyotomi, ampütasyon

Introduction

Hyperbaric oxygen (HBO) therapy is a treatment method based on intermittent breathing of 100% oxygen from a mask, hood placed over the head, endotracheal tube, or environment at pressures higher than 1 [atmosphere absolute (ATA) =760 mmHg] in completely closed single or multi-person hyperbaric chambers (Figures 1, 2). The pressure should be at least 1.4 ATA or more for clinical effect[1]. Indications determined by the Ministry of Health in Turkey are decompression sickness and arterial gas embolism, carbon monoxide and cyanide poisoning, necrotizing soft tissue infections, necrotizing fasciitis, clostridial myonecrosis (gas gangrene), crush injury, compartment syndrome and other acute traumatic ischemias, diabetic and non-diabetic chronic ulcers, thermal burns, radiation injuries, chronic

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refractory osteomyelitis, sudden and painless vision loss, sudden deafness, avascular necrosis, and some brain abscesses[1,2]. Each treatment is administered for 90-120 minutes, at pressures between 2 and 3 ATA and in one or more sessions per day depending on the condition of the disease[3].

The use of HBO in modern medicine began in 1937 with the treatment of decompression in patients by Benkhe and Shaw. Scientific societies named the European Undersea Biomedical Society were established in 1965 and the Undersea Medical Society in 1967. In Turkey, studies on underwater medicine started in the same years.

The Marine and Undersea Medicine Department was established by Professor Maide İmşit at İstanbul University, İstanbul Faculty of Medicine in 1981, and it was transformed into a department in 1989. The name of the specialty and department was changed to "Undersea Medicine and Hyperbaric Medicine". Currently, HBO therapy services are provided in 54 secondary and tertiary hospital centers in public and private sector in Turkey.

Mechanism of HBO Therapy

The HBO treatment session consists of three phases. The first stage is called diving (compression), in which the ambient pressure is increased until the treatment pressure. The second stage is the treatment stage in which the patient breathes 100% oxygen. The last stage is the stage where the pressure is reduced to 1 ATA and is called ascent or decompression.

HBO therapy exerts its effect through the direct (mechanical) effect of high pressure and increased partial pressure of oxygen.

Mechanical Effect of HBO

According to Boyle's gas law, at a constant temperature, the pressures and volumes of gasses are inversely proportional. With increasing pressure, the volumes of gasses in the circulation and tissues decrease. In addition, the surface tension of the bubbles is inversely proportional to their size. The mechanical effect of pressure is best observed for treating arterial or iatrogenic gas embolisms and decompression sickness. In these diseases that require urgent treatment, tissue perfusion can be restored as the bubbles shrink and deflate under high pressure[4].

Figure 1. Monoplace pressure chamber (Hipertech, Turkey)

Figure 2. Multiplace pressure chamber at the İzmir City Hospital, Clinic of Underwater and Hyperbaric Medicine, Baroks, Turkey

Effects of Dissolved Oxygen

Antihypoxic Effect

The second effect of HBO treatment is an increase in partial oxygen pressure. According to Henry's gas law, there is a direct proportionality between the partial pressures of gasses and their solubility at a constant temperature. Even if the amount of oxygen in the breathing air is increased under normal conditions, it is not possible to increase the oxygen carried to the tissues by hemoglobin. However, because of the increase in the partial pressure of inhaled oxygen under hyperbaric conditions, the amount of oxygen dissolved in the plasma also increases (Figure 3)[4,5]. By breathing 100% oxygen at 3 ATA, the dissolved oxygen in 100 mL of blood increased to 6.8 mL (1.5) (Table 1). Thus, without the need for oxyhemoglobin, sufficient oxygen is provided to meet the needs of the tissues. This effect of HBO is particularly evident in cases of carbon monoxide intoxication and cyanide poisoning.

Antiedema Effect

The antiedema effect of HBO occurs due to both the reduction of vasoconstriction and total perfusion and the prevention of fluid transfer to the extravascular compartments by fixing the increased permeability due to hypoxia[6].

Antitoxic Effect

HBO has an antitoxic effect by inhibiting the production of toxins or their effect on metabolism. It shows its effect on CO poisoning through CO metabolism. Owing to the high partial pressure of oxygen obtained with HBO, the refunction of the mitochondrial respiratory chain is ensured by the dissociation of CO from hemoproteins and the prevention of tissue hypoxia[4,5]. The best example of this is the inhibition of alpha toxin production by *Clostridium perfringens*, which is the most common cause of gas gangrene.

Antibacterial Effect

HBO treatment achieves its antibacterial effect in three different ways. It acts directly on bacteria, increases the effect of antibiotics such as aminoglycoside, fluoroquinolone, vancomycin, and teicoplanin, and improves the immune system response by increasing the antibacterial functions of polymorphonuclear leukocytes and macrophages. HBO treatment has a bactericidal effect on anaerobic bacteria and a bacterşostatic effect on aerobic bacteria[7,8].

Effect on Wound Healing

Wound healing occurs in the stages of inflammation, proliferation, and remodeling/maturation. The main problems associated with delayed healing wounds are

Table 1. Effect of pressure on arterial O_2[5]

Total pressure		Ideal dissolved oxygen content (vol%)	
ATA	**mmHg**	**Breathing air**	**Berahting 100% O_2**
1	760	0.32	2.09
1.5	1140	0.61	3.26
2	1520	0.81	4.44
2.5	1900	1.06	5.62
3	2280	1.31	6.80
4	3040	1.80	O_2 not administered at pressure >3 ATA
5	3800	2.30	
6	4560	2.80	

ATA: Atmosphere absolute

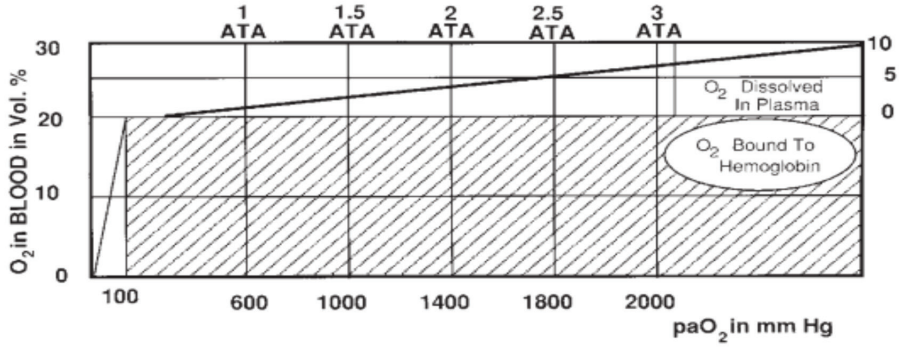

Figure 3. Oxygen uptake curve under HBO in humans[5]

HBO: Hyperbaric oxygen

tissue hypoxia and infections. HBO therapy increases the oxidative and non-oxidative functions of neutrophils during the inflammatory phase of wound healing[8]. During the proliferation stage, it provides the necessary vascularization for fibroblasts and endothelial cells to form the tissue matrix and perform neovascularization. With HBO therapy, the synthesis, release, and stabilization of collagen are performed. Because of the increase in tissue hydroxyproline, ATP, and phosphocreatinine levels with HBO, the fibroblast-collagen matrix support required for neovascularization is provided. In addition, by increasing the bactericidal activities of leukocytes, optimum conditions for wound healing are obtained. In the maturation and restructuring phase, the formation of cross-links between collagen fibers and the strengthening of connective tissue are also achieved by HBO therapy[9].

Indications for HBO Therapy

Indications for HBO therapy are determined by the European Committee for Hyperbaric Medicine and the Undersea and Hyperbaric Medical Society, and consensus reports and indications are published with evidence levels (Tables 2, 3)[1,10]. Indications for HBO therapy determined by the "Regulation on Private Health Institutions Applying HBO Therapy" published by the Ministry of Health in Turkey in 2001 are given in Table 4[2].

Table 2. Recommendations on the indications accepted for HBOT (there was no Level A evidence)[10]

Condition	Level of evidence		Agreement level
Type 1	**B**	**C**	
CO poisoning	X		Strong agreement
Open fractures with crush injury	X		Strong agreement
Prevention of osteoradionecrosis after dental extraction	X		Strong agreement
Osteoradionecrosis (mandible)	X		Strong agreement
Soft tissue radionecrosis (cystitis, proctitis)	X		Strong agreement
Decomprssion illness		X	Strong agreement
Gas embolism		X	Strong agreement
Anaerobic or mixed bacterial infections		X	Strong agreement
Sudden deafness	X		Strong agreement

Side Effects and Risks of HBO Therapy

The side effects of HBO therapy include high-pressure side effects and high-pressure oxygen inhalation toxic effects. The most common side effect that we encounter in our daily practice is middle ear barotrauma due to high pressure. Ear equalization maneuvers are taught to the patient before the

Table 2. Continued

Condition	Level of evidence		Agreement level
Type 2			
Diabetic foot lesions	X		Strong agreement
Femoral head necrosis	X		Strong agreement
Compromised skin grefts and musculo-cutaneous flaps		X	Strong agreement
Central retinal artery occlusion		X	Strong agreement
Crush injury without fracture		X	Agreement
Osteoradionecrosis (bones other than mandible)		X	Agreement
Radio-induced lesions of soft tissues (other than cystitis and proctisis)		X	Agreement
Surgery and implant in irradiated tissue (preventive treatment)		X	Agreement
Ischemic ulcers		X	Agreement
Refractory chronic osteomyelitis		X	Agreement
Burns, 2nd degree more than 20% BSA		X	Agreement
Pneumatosis cystoides intestinalis		X	Agreement
Neuroblastoma, stage IV		X	Agreement
Type 3			
Brain injury (acute and chronic TBI, chronic stroke, post anoxic encephalopathy) in highly selected patients		X	Agreement
Radio-induced lesions of larynx		X	Agreement
Radio-induced lesions of CNS		X	Agreement
Post-vascular producer reperfusion sydrome		X	Agreement
Limb replantation		X	Agreement
Selected non-gealing wounds secondary to systemic processes		X	Agreement
Sicckle cell disease		X	Agreement
Interstitial cystitis		X	Agreement

CNS: Central nervous system, HBOT: Hyperbaric oxygen therapy, BSA: Body surface area, TBI: Traumatic brain injury

Table 3. Uses of HBO approved by Undersea and Hyperbaric Medical Society, USA[5]
Air or gas embolism
Carbon monoxide poisoning and carbon monoxide poisoning complicated by ciyanide poisoning
Clostridial myonecrosis (gas gangrene)
Compromised skin grafts and flaps
Crush injury, compartment syndrome and other acute traumatic ischmias
Decompression sickness
Enhanement of healing in selected problem wounds
Exceptional anemia resülting from blood loss
Intracranial abcess
Necrotizing soft tissue infections (of subcutaneous tissue, muscle or fascia)
Radiation tissue damage (osteoradionecrosis)
Refractory osteomyelitis
Sensory neural hearing loss
Skin grafts and flaps
Thermal burns
HBO: Hyperbaric oxygen

Table 4. Indications for hyperbaric oxygen therapy in Turkey[2]
Decompression sickness
Air or gas embolism
Carbon monoxide, cyanide poisoning, acute smoke inhalation
Gas gangrene
Necrotizing infections of soft tissue (subcutaneous, muscle, fascia)
Crush injuries, compartment syndrome and other acute traumatic ischemia
Enhancement of healing in selected problem wounds (diabetic and non-diabetic)
Chronic refractory osteomyelitis
Excessive blood loss
Radiation necrosis
Skin grafts and flaps (compromised)
Thermal burns
Brain abscess
Anoxic encephalopathy
Sudden sensory neural hearing loss
Retinal artery occlusion
Acute osteomyelitis of the skull bones, sternum and vertebrae

treatment, and the patient's ear equalization is ensured by the guidance of the assistant personnel accompanying the treatment. However, the presence of edema and congestion in the respiratory tract may prevent equalization. In such cases, treatment may be interrupted until the patient recovers. In uncooperative children and unconscious patients, prophylactic tympanocentesis may be required to avoid barotrauma.

Lung barotrauma occurs either because of the expansion of the trapped air in the decompression phase due to lesions such as cysts, caverns, bullae, and blebs in the lung or because of the patient's breathlessness during the exit phase of the treatment. Pulmonary barotraumas can be observed as alveolar rupture, pneumothorax, pneumomediastinum, subcutaneous emphysema, and gas embolism[3,11,12]. To prevent these side effects, the patient should be evaluated with respiratory system examination and chest X-ray before treatment. In suspected cases, further investigations may be required.

Inhalation of 100% oxygen at pressures of 2 ATA or higher may produce toxic effects on the central nervous system (CNS). This effect manifests itself in the form of tonic-clonic contractions in the patient. To avoid this side effect, air breaks are administered in HBO therapies. In various studies, it has been reported that the frequency of CNS oxygen toxicity is 1-6/10000 HBO therapy sessions[12,13]. Prodrome symptoms can be observed in less than half of the cases. These include muscle twitching, fixed gaze in the eyes, auditory hallucinations, tunnel vision, restlessness, and anxiety[12]. As soon as the signs of toxicity are observed, the patient's oxygen mask is removed, the cabin pressure is kept constant, and the patient is allowed to breathe from the ambient air. Thus, the symptoms regress. Oxygen toxicity does not cause sequelae. The subsequent treatment of the patient can be continued as planned. However, as a precaution, longer air breaks can be given for these patients[11-13]. Pulmonary oxygen toxicity does not occur with routine HBO therapy. It is usually seen in long-term treatment scedules such as decompression sickness or arterial gas embolism. Symptoms begin with substernal pain on deep inspiration. With continued exposure, pleuritic chest pain, cough, and dyspnea occur. Symptoms disappear with the cessation of oxygen exposure[11,13].

Myopia occurs at a rate of 25-100% in long-term treatments with HBO and reverts within a few weeks after treatment is stopped[13]. Cataract is a very rare side effect. Claustrophobia is mostly seen in single rooms. Although anxiety is rare in

multi-person pressure chambers, very few require sedation. The presence of auxiliary personnel in the pressure room is a factor preventing claustrophobia.

Contraindications to HBO Therapy

The absolute contraindication for HBO is untreated pneumothorax. Relative contraindications include conditions such as borderline heart failure, pregnancy, uncontrolled asthma, obstructive pulmonary diseases, epilepsy, asymptomatic lung lesions on X-ray, lesions such as bulla-bleps that may cause air trapping, and a history of chest or ear surgery[3,11,12]. Pacemakers produced recently can generally be used safely under pressures below 3 ATA. However, the reliability of the batteries of pacemakers under pressure should be checked from the user manuals.

Crush Injuries

Crush injuries are serious injuries that result from the exposure of any part of the body to high-energy trauma or pressure, such as dents, traffic accidents, or gunshot wounds. In these injuries, at least two of the bone, soft tissue, nerve, and vascular structures are affected, and the viability of the affected tissue is threatened. In cases where treatment is delayed, irreversible damage may occur. In severe crush injuries, osteomyelitis, non-union of the fractures, unsuccessful flaps, and amputations are seen in approximately 50%[14]. In injured tissues, there is a gray zone between the minimally affected area and the areas of irreversible damage. The aim of this treatment is to maintain the vitality of the tissues in the partially viable gray zone and to prevent further tissue damage. For this, immediate tissue perfusion is required. Decreased blood flow and thrombosis in microvessel impair tissue perfusion and cause tissue hypoxia. Because of hypoxia at the cellular level, cells lose their water content and bacterial defense systems become irreversible due to insufficient energy production. In addition, leakage of intracellular fluid into the intercellular space and extravasation from blood and lymphatic vessels lead to edema formation[15]. Consequently, edema, ischemia, hypoxia, and deterioration in microcirculation around the injured area create a vicious circle with secondary ischemia.

Treatment of Crush Injuries

In crush injuries, diagnosis should be made without delay and treatment should be started quickly to minimize the permanent damage that may occur not only in the damaged tissue but also in the surrounding tissues. This is because the complication rate is high and requires surgery at rates exceeding 50%, even under most conditions[14,15]. Therefore, the treatment of crush injuries requires a multidisciplinary approach. The primary goal of treatment is to restore circulation. The vitality of the extremity depends on the time elapsed between injury and treatment. Tissue hypoxia in crush injuries is caused by ischemia. By preventing hypovolemia and blood loss, the patient's hemodynamics should be fixed, and antibiotherapy should be arranged. Another primary treatment is the debridement of necrotic tissue in open wounds. However, care must be taken to protect living tissues at this time.

HBO Therapy

HBO therapy in crush injuries is an adjunctive treatment method that should be used in the early period to reduce edema formation and provide hyperoxygenation in hypoxic tissues[15].

HBO therapy is recommended by international HBO societies along with open fractures or isolated crush injuries[1,10]. Because tissue infection and necrosis may be associated with severe open fractures, HBO therapy should be initiated in the early period. In the presence of host or injury-related risk factors, HBO therapy should be considered even if the injury is less severe[10]. Similarly, HBO therapy is recommended in cases where there are open wounds where tissue viability is at risk due to infection, even if there is no fracture. HBO therapy is generally recommended as 90 min at 2.4 ATA, three sessions a day in the first 24 h, and then two sessions a day[14,15].

Compartment Syndrome

Compartment syndrome is a situation in which increased pressure within the myofascial compartment threatens the circulation and function of tissues in that area. Crush injuries of the extremities, especially long-term tourniquet applications, tight plaster and bandages, burns, ischemia-reperfusion injury, or toxic coma are the conditions that occur as a result of long-term compression of the extremity. The most important criterion in the diagnosis of compartment syndrome is the presence of trauma. Classical diagnostic criteria, defined as 6P, are pain (disproportionate to trauma), extremity pallor, pressure, paralysis, paresthesia, pulselessness, and progression of symptoms. The diagnosis is confirmed by increasing complaints and rising intracompartmental pressure in hourly repetitive examinations[15]. Pain that does not respond

to analgesics and increases with passive stretching is typical in this patient. Intracompartmental pressure is not a direct indicator of tissue damage, and there are different tolerance levels among patients. Note that the greater the initial soft tissue damage, the higher the intracompartmental pressure. In patients who are unconscious or uncooperative, intracompartmental pressure measurements should be routinely performed[14]. When the interstitial fluid pressure in the compartment exceeds the capillary perfusion pressure, the flow within the capillary bed is blocked and the compartment contents become ischemic. Thus, ischemia, necrosis, and loss of function occur in the tissue. In these cases, surgical decompression of the compartment, ie fasciotomy, is required in the presence of neuropathy. Thus, tissue perfusion is restored. However, tissue necrosis is not always reversible[14,15].

HBO Therapy for Compartment Syndrome

It shows its effect in HBO compartment syndrome by restoring perfusion with the hyperoxygenation it provides in the tissue. Thus, oxygen delivery to the tissue is ensured and the vitality of hypoxic tissues is preserved. The other effect is to reduce intracompartmental pressure by reducing tissue edema with vasoconstriction due to hyperoxia[16]. In experimental models, it has been shown that HBO therapy reduces the intracompartmental volume[17]. HBO therapy cannot be used instead of fasciotomy, which is the main treatment for compartment syndrome. However, in cases where surgery will be delayed, the patient can be treated with HBO to control the compartment pressure. Hyperoxia also stimulates collagen synthesis and fibroblast proliferation and induces neovascularization. Thus, it is possible to control infection in fasciotomy wounds and limit muscle necrosis (Figure 4)[16,17].

In the literature, it has been reported that amputations can be reduced with the use of HBO in two randomized controlled studies on the use of HBO therapy in acute traumatic ischemia[18,19]. The use of vacuum-assisted closure systems together with HBO therapy in the follow-up of fasciotomy wounds provides a synergistic effect and earlier closure of wounds[20]. In another study, a decrease in amputation rates was noted with HBO therapy in crush injuries with open fractures[21]. In the first multicenter, randomized controlled clinical study in which HBO therapy was used in acute musculoskeletal trauma, it was shown that HBO therapy was effective in reducing tissue necrosis and infections[22].

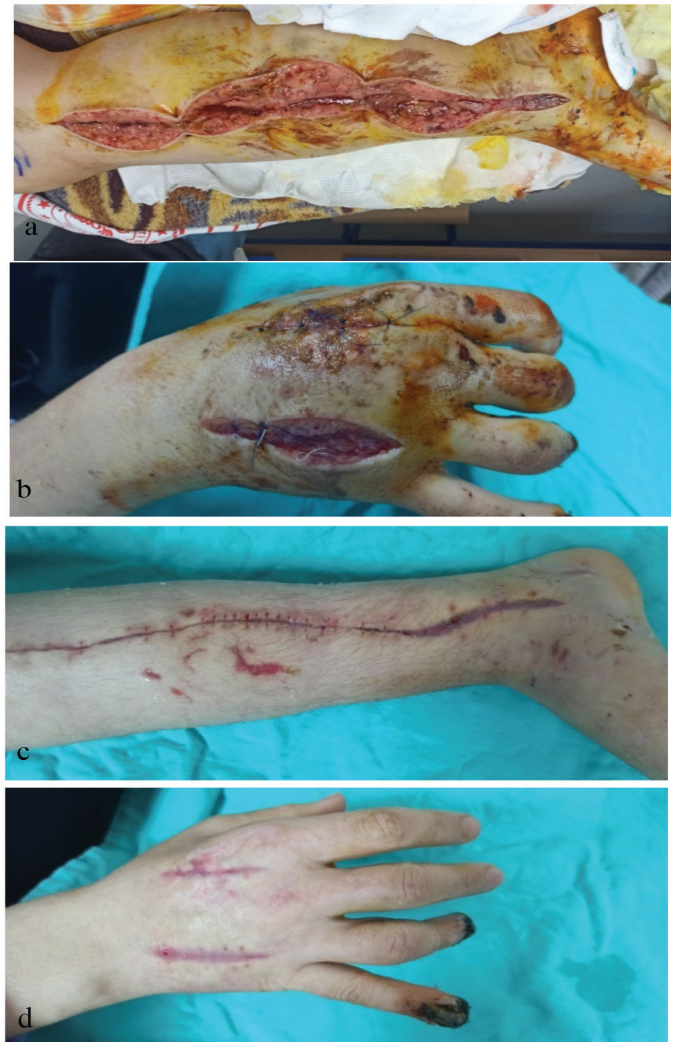

Figure 4. Fourteen-year-old girl who was trapped under the rubble for 3 hours

a, b: Before treatment, c, d: After 25 sessions of HBO therapy and surgical closure

HBO: Hyperbaric oxygen

According to official records, 17,127 people lost their lives in the 7.8 magnitude Marmara Earthquake that occurred in 1999. HBO therapy was widely used for the first time in this earthquake, and its results have been published by various researchers. Sever et al.[23] reported that 28 of 639 patients underwent HBO therapy and were followed up because of crush syndrome and acute renal failure. While mortality was 15.2% in patients who did not receive HBO therapy, no death was recorded in the HBO receiving group (p=0.002)[23]. In another study by Kazancioglu et al.[24], they reported that 8 of 37 cases, followed up for crush syndrome and acute renal

failure, underwent HBO therapy. They revealed that, although no difference was observed in the hemodialysis duration of eight patients who were treated with HBO therapy, no major amputation was required in the HBO group, whereas major amputation was performed on three of the group that did not receive HBO therapy[24]. In the 52 case series of Yildiz et al.[25], it was reported that the most important factor protecting earthquake survivors from amputation was the time to start HBO therapy. In the experimental compartment syndrome study of Aydin et al.[17], HBO therapy was not as effective as fasciotomy alone or fasciotomy + HBO therapy in reducing intracompartmental pressure; however, the group with the least tissue necrosis and infection was the isolated HBO receiving group. This situation has been associated with infection and tissue damage caused by fasciotomy[17]. In the special issue of Turkish association of Orthopedics and Traumatology, titled Earthquake Injuries, published in May 2022, although the subject was evaluated in all its aspects, the subject of HBO therapy was not discussed[26].

Conclusion

Crush injuries and compartment syndromes are injuries that occur massively during earthquakes. Anatolia, one of the most complex regions in the world in terms of earthquake activity, is located in the middle of the Arabian, African, and Eurasian plates. Tens of thousands of our citizens have lost their lives in major earthquakes in our country, which has faced devastating earthquakes for centuries. In the 1999 Marmara Earthquake, many patients who were treated at the İstanbul Medical Faculty and GATA Haydarpaşa Hospitals were also given HBO therapy. In the published studies, it has been revealed that the success rates of patients who receive HBO therapy are significantly higher than those of others. In the same way, HBO therapy was started as soon as possible in the Kahramanmaraş-centered earthquake that occurred on February 6, 2023 and was effective in 11 provinces in regional hospitals with HBO facilities.

However, patients in other hospitals did not have such a chance. When the results of these patients, who are still under treatment in various centers, are published, it will be possible to compare the patient groups who did not receive HBO therapy.

Today, because of developments in orthopedics, plastic surgery, and vascular surgery, protection of the extremities in crush injuries and compartment syndrome can be achieved at a higher rate than in the past. However, amputations may still be inevitable because of infection, tissue necrosis, and repetitive surgeries.

HBO therapy provides tissue perfusion by regressing edema and hypoxia in both compartment syndrome and crush injuries and since it reduces the patient's need for repetitive surgery with additional infection control in fasciotomy ulcers. Therefore, we strongly recommend this adjunctive therapy. In this way, it is possible to both reduce amputation rates and obtain a more functional extremity. In order for more patients to benefit from this treatment in the early period, it is necessary to know more about the subject and to be kept in mind by specialists in pediatrics, plastic surgery, and cardiovascular surgery, especially in the field of orthopedics. Because we can encounter hundreds, sometimes thousands, of patients at the same time in major disaster situations such as earthquakes, it is important that patient triage for HBO therapy is carried out with pre-made action plans in such cases.

Ethics

Authorship Contributions

Surgical and Medical Practices: F.A., A.K., Concept: F.A., A.K., Design: F.A., A.K., Data Collection or Processing: F.A., A.K., Analysis or Interpretation: F.A., A.K., Literature Search: F.A., A.K., Writing: F.A., A.K.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Assessment of Female Researchers Presented as First Author or Senior Author in the 100 Most Cited Articles in Intensive Care Literature

Yoğun Bakım Literatüründe En Çok Atıf Alan 100 Makalede İlk Yazar veya Kıdemli Yazar Olarak Sunulan Kadın Araştırmacıların Değerlendirilmesi

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Abstract

Objective: To present potential mechanisms for female authorship in intensive care research by evaluating the ratio of female first author to senior author in the top 100 most cited articles.

Methods: In the Web of Science search engine, by typing the search key "SU=CRITICAL CARE OR WC=CRITICAL CARE" and in advanced mode; to investigate the female sex ratio in the first and senior author in the top 100 most cited research articles in the international literature written in the field of intensive care.

Results: When the first 100 most cited articles were analyzed regarding the first name and last name gender difference, the rate of first name female authors was 16%. The country with the highest number of female authors writing first names was the United States. In the analysis, when the gender of the first name and the gender of the last name was evaluated, no statistically significant relationship was found between them (p=0.327). A statistically significant difference was found between the gender of the first author and the journal in which the article was published (p=0.021). A significant relationship was found between the gender of the first name and the country of the journal in which the article was published (p=0.032).

Conclusion: When evaluated in terms of article authorship, gender inequalities were identified in scientific activities and academic leadership positions in intensive care. Female gender is underrepresented in the international literature in the field of intensive care.

Keywords: Gender differences, female, first author, last author, intensive care medicine

Öz

Amaç: En çok atıf yapılan ilk 100 makaledeki ilk kadın yazar ve kıdemli yazar oranını değerlendirerek, yoğun bakım araştırmalarında yazarlar arasındaki kadın cinsiyet oranını ve rol oynayan potansiyel mekanizmaları tespit etmeyi hedeflemiş bulunmaktayız.

Yöntem: Web of Science arama motorunda "SU=CRITICAL CARE OR WC=CRITICAL CARE" arama anahtarını yazarak ve gelişmiş modda; Uluslararası literatürde yoğun bakım alanında yazılmış en çok atıf alan ilk 100 araştırma makalesi ve bu ilk 100 makaledeki ilk ve kıdemli yazarda kadın cinsiyet oranını araştırıldı.

Bulgular: En çok atıf alan ilk 100 makalenin, ilk isimleri ve son isimleri cinsiyet açısından incelendiğinde, ilk isimde kadın yazar oranı %16 olarak bulundu. İlk isim yazarın kadın yazar sayısının en fazla olduğu ülke Amerika Birleşik Devletleri oldu. Analizde ilk ismin cinsiyeti ile son ismin cinsiyeti arasında istatistiksel olarak anlamlı bir ilişki bulunmadı (p=0,327). Buna karşı ilk yazarın cinsiyeti ile makalenin yayınlandığı dergi ve makalenin yayınlandığı derginin ülkesi arasında anlamlı bir ilişki bulundu (p=0,021, p=0,032).

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Öz

Sonuç: Yoğun bakım alanındaki bilimsel faaliyetler ve akademik liderlik pozisyonları, makale yazarlığı açısından değerlendirildiğinde cinsiyet eşitsizlikleri tespit edilmiştir. Yoğun bakım alanında uluslararası literatürde kadın cinsiyeti yeterince temsil edilmemektedir.

Anahtar Kelimeler: Cinsiyet farklılığı, kadın, ilk yazar, son yazar, yoğun bakım hekimliği

Introduction

In the international literature, interest in raising awareness about gender inequalities in academic medicine and scientific studies on this subject has increased significantly in the last decade[1]. Studies show that the number of female medical school graduates has increased by 1% each year in the last two decades, and women now represent 50.2% of the medical profession[2]. Despite the increasing number of female physicians in medical faculties, the data in the literature emphasize that there are inequalities in areas such as academic progress, academic production and participation in production, promotion, leadership positions, and payment[3]. In support of these data, in our study, we analyzed the scientific production of academic anesthesiology and reanimation specialists (ARS) working in educational institutions in our country with H-index and bibliometric parameters, the number of publications, citation numbers, and H-index averages of the male anesthesiology and Reanimation specialists, and the ARS in the female gender. Found significantly higher than the experts[4].

Worldwide, women comprise 20% and 50% of the intensive care workforce[5]. Only 30% of graduate trainees admitted to the intensive care unit (ICU) in the United States of America (USA) are women[6]. In a study on the subject, we found 473 intensive care specialists in Turkey[7]. While 214 (45.24%) of the intensive care specialists were female, the number of male intensive care specialists was 259 (56.87%). The same study determined that 95 (44.39%) of the female intensive care specialists and 143 (55.21%) of the male intensive care specialists were in the academic staff.

Academic productivity is an essential criterion for researchers taking leadership roles in their fields[8]. Past studies have examined academic achievement by analyzing an individual H-index, indicating that a higher H-index is associated with a higher academic level[9]. However, the fact that researchers with a high H-index receive more scholarships and are in leadership positions, especially in the USA, and that male researchers have a higher H-index in the academic medical literature may cause this to result against the female gender[10]. Academic progress is primarily driven by original research in peer-reviewed journals[10]. Peer-reviewed publications are significant for career development, but data on gender differences in the authorship of studies in the ICU are limited[5].

The concepts of the first and senior authors are as crucial as the number of articles published in peer-reviewed journals[11]. Although there are different opinions on this issue, the most accepted recommendation was that presented by Riesenberg and Lundberg[3]. According to this suggestion, the first author should be the person who contributed the most to the study, including article writing[3]. For clinical studies, the person who plans and conducts the study, evaluates the data, and writes the article should be the first author. A senior author is an author who contributes to the planning and writing of the study, supervises it, and has at least 10 publications on that subject[12]. The authorship of academic articles is professionally stimulating and develops the researcher. However, the representation of gender in article writing is unclear[3].

Our aim in this research is to understand gender differentiation in this field and to present potential mechanisms for female authorship in intensive care research by evaluating the ratio of the female first author and senior author in the top 100 most cited articles in the international literature in the field of intensive care in terms of article authorship, which is an important indicator of academic productivity.

Materials and Methods

Data Source

The study was initiated with the approval of the Dokuz Eylül University Ethics Committee (acceptance number: 2021-16-18, date: 27.05.2021). Because patient data were not used in the study, informed consent was not required. In the Web of Science search engine of the Institute for Scientific Information, the first 100 most cited research articles in the international literature written in the field of intensive care, by typing the phrase "SU=CRITICAL CARE OR WC=CRITICAL CARE" in the advanced mode, were scanned on 06.24.2021. Letters to the editor and case reports were excluded from this study.

Author Identification and Journal Features

Authors were categorized in order of authorship as first and senior authors. The author rank method was used to determine the initial and senior authorship[3,12]. Author gender was determined by searching the author's names from a previously validated Genderize database containing 216,286 names in 79 countries and 89 languages[13]. To investigate the gender of authors whose names were not found in this database, they were identified by manual internet searches from author's professional websites, including author's photographs and/or references to authors with male or female pronouns. Articles whose first and last names and genders could not be found were excluded from the study.

Statistical Analysis

The SPSS 24.0 package program was used in the analysis of the study. Variables with continuous values in the study are shown as mean ± standard deviation, and variables indicating frequency are shown as frequency (n) and percentage (%). Kolmogorov-Smirnov and Shapiro-Wilk tests examined the standard test assumptions of the variables with continuous values. The data with continuous values in the study were tested using the Mann-Whitney U test and Kruskal-Wallis test, considering the group numbers and the results of normality tests. Pearson's chi-square and Fisher's Exact chi-square tests were used for group comparisons of frequency variables. A p-value of 0.05 was set as statistically significant.

Results

In our study, the top 100 most cited articles in the field of intensive care in the international literature were analyzed. Studies were analyzed by an intensive care minor faculty member (VH) and an intensive care minor specialization assistant (OS). Studies not included in intensive care were excluded. All data are summarized in Table 1.

When the first 100 most cited articles were analyzed regarding the first name and last name gender difference, the rate of first name female authors was 16%. The country with the highest number of female authors writing first names was the USA. However, when the articles were evaluated based on the continent in which they were published, the rate of the female first name was 12% in the articles published in America. The rate of female first names from other continents was 23.5%. When the first name was evaluated according to the continent, no statistically significant difference was found between them (p=0.140).

In the analysis, when the gender of the first name and the gender of the last name was evaluated, no statistically significant relationship was found between them (p=0.327). When the 100 most cited articles in the international literature in the field of intensive care were evaluated, it was found that 16% of the publications were by female authors as senior authors. While the last name is a female author in 25% of the studies with the first name female author, 15% of the studies in which the first name is male author have been found as the last female author.

A statistically significant difference was found between the gender of the first author and the journal in which the article was published (p=0.021). A significant relationship was found between the gender of the first name and the country of the journal in which the article was published (p=0.032). The USA was found to be the host country of the journal in which the articles written by the first name female author were published. It was found that the articles with the first female eulogy author were published in 16 journals in total, while the other two journals were from England. Seventy-five percent of the journals in which the first name male authors' research is published are in American Journals; it was determined that 26.2% of them were published in journals of Dutch origin.

No significant relationship was found between the gender of the first name and the continents of origin of the journals (p=0.154).

Discussion

In our study, in which the top 100 most cited articles in the international literature in the field of intensive care were analyzed, the rate of first-name female authors was 16% and that of senior female authors was 16%. A statistically significant difference was found between the gender of the first author, the journal in which the article was published, and the country in which the journal was published. It was found that the country was hosting a journal in which the first female author's articles were published in the US. When evaluated in terms of the authorship of articles published in peer-reviewed journals, gender inequalities were determined in academic leadership positions and scientific activities in intensive care. Our findings show that the female gender is underrepresented in the international literature in the field of intensive care.

The participation of women in the medical profession has increased in the last two decades, but the "gender gap"

Table 1. Characteristic features of the first and last authors

		First author		Last author		p
		Female	Male	Female	Male	
First author's country	USA	8	58			0.140
	Other	8	26			
	Total	16	84			
First author's gender	Female			4	12	0.327
	Male			12	68	
First author's journal	Critical care medicine	1	15			0.021
	Chest	0 (0%)	20			
	American Journal of Respiratory and Critical Care Medicine	9	33			
	Critical Care	0	2			
	The Journal of Trauma	1	5			
	Intensive Care Medicine	1	5			
	Lancet Respiratory Medicine	2 (66.6%)	1 (33.3%)			
	Injury	0	2			
	Journal of Neurotrauma	2	1			
	Total	16	84			
First autohor's journal country	USA	14	59			0.032
	Holland	0	22			
	England	2	3			
	Total	16	84			
First autohor's journal continent	America	14	59			0.154
	Europe	2	25			
	Total	16	84			
First autohor's journal	Impact	18.30±8.45	13.95±7.05			0.083
	Citations	1832.12±945.47	2313.55±1737.42			0.297

continues, especially in the surgical field. Although the number of male and female medical students is similar, only 32% of surgical residents and only 9.8% of surgical professors are women[14]. At this rate, it will take until 2096 for men and women to be represented in surgery in equal numbers as professors. A systematic review of the clinician workforce found that the representation of certain groups (women, racial and ethnic minorities in medicine, sexual and gender minorities, and people with disabilities) in the workforce needed to optimize patient care is at high risk[6]. However, recent studies have shown that female physicians report greater satisfaction and lower 30-day mortality and readmission rates than male physicians[15].

The role of women in academic advancement and leadership, and their underrepresentation in the profession, remains unclear. In the report of the American National Institutes of Health Career Development Awards, they found that the rate of the senior female author is 4-6% in the academic literature, and there are "gender differences" in the representation of women as authors, especially in the surgical branch[16].

Academic progress is largely driven by peer-reviewed original research, so Jagsi and Silver[17] sought to identify the number of female physician-researchers among authors of selected publications in medicine over the past 35 years; New England Journal of Medicine (NEJM), Journal of the American Medical Association (JAMA), Annals of Internal Medicine (Ann Intern Med), Annals of Surgery (Ann Surg), Obstetrics and Gynecology (Obstet Gynecol), and Journal of Pediatrics (J Pediatr) investigated gender analyses of both

primary and senior authors in six major medical journals. In their analysis, they found that the proportion of female first authors increased from 5.9% in 1970 to 29.3% in 2004, and the proportion of senior female authors increased from 3.7% to 19.3%. The proportion of female authors has increased sharply in obstetrics and gynecology. In the Obstet Gynecol Journal, while the rate of female first authors was 6.7% and that of senior authors was 6.8% in 1970, the rate of female first authors increased from 40.7% of senior authors to 28% in 2004. Int J Pediatr, while the rate of the female-first author was 4.3% and the rate of the senior author was 4.3% in 1970, the rate of the female-first author in this field was determined as 38.9% in 2004, and the rate of senior authors increased to 38% in 2004.

Similarly, it was determined that the rate of female first names and author writers in three journals with high impact values increased between 2001 and 2016 in academic pediatrics[11]. While the rate of female first author and 0.7% senior author in Ann Surg Journal was 2.3% in 1970, these rates increased to 16.7% for first author and 6.7% for senior author in 2004[17]. This slow upward trend in the surgical field was reported by Hunter et al.[18] and was also compatible with his study in the fields of orthopedics and traumatology. This situation supports the results of our study. Regarding academic progress, although the situation has progressed in favor of the female gender over the years, the rates are still very insufficient.

In the field of intensive care, Vranas et al.[5] in their study, in the journals where more than 18,000 articles from intensive care and basic science and more than 40 cited articles were published between 2008 and 2018, the rate of the first-name female author was 30.8%, and the last-name author was 19.5%. When the senior author is a female author, the chances of female co-authorship increase significantly. In high-impact journals, the rate of female first author is 30.4%, whereas this rate decreases to 20.1% for senior authors. However, this study did not evaluate the 100 most cited studies in the field of intensive care. In our study, among the 100 most cited studies in the field of intensive care, the rate of female-first author was 16%, and the rate of senior author was 16%. In our study, although the average of the impact factors of the journals in which the first 100 articles were published in the most cited articles was higher, no significant difference could be determined between the groups.

Holliday et al.[19] in The Journal of the American Society of Radiation Oncology, in the study in which the last 30 years of radiation oncology were analyzed in the USA, the first author reported that the female sex ratio from 13.4% in 1980 to 29.7% in 2012 and the female gender ratio of the senior author. It was determined that it increased from 3.2% to 22.6%. These findings are consistent with those of our study. Of the 16 journals in which the first author was female, 14 originated in the USA, and the highest number of female first authors were in the literature.

Although there has been an increase in the rate of female authors from past to present, this rate is lower, and progress is slower than that of male authors[20]. The low academic productivity of women reduces the possibility of gaining leadership roles in their departments[21,22]. Studies emphasize that women are less likely to hold leadership positions and more likely to leave academic medicine[21]. In particular, in much of the world, department heads are often chosen among those with high academic productivity. However, the low number of publications of female authors, the higher number of publications in low-impact journals, and the lower rate of being a senior author may prevent them from leading positions in their institutions[21]. Previous research has shown that lack of mentoring, an unfavorable work culture, and barriers to research contribute to female academic withdrawals[21,22].

Unfortunately, there is no easy way to address gender inequality in academic medicine. Considering that institutions are extensions of the cultural codes of their societies, changing the established social practices and creating an organizational climate where leadership roles are appropriate for women can help solve the problem[23]. Organizational climate is often cited as a possible cause of gender disparities in academic medical school careers[24]. Institutions should work to address gender inequality. At the same time, women should be encouraged to participate in organizational initiatives and rise to leadership positions in the institutions where they work. The burnout of female academics and the prejudices they face should be addressed[24].

According to the authors' literature knowledge, our study is the first to analyze gender differences in the first author and senior authorship of the top 100 most cited articles in the field of intensive care. When evaluated in terms of article authorship, gender inequalities were identified in scientific activities and academic leadership positions in intensive care. Female gender is underrepresented in the international literature in the field of intensive care. They were making women working in intensive care medicine equal to their male counterparts in terms of participation in

literary production, which should be among the first targets of intensive care medicine in the future.

Study Limitations

Our study has some limitations. There may be information inaccuracies in the lists of websites used to obtain data in our study. In addition, female academics may have changed their surnames after marriage. Therefore, the name order in the publications was checked before and after the surname change.

Conclusion

In terms of article authorship, which is one of the important indicators of academic productivity, our study evaluated the rates of female first authors and senior authors in the top 100 most cited articles in the international literature in the field of intensive care; when evaluated in terms of authorship of articles published in peer-reviewed journals, gender inequalities were identified in academic leadership positions and scientific activities in intensive care. Our findings show that female gender is underrepresented in the international literature in the field of intensive care and that more research is needed on this subject.

Ethics

Ethics Committee Approval: The study was initiated with the approval of the Dokuz Eylül University Ethics Committee (acceptance number: 2021-16-18, date: 27.05.2021).

Informed Consent: Informed consent was not required.

Authorship Contributions

Concept: Ö.Ö., V.H., Design: Ö.Ö., V.H., Data Collection or Processing: Ö.Ö., V.H., Analysis or Interpretation: Ö.Ö., V.H., Literature Search: Ö.Ö., V.H., Writing: Ö.Ö., V.H.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Comparison of Mechanical Thrombectomy Outcomes Before and During COVID-19 Pandemic

COVID-19 Pandemi Öncesi ve Sırasında Mekanik Trombektomi Sonuçlarının Karşılaştırılması

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Abstract

Objective: To evaluate the reflection of the pandemic on the management of acute stroke mechanical thrombectomy (MT).

Methods: We retrospectively evaluated 100 acute ischemic stroke patients between March 1, 2019-Februray 29, 2020, and between March 1, 2020-March 1, 2021, who underwent (MT) at our institute. Patients were divided into two groups as those who underwent thrombectomy before the Coronavirus disease-2019 (COVID-19) pandemic (group 1) and those who underwent thrombectomy during the period of COVID-19 pandemic (group 2). All the diagnosis of stroke patients was confirmed by magnetic resonance imaging and computed tomography. Demographics, clinical and laboratory data were recorded. The SPSS version 26.0 was used for statistical analysis.

Results: A total of 100 patients, 50 before and 50 after the pandemic, were included in the study. No statistically significant difference was observed between the groups in terms of demographic data and risk factors. The time from symptom onset to groin puncture was significantly longer during the pandemic period than before (p=0.001). No significant difference was observed in the time from groin puncture to recanalization (p=0.251), recanalization rates (p=0.806) and the number of passes (p=0.889). There was no difference between the pre-pandemic and post-pandemic groups in terms of the frequency of intracranial hemorrhage (p=0.501), complication (p=0.153) and decompression (p=0.538) after thrombectomy. The modified Rankin scores scores at 3 months were similar (p=0.316).

Conclusion: As a result, the time from symptom to procedure is prolonged in acute ischemic stroke patients who underwent MT in our center during the pandemic period. In the respect of procedural findings and outcomes of thrombectomy before and during pandemic, there had been no significant change at our center.

Keywords: Mechanical thrombectomy, acute stroke, COVID-19

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Öz

Amaç: Pandeminin akut inmede mekanik trombektomi (MT) yönetimi üzerindeki yansımasını değerlendirmektir.

Yöntem: Kliniğimizde MT uygulanan 100 akut iskemik inme hastası retrospektif olarak değerlendirildi. Hastalar, Koronavirüs hastalığı-2019 (COVID-19) pandemisinden önce trombektomi geçirenler (grup 1, 1 Mart 2019-29 Şubat 2020) ve COVID-19 pandemi döneminde trombektomi geçirenler (grup 2, 1 Mart 2020-1 Mart 2021) olmak üzere iki gruba ayrıldı. İnme tanıları manyetik rezonans görüntüleme ve bilgisayarlı tomografi ile doğrulandı. Demografik, klinik ve laboratuvar verileri kaydedildi. İstatistiksel analiz için SPSS sürüm 26,0 kullanıldı.

Bulgular: Çalışmaya her biri 50 hastadan oluşan toplam 100 hasta dahil edildi. Demografik veriler ve risk faktörleri açısından gruplar arasında istatistiksel olarak anlamlı bir fark gözlenmedi. Ancak, semptom başlangıcından kasık ponksiyonuna kadar geçen süre pandemi döneminde önemli ölçüde daha uzundu (p=0,001). Kasık ponksiyonundan yeniden kan akışının sağlanmasına kadar geçen süre (p=0,251), yeniden kan akışının sağlanma oranları (p=0,806) ve geçiş sayıları (p=0,889) açısından anlamlı bir fark gözlenmedi. Ek olarak, pandemi öncesi ve sonrası gruplar arasında intrakraniyal kanama sıklığı (p=0,501), komplikasyonlar (p=0,153) ve trombektomi sonrası dekompresyon (p=0,538) açısından fark yoktu. Üç ay sonraki modifiye Rankin skorları da iki grup arasında benzerdi (p=0,316).

Sonuç: Pandemi döneminde MT uygulanan akut iskemik inme hastalarında semptom başlangıcından işlemin gerçekleştirilmesine kadar geçen süre uzamıştır. Ancak, merkezimizde pandemi öncesi ve sonrası trombektomi prosedürel bulguları ve sonuçları açısından önemli bir değişiklik olmamıştır.

Anahtar Kelimeler: Mekanik trombektomi, akut inme, COVID-19

Introduction

The Coronavirus disease-2019 (COVID-19) pandemic has created a public health crisis worldwide. One of the significant complications of COVID-19 is acute ischemic stroke[1]. As previously mentioned in numerous publications, COVID-19 induces a prothrombotic state with high levels of factor 8, fibrinogen, and D-dimer, leading to occlusive and embolic pathologies[2]. This proclivity to clotting intensifies the embolic process, resulting in stroke. It is believed to have led to a higher incidence of acute ischemic stroke. A study conducted with 214 patients in Wuhan reported the incidence of stroke as 2.34%[3], whereas another study from New York reported it as 0.9%[4].

Our aim in this study was to investigate the effect of hospital and transport measures implemented during the pandemic on the process in the stroke center, regardless of the COVID-19 status of the stroke patients. We evaluated the impact of the pandemic on the management of acute stroke mechanical thrombectomy (MT) at our center. We compared the outcomes and MT data of acute stroke patients who underwent MT before the COVID-19 pandemic and after its onset.

Materials and Methods

We retrospectively evaluated 100 acute ischemic stroke patients from March 1, 2019, to February 29, 2020, and from March 1, 2020, to March 1, 2021, who underwent MT at our institute. Patients were divided into two groups: Those who underwent thrombectomy before the COVID-19 pandemic (group 1) and those who underwent thrombectomy during the COVID-19 pandemic (group 2). The stroke diagnosis for all patients was confirmed by magnetic resonance imaging and computed tomography. Demographic, clinical, and laboratory data were recorded. Age, gender, preexisting vascular risk factors, laboratory values, anticoagulant and antiplatelet premedications, National Institutes of Health Stroke Scale score upon admission and at discharge, ASPECT score, occluded vessel location, use of preprocedural lytic medication, modified Rankin scores (mRS), procedure times (onset to groin puncture, door to needle, groin puncture to recanalization), device pass counts until successful recanalization or last angiogram if recanalization failed, thrombolysis in cerebral infarction (TICI) scales, early neurological improvements, post-procedure hemorrhage, decompression surgery, type of anesthesia during the procedure, and periprocedural complications were analyzed between the groups. The TOAST classification was used to determine stroke etiology.

Local ethics committee approval was obtained from the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethical Committee in compliance with the Declaration of Helsinki Ethical Standards for this retrospective single-center study (approval no: 2020 8-9, 08.07.2020).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as means ± standard deviation and categorical variables as percentages. The distribution of variables was assessed by

the Kolmogorov-Smirnov test. Patients were divided into two groups: Pandemi and non-pandemic. Chi-square test or Fisher's Exact test was used for categorical variables. Mann-Whitney U test or independent t-test was performed to compare continuous variables.

Results

Demographics and Clinical Characteristics

A total of 100 patients, 50 before and 50 during the pandemic, were included in the study. No statistically significant difference was observed between the groups regarding demographic data and risk factors. Gender (p=0.216), diabetes mellitus (p=0.534), hypertension (p=0.687), and atrial fibrillation (p=0.517) showed no significant differences. In terms of the TOAST classification, the groups were similarly distributed (p=0.259). The frequency of antiplatelet use was nearly the same (p=0.488), but anticoagulant use was higher in the pre-pandemic group (p=0.046). Demographic and preprocedural clinical statistics details are shown in Table 1.

The time from symptom onset to groin puncture was significantly longer during the pandemic than before (p=0.001). No significant differences were observed in the time from groin puncture to recanalization (p=0.251), recanalization rates (TICI 2b-3) (p=0.806), number of passes (p=0.889), or general anesthesia rates (p=0.656). Frequencies of intracranial hemorrhage (p=0.501), complications (p=0.153), and decompression (p=0.538) post-thrombectomy did not differ between the pre-pandemic and post-pandemic groups. The 24-h NIHHS scores (p=0.173) and the mRS scores at 3 months were also comparable (p=0.316). Procedural and postprocedural statistics are presented in Table 2.

Discussion

The impacts of COVID-19 on the early and late outcomes of ischemic stroke patients undergoing thrombectomy need clarification[5]. The demographic data and TOAST classification of our patients remained consistent during the pandemic. Our sample size is relatively small, limiting definitive conclusions about the relationships among the pandemic, risk factors, and etiological causes of ischemic stroke. In addition, the inclusion of only MT patients in the study limits our understanding of these relationships. Although the frequency of AF and etiological causes remained unchanged, there was a reduced frequency of anticoagulant use during the pandemic. This suggests that the pandemic might have affected drug use or hindered the diagnosis of other indications. Larger and more comprehensive stroke studies can shed more light on this.

We found that the time from symptom onset to groin puncture was significantly longer during the pandemic. This delay could be attributed to patients avoiding hospitals for fear of COVID-19 transmission and potential in-hospital delays due to heightened COVID-19 precautions. Our study only

Table 1. Demographic and preprocedural clinical statistics

	Before pandemic	During pandemic	p-value
Age (mean)	61.62	63.06	0.375
Gender	28	34	0.216
DM	17 (34%)	20 (40%)	0.534
HT	27 (54%)	29 (58%)	0.687
AF	17 (34%)	14 (28%)	0.517
TOAST classification			
LAA	28 (54%)	28 (54%)	
Cardioembolic	19 (38%)	18 (36%)	
Other	3 (6%)	1 (2%)	0.259
Cryptogenic	0	3 (6%)	
Initial NIHSS score	16.2	15.4	0.777
Initial ASPECT skor	9	9	0.732
iv-tPA medication	11 (22%)	18 (36%)	0.123
Anticoagulant medication	38 (76%)	12 (24%)	**0.046**
Antiagregan medication	20 (40%)	22 (44%)	0.488

DM: Diabetes mellitus, HT: Hypertension, AF: Atrial fibrillation, NIHSS: National Institutes of Health Stroke Scale

Table 2. Procedural and postprocedural statistics			
	Before pandemic (n=50)	**During pandemic (n=50)**	**p-value**
Onset to groin puncture time (mean min.)	171.50	240.46	**0.001***
Groin to recanalisation time (mean min.)	60.23	58.27	0.251
Number of passes	2	1.84	0.889
Recanalisation (TICI 2b-3) (n)	39 (78%)	40 (80%)	0.806
General anestesia (n)	13 (26%)	15 (30%)	0.656
Complication (n)	0	2 (4%)	0.153
24. hour NIIHS score	12.6	9.82	0.173
Intracranial hemorrhage (n)			
Hi-1	1 (2%)	2 (4%)	0.501
Hi-2	5 (10%)	7 (14%)	
PH-1	3 (6%)	6 (12%)	
PH-2	10 (20%)	5 (10%)	
Decompresion surgery (n)	7 (14%)	5 (10%)	0.538
3. month mRS 0-2 (n)	21 (42%)	26 (54%)	0.316
NIHSS: National Institutes of Health Stroke Scale, mRS: Modified Rankin scores, TICI: Thrombolysis in cerebral infarction			

captured the time from symptom onset to groin puncture. Future studies should delve deeper, measuring times both pre-hospital and in-hospital, to better understand these delays.

Our study's procedural durations remained consistent between the groups. Potential reasons might include the consistency of interventional physicians performing the procedures across both periods and the fact that COVID-19 precautions were implemented before groin puncture, negating any additional delays. The fact that the number of passes and recanalization rates remained unchanged suggests that thrombus structures may have remained consistent, although larger histopathological studies are needed to confirm this.

Study Limitations

There are inherent limitations to our study, including its retrospective nature and the need for emergency indications for stroke treatment. Additionally, because of the pandemic's impact on emergency room admissions, our sample size is limited. Despite these limitations, our research aligns with similar studies on the subject. Comparable results were found in a study by Kurnianto et al.[6], and Kerleroux et al.[7] observed a 21% decrease in MT procedures and an increase in imaging and groin access times during the pandemic. Zureigat et al.[8] reported that COVID-19 adversely impacted clinical outcomes in stroke patients.

In our study, clinical outcomes remained consistent during the pandemic. The delay in symptom onset to the procedure did not significantly impact outcomes, but this may be attributed to the small sample size. Further studies with larger populations are required to validate these findings.

Conclusion

The time from symptom onset to the procedure was longer for acute ischemic stroke patients who underwent MT at our center during the pandemic. However, procedural findings and outcomes remained consistent both before and during the pandemic at our center.

Ethics

Ethics Committee Approval: Local ethics committee approval was obtained from the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethical Committee in compliance with the Declaration of Helsinki Ethical Standards for this retrospective single-center study (approval no: 2020 8-9, 08.07.2020).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.E.Ç., D.F.B., O.S., Ü.B., Concept: D.F.B., U.Ş., Ü.B., Design: A.E.Ç., D.F.B., Ü.B., Data Collection or Processing: G.S.B., K.E.A., G.A., Analysis or Interpretation: O.S., Literature Search: A.E.Ç., G.S.B., G.A., Ş.K., U.Ş., Writing: A.E.Ç., G.S.B.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Is Axillary Reverse Mapping Oncologically Safe in Breast Cancer Surgery?

Meme Kanseri Cerrahisinde Ters Aksiller Haritalama Onkolojik Olarak Güvenli midir?

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Abstract

Objective: Axillary reverse mapping (ARM) has been described to protect against lymphedema. This study aimed to explore the oncological safety of ARM in terms of tumor characteristics and other factors.

Methods: The study included 81 patients who received mastectomy or breast-conserving surgery for diagnosis of breast cancer and undergo ARM as clinically axillary positive disease.

Results: No axillary reverse mapping lymph node (ARMLN) was found for 26 patients (32%). Of the 55 patients with ARMLN, 19 (34%) were malignant and 36 (66%) were benign. A statistically significant relationship was found between ARMLN and the number of lymph nodes dissected (p=0.004). The larger the size of ARMLN dissected, the more likely it is that the lymph nodes will be malignant (p=0.001).

Conclusion: Our study suggests that the higher the axillary burden, the more likely it is for ARMLN to be malignant and the less safe its preservation. Additional randomized prospective studies with a focus on patient survival time and recurrence are warranted to verify the potential feasibility of the ARM technique and confirm the reliability of the reported protocols.

Keywords: Axillary dissection, axillary reverse mapping, breast cancer, lymphedema

Öz

Amaç: Aksiller ters haritalama lenfödemi önlemek için tarif edilmiştir. Bu çalışma, tümör özellikleri ve diğer faktörler açısından aksiller ters haritalamanın onkolojik güvenliğini araştırmayı amaçlamaktadır.

Yöntem: Çalışmaya meme kanseri tanısı ile mastektomi veya meme koruyucu cerrahi uygulanan ve klinik olarak aksiller pozitif hastalık nedeniyle aksiller ters haritalama uygulanan 81 hasta dahil edildi.

Bulgular: Yirmi altı hastada (%32) aksiller ters haritalama lenf nodu (ATHLN) bulunamadı. ATHLN 55 hastanın, 19'u (%34) malign, 36'sı (%66) benigndi. ATHLN sayısı ile disseke edilen lenf nodu sayısı arasında istatistiksel olarak anlamlı ilişki bulundu (p=0,004). Disseke edilen ATHLN'nin boyutu ne kadar büyükse, lenf nodlarının malign olma olasılığı da o kadar yüksektir (p=0,001).

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Öz

Sonuç: ATHLN malignitesi açısından, hastaların aksiller yükünün fazla olması, intraoperatif olarak seviye III diseksiyon yapılması, aksiller lenf nodu diseksiyonu (ALND) ile 20'den fazla lenf nodu rezeksiyonu yapılması, ekstrakapsüler invazyonun olması ve ATHLN'leri 1 cm'den büyük olmasının malignite ile istatistiksel olarak anlamlı bir bağlantısı vardır. Çalışmamız, koltuk altı yükü ne kadar yüksekse, ATHLN'nin malign olma ihtimalinin o kadar yüksek olduğunu ve korunmasının daha az güvenli olduğunu ileri sürüyor.

Anahtar Kelimeler: Aksiller diseksiyon, ters aksiller haritalama, meme kanseri, lenfödem

Introduction

Although the surgical approach to the axilla in patients with a low axillary tumor burden is changing, axillary dissection remains a frequently used procedure in clinical practice. One of the most serious complications associated with axillary dissection is lymphedema. 5-20% of patients undergoing axillary dissection are reported to experience lymphedema, and this figure can go up to 50% for patients undergoing adjuvant radiotherapy. The search for prevention of lymphedema for treating breast cancer continues. Among the techniques used is axillary reverse mapping (ARM), which enables the preservation of arm lymphatic vessels[1]. This procedure, in which lymph nodes (LN) considered to be located within the arm lymphatic drainage area are not dissected intraoperatively, needs to be tested for oncological safety. This study explores the oncological safety of ARM in terms of tumor characteristics and other factors.

Materials and Methods

This prospective study was approved by the Ethical Board of the Institutional Ethics Committee of University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey (2016-12/02). Informed consent was obtained from all participants included in the study.

The study included 81 patients who were to undergo mastectomy or breast-conserving surgery for having been diagnosed with breast cancer and who were clinically axillary-positive. Three minutes before skin incision for mastectomy, 3-5 cc of isosulfan blue dye was injected into the inner aspect of the ipsilateral arm using intradermal injections. The patients then underwent axillary dissection. No extra or inadequate dissections were performed as part of the study. Level III axillary dissection was left to the discretion of the surgeon. Following the completion of axillary dissection and collection of specimens, all blue LN marked with ARM were removed from the specimens and were separately sent to pathology. Patients undergoing sentinel lymph node biopsy (SLNB) (due to the risk of interfere between blue dyes) and neoadjuvant chemotherapy were excluded from the study. The data about the patients were recorded, including age, body mass index (BMI), comorbidities, type of biopsy, level of axillary dissection, type of surgery and tumour characteristics [tumour location, grade, Ki-67 proliferative index, Cerbb2, estrogen receptor (ER) and progesterone receptor (PR), lymphovascular invasion (LVI), extracapsular invasion].

Statistical Analysis

IBM SPSS Statistics 20.0 was used for data analysis. The relationship between the categorical variables and ARM lymph node status was analyzed using Mantel-Haenszel chi-square test, while Pearson correlation was used in the analysis of this relationship with rank order variables. $P<0.05$ was used as a cut-off for statistical significance.

Results

All patients included in the study were females with a mean age of 53.2+/-12.2. Sixty-one (75%) patients were diagnosed with trucut biopsy, 18 (22.5%) with excisional biopsy, and 2 (2.5%) with incisional biopsy. Seventy-two (89%) of the patients underwent mastectomy, and nine patients underwent breast-conserving surgery. Fifty-five (68%) patients received levels I and II axillary dissection, while 26 (32%) patients received level III axillary dissection intraoperatively at the surgeon's discretion. Tumor location was in the upper outer quadrant for 49 (60%) patients, in the upper inner quadrant for 11 patients, in the lower outer quadrant for 9 (11%) patients, in the lower inner quadrant for 6 (7%) patients, and in the central region for 6 (7%) patients. Table 1 presents the clinicopathological characteristics of patients. The pathology of all patients was invasive ductal carcinoma. Mean tumor size was 3.8+/-2.2 cm. Tumor grade for 67 patients (83%) was 3. Regarding hormone receptor status, 66% were ER positive, 44% were PR positive, and 26% were Cerbb2 positive. The Ki-67 proliferative index was between 0-14% for 20%, 15-30% for 16%, and above 30% for 63%. Fifty-two patients (65%) had LVI, and 42 patients

(52%) had extracapsular invasion. Table 2 presents tumor characteristics.

The mean number of LN resected with axillary dissection was 23.1+/-7.1 (9-42). Fify-one patients (63%) had more than 20 LN resected. On average, 7 (0-38) LN dissected contained malignancy. The mean number of LNs resected with axillary reverse mapping lymph node (ARMLN) was 2.7+/-2.3 (1-9). No ARMLN was found in 26 patients (32%). Of the 55 patients (68%) with ARMLN, 19 (34%) were malignant and 36 (66%) were benign.

The relationship between ARMLN malignancy rates and patients' clinicopathological characteristics was analyzed, and no significant differences were found in relation to age, BMI, comorbidities, type of biopsy, type of surgery, and tumor location. In patients who received level III axillary dissection intraoperatively at surgeon discretion because of a high axillary burden, the more frequent presence of malignant ARMLN was found to be statistically significant (p=0.03) (Table 3).

An analysis of ARMLN malignancy rates and tumor characteristics found no significant relationship in relation to tumour size, grade, ER, PR, Cerbb2, Ki-67 and LVI. The more frequent presence of positive ARMLN in patients with extracapsular invasion was found to be significant

Table 1. Clinicopathological characteristics of patients

Age	≤50	32 (40%)
	>50	49 (60%)
BMI	≤25	28 (35%)
	>25	53 (65%)
Comorbidity	Yes	31 (38%)
	No	50 (62%)
Type of biopsy	Tru-cut	61 (75%)
	Excisional	18 (22.5%)
	Incisional	2 (2.5%)
Type of surgery	Mastectomy	72 (89%)
	Lumpectomy	9 (11%)
Axillary dissection	Level I, II	55 (68%)
	Level I, II, III	26 (32%)
Location	Upper outer	49 (60%)
	Upper inner	11 (13.5%)
	Lower outer	9 (11%)
	Lower inner	6 (7%)
	Central	6 (7%)

BMI: Body mass index

Table 2. Pathologic characteristics of tumours

Tumour size	≤3 cm	40 (50%)
	>3 cm	40 (50%)
Grade	1-2	14 (17%)
	3	67 (83%)
ER	+	53 (66%)
	-	27 (34%)
PR	+	35 (44%)
	-	45 (56%)
Cerbb2	+	21 (26%)
	-	59 (74%)
Ki-67	0-14	16 (20%)
	15-30	13 (16%)
	>30	51 (63%)
Lymphovascular invasion	Yes	52 (65%)
	No	25 (31%)
Extracapsular invasion	Yes	42 (52%)
	No	37 (46%)

ER: Estrogen receptor, PR: Progesterone receptor

Table 3. The relationship between ARMLN involvement and clinicopathological characteristics

Characteristic		ARMLN benign (%)	ARMLN malignant (%)	p-value
Age	≤50	15 (68%)	7 (32%)	0.93
	>50	21 (64%)	12 (36%)	
BMI	≤25	15 (68%)	7 (32%)	0.30
	>25	21 (64%)	12 (36%)	
Comorbidity	No	26 (68%)	12 (32%)	0.11
	Yes	10 (58%)	7 (42%)	
Type of biopsy	Tru-cut	23 (59%)	16 (41%)	0.23
	Excisional	11 (78%)	3 (22%)	
	Incisional	2 (100%)	0	
Type of surgery	Mastectomy	33 (66%)	17 (34%)	0.68
	Lumpectomy	3 (60%)	2 (40%)	
Axillary dissection	Level I, II	30 (73%)	11 (27%)	0.03
	Level I, II, III	6 (43%)	8 (57%)	
Location	Upper outer	24 (68%)	11 (32%)	0.38
	Upper inner	2 (33%)	4 (67%)	
	Lower outer	5 (71%)	2 (29%)	
	Lower inner	3 (60%)	2 (40%)	
	Central	2 (100%)	0	

ARMLN: Axillary reverse mapping lymph node, BMI: Body mass index

(p=0.001) (Table 4). Of the 14 patients who had less than 20 LN resected with ALND, 3 contained malignancy, whereas of the 41 patients who had more than 20 LN resected, ARMLN in 16 was found to be positive for malignancy. A statistically significant relationship was found between ARMLN and the number of LNs dissected (p=0.004). The more the number of ARMLN resected, the more likely it is for ARMLN to overlap with breast lymphatics and become malignant. A statistically significant relationship between the number of ARMLN identified and ARLMN malignancy was found (p=0.001). The larger the size of ARMLN dissected, the more likely it is for LN to be malignant (p=0.001) (Table 5).

Discussion

The ARM procedure is based on the assumption that both the upper extremity and breast have separate pathways of lymphatic drainage. Studies have also found that they are not as distinct as once thought, though, with the reporting of interconnections between these pathways[2].

There are different views on the oncological safety of ARM. A research study conducted by Bedrosian et al.[1] with 30 patients found that the rate of identifying axillary reverse mapping ARMLN with the use of blue dye injected in the upper inner ipsilateral arm was 50%. Because 20% of ARMLN cases were identified in patients with pathologically evidenced LN containing malignancy, preservation of ARMLN was not considered oncologically safe[1]. Nos et al.[3] found that 14% of ARMLN cases were malignant and that there was a statistically significant relationship between N3 and ARMLN positivity. Kang et al.[4] identified ARMLN in 101 (78%) of 129 patients. ARMLN was identified in 55 (68%) of the 81 patients included in our study and ARMLN malignancy rate was 34%.

Some studies have employed radioisotopes to increase ARMLN identification rates. In a series that included 172 patients, the patients were injected in the ipsilateral hand on the day of surgery, and ARMLN was identified in all patients. It was reported that 92% of the ARMLN identified occurred in the area referred to as zone D, above the second intercostobrachial nerve and lateral to the lateral thoracic vein. This study reported the rate of ARM malignancy as 31%[5]. Arm lymphatics overlap with breast lymphatics more frequently in the radioisotope technique than in the blue dye technique[6,7]. ARM-preserving selective ALND does not seem safe oncologically due to this relationship; thus, the involvement of ARM according to its location was taken into account, and 9.4% of ARMLN in zone D were found to be positive for malignancy. Because of low involvement in zone D, it was suggested that emphasis should be placed on the preservation of LN in zone D[8]. Ikeda et al.[9] found that the ARM LN were located between the second intercostobrachial nerve and the axillary vein. The mean number of ARMLN resected is 2. In patients undergoing ALND on the grounds of having clinically positive nodes, 24% of ARMLN patients had positive ARM nodes, whereas 3% of patients with SLNB had metastasis[9]. Other studies have reported that preservation

Table 4. The relationship between ARMLN involvement and pathologic characteristics of tumours

Characteristic		ARMLN benign (%)	ARMLN malignant (%)	p-value
Tumour size	≤3 cm	21 (72%)	8 (28%)	0.44
	>3 cm	14 (56%)	11 (44%)	
Grade	1-2	6 (75%)	2 (25%)	0.60
	3	30 (64%)	17 (36%)	
ER	-	12 (60%)	8 (40%)	0.54
	+	24 (68%)	11 (32%)	
PR	-	18 (67%)	9 (33%)	0.21
	+	18 (64%)	10 (36%)	
Cerbb2	-	27 (67%)	13 (33%)	0.64
	+	9 (60%)	6 (40%)	
Ki-67	0-14	7 (63%)	4 (37%)	0.69
	15-30	5 (71%)	2 (29%)	
	>30	24 (65%)	13 (35%)	
Lymphovascular invasion	No	17 (89%)	2 (11%)	0.07
	Yes	18 (54%)	15 (46%)	
Extracapsular invasion	No	27 (93%)	2 (7%)	**0.001**
	Yes	8 (33%)	16 (67%)	

ARMLN: Axillary reverse mapping lymph node, ER: Estrogen receptor, PR: Progesterone receptor

Table 5. The relationship between ARMLN involvement and LN characteristics

Characteristic		ARMLN benign (%)	ARMLN malignant (%)	p-value
ALND number of LN resected	≤20	11 (78%)	3 (22%)	**0.004**
	>20	25 (61%)	16 (39%)	
ARMLN number	≤2	24 (61%)	15 (39%)	**0.001**
	>2	4 (25%)	12 (75%)	
ARMLN size	≤1 cm	22 (100%)	0	**0.001**
	>1 cm	13 (40%)	19 (60%)	

ARMLN: Axillary reverse mapping lymph node, LN: Lymph nodes, ALND: Axillary lymph node dissection

of ARMLN in SLNB-positive patients undergoing ALND is safe[10].

as the axillary tumor burden increases, the malignancy rates in ARMLN also increase. In a series, two-thirds of the subjects consisted of patients with a low axillary burden (N1), ARMLN were less likely to have metastasis compared with N2-3[11]. A low malignancy rate of 6% was found in zone D ARMLN in patients who were considered axillary-negative following clinical and radiological classifications and underwent ALND because of malignancy after SLNB. It was reported that it is theoretically possible to perform ARM-preserving ALND with these patients as well, which could be regarded as a good example of the selection of the right patients using preoperative axillary USG.

Lymphedema often occurs as a result of damage to the lymphatic system, and several risk factors have been associated with its development. Some of these risk factors: Extensive surgery, chemotherapy especially taxane-based regimens, and radiation therapy. However, there is also a risk of lymphedema in patients who undergo SLNB due to breast cancer; lymphedema can be seen in 4-6%[12].

When examining the effectiveness and safety of ARM, it is necessary to determine the long-term results of axillary recurrence and arm lymphedema. In the study evaluating patients who underwent selective dissection with reverse axillary mapping, nanocoll containing 5 MBq technetium 99 was intradermally administered to the patients from the dorsal hand on the same side 6-24 hours before surgery. During axillary dissection, nodules close to the axillary vein with high uptake were preserved. During the 51-month follow-up of 100 patients included in the study, ipsilateral axillary recurrence was detected in only 1 patient[13].

The effectiveness of ARM was also investigated in patients receiving neoadjuvant therapy. In a meta-analysis of published studies on this subject examining nearly 5000 patients, there was no statistically significant reduction in the risk of metastases in the ARMLN for patients who underwent neoadjuvant chemotherapy compared with those who did not. In other words, neoadjuvant chemotherapy did not appear to have a meaningful impact on reducing the risk of metastasis in this context. It is clear that this result is closely related to the biological characteristics of the tumors due to the response to neoadjuvant therapy. As the response to treatment increases, the rate of ARMLN will decrease[14].

In a randomized controlled study conducted on clinically node-negative breast cancer patients, ALND was performed in 98 patients because of SLNB positivity. While ARMLN-preserving axillary dissection was performed in 49 patients, whereas conventional axillary dissection was performed in 49 patients. In the group that underwent conventional ALND, metastasis in ARMLN was detected in only 1 patient. During the 24-month follow-up, lymphedema was detected in only 3 patients (6.5%) in the ARMLND preserved group, whereas lymphedema was detected in 9 patients (20.9%) in the conventional axillary dissection group (p=0.04). This approach to ALND in early breast cancer patients is seen as a way to achieve a better balance between reducing the risk of arm lymphedema, a quality of life concern, and ensuring the oncological safety of the treatment, which is critical for cancer control[15].

In another randomized controlled study, the combination of ARM and ALND resulted in fewer reported complaints of lymphedema at 6, 12, and 24 months after the surgery ($p<0.05$). Importantly, no axillary recurrence was found in either group. This suggests that the combination of ARM-ALND did not compromise the oncological safety of the procedure, as there were no instances of cancer recurrence in the axillary LN[16].

Study Limitations

The limitations of our study were restricted study population, not comparing the patients with control group and lack of postintervention follow-up evaluation.

Conclusion

The need for axillary dissection in the surgical treatment of breast cancer has rapidly decreased. SLNB has become a sufficient procedure for the regional treatment of many patients. The increased effectiveness of neoadjuvant therapy has also reduced the need for ALND. Our study did not find the ARM procedure safe in patients with a heavy burden of axillary metastasis. ARM may protect patients from lymphedema in patients without a heavy burden of axillary metastasis but are indicated for ALND. Considering that SLNB is not completely immune to lymphedema, ARM may improve the quality of life by preventing lymphedema in early stage breast cancer.

Ethics

Ethics Committee Approval: This prospective study was approved by the Ethical Board of the Institutional Ethics

Committee of University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey (2016-12/02).

Informed Consent: Informed consent was obtained from all participants included in the study.

Authorship Contributions

Surgical and Medical Practices: M.O.K., A.K., İ.B.Ç., Concept: B.A., L.D., İ.B.Ç., A.U.B., Design: M.O.K., A.K., L.D., C.Ö., İ.B.Ç., A.U.B., Data Collection or Processing: Z.M.B., C.Ö., Analysis or Interpretation: N.K., C.Ö., Literature Search: B.A., N.K., Writing: M.O.K., L.D., A.U.B.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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COVID-19 and Patients with Muscular Dystrophy: How Did the Pandemic Affect Patients and Their Medical Care?

COVID-19 ve Kas Distrofili Hastalar: Pandemi Hastaları ve Tıbbi Bakımlarını Nasıl Etkiledi?

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Abstract

Objective: This study investigated the effects of Coronavirus disease-2019 (COVID-19) related lockdowns and the pandemic in patients with muscular dystrophy who require regular hospital admissions and follow-ups. Moreover, the effects of "fear of COVID-19" on these effects were also measured.

Methods: One hundred and five muscular dystrophy patients who were admitted to the neuromuscular diseases tertiary care clinic were evaluated. The patients' socio-demographic and clinical characteristics were recorded, and their fear of COVID-19 was assessed using the "fear of COVID-19 scale", and they were asked about the problems they encountered during the pandemic and lockdowns.

Results: We found that the patients had major restrictions in their access to healthcare, physical therapy/rehabilitation, and reduced physical and social activities. Moreover, they subjectively stated that their disease worsened with the pandemic. These restrictions were found to correlate with their fear of COVID-19 levels.

Conclusion: Patients with muscular dystrophy were found to have changes in their physical activity, participation in rehabilitation, problems with reaching healthcare services, and social problems. These problems were associated with their fear of COVID-19. As routine access to healthcare and therapies is crucial for these patients, both patients and health professionals should keep the potential harm of restrictions and fear in mind and strive for optimal solutions.

Keywords: Neuromuscular diseases, muscular dystrophy, COVID-19, medical care, rehabilitation

Öz

Amaç: Bu çalışma, düzenli hastaneye yatış ve takip gerektiren musküler distrofi hastalarında Koronavirüs hastalığı-2019 (COVID-19) ile ilgili sokağa çıkma kısıtlamalarının ve pandeminin etkilerini araştırmayı amaçladı. Ayrıca bu etkiler üzerinde "COVID-19 korkusu"nun etkisi de ölçüldü.

Yöntem: Nöromusküler hastalıklar üçüncü basamak kliniğine başvuran 105 musküler distrofi hastası değerlendirildi. Hastaların sosyo-demografik ve klinik özellikleri kayıt altına alınarak, "COVID-19 korku ölçeği" ile COVID-19 korkuları değerlendirildi, pandemi ve karantina sürecinde karşılaştıkları sorunlar sorgulandı.

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Öz

Bulgular: Hastaların sağlık hizmetlerine erişiminde, fizik tedavi/rehabilitasyonda önemli kısıtlamalar olduğu, fiziksel aktivite ve sosyal aktivitelerinde azalma olduğu saptandı. Üstelik pandeminin getirdiği değişikliklerle hastalıklarının kötüleştiğini sübjektif olarak belirtmişlerdir. Bu kısıtlamaların COVID-19 seviyelerinden duydukları korku ile ilişkili olduğu bulundu.

Sonuç: Musküler distrofili hastaların fiziksel aktivitelerinde değişiklik, rehabilitasyona katılım, sağlık hizmetlerine ulaşmada sorunlar ve sosyal sorunlar yaşadıkları saptanmıştır. Bu sorunların COVID-19 korkularıyla ilişkili olduğu tespit edildi. Bu hastalar için sağlık ve tedavilere rutin erişimleri çok önemli olduğundan, hem hastalar hem de sağlık çalışanları kısıtlamaların olası zararlarını ve korkularını akılda tutmalı ve optimal çözümler için çaba göstermelidir.

Anahtar Kelimeler: Nöromusküler hastalıklar, musküler distrofi, COVID-19, tıbbi bakım, rehabilitasyon

Introduction

Muscular dystrophies are a group of diseases that affect the structure of skeletal muscles and cause the muscles to break down over time[1]. This causes the patients to become weaker as the disease progresses, their movements and mobility are inhibited, and death may occur because of respiratory or other organ failures[2,3].

Most of these diseases are caused by genetic mutations in the structural proteins of the muscle, and a definitive diagnosis is made by genetic testing or biopsy[4]. Muscular dystrophies include Duchenne muscular dystrophy, Becker muscular dystrophy, facioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophy, and myotonic dystrophy[1,2].

Although there is no definitive cure for muscular dystrophy, there are some therapeutic options for alleviating the symptoms. These options include physical therapy, bracing, or surgery to relieve symptoms and, in some cases, pharmacologic interventions[4]. Respiratory involvement may require the use of assisted ventilation. Pharmacological treatment options include steroids to slow muscle degeneration, anticonvulsants to control seizures and certain muscle activities, and immunosuppressants to delay muscle damage[5]. Physical therapy and rehabilitation are therapeutic options that should always be included, as maintaining mobility and functionality is crucial to both prognosis and quality of life. They help the patient maintain muscle strength and prevent complications due to inactivity and deformities that may occur over time[4,6].

The management of muscular dystrophies often involves more than one specialist in this field, namely neurologists, physical medicine specialists, surgeons, and therapists. Therefore, the follow-up of patients is essential for those who work for their management, to intervene at the right time and do their best.

The recent Coronavirus disease-2019 (COVID-19) pandemic has harmed not only those who are infected but also those who need medical care for other illnesses. While the hospitals' policy of accepting fewer patients than before puts a group of patients in distress, there were also patients who hesitated to seek medical help even when they needed it[7]. Hospital access was delayed for people with chronic neurodegenerative conditions, such as multiple sclerosis, movement disorders, or dementia, who are at a greater risk of serious consequences from infection[8]. Patients also received less service at the hospital, and it has been shown that admissions for stroke have decreased by 50%[9].

In parallel with these reports, we observed that the postponement or cancelation of routine follow-ups is increasing in patients with muscular dystrophy, and the excuse is fear of hospitalization after the pandemic. The patients seemed to avoid therapy because their illness made them more vulnerable and prone to complications from an infectious disease. However, no studies have demonstrated the existence of such a reservation or its possible causes in this population. Uncovering their problems with follow-up and rehabilitation can enable clinicians to offer possible solutions and increase the effectiveness of their treatments.

This study aimed to reveal whether patients with muscular dystrophy show fear and anxiety related to the pandemic that hinders their medical care. Another aim of the study was to reveal the possible causes of their fears and to offer solutions to the problem.

Materials and Methods

The participants with muscular dystrophy who had been followed up at the Neuromuscular Diseases Center of University of Health Sciences Turkey, İzmir Tepecik Education and Training Hospital, were included in this study. The study was approved by University of Health Sciences Turkey, İzmir Tepecik Education and Training Hospital (number: 2020/14-

36, date: 23.12.2020). Institutional Review Board for ethics. The questionnaires were administered from January 2021 to June 2021. All patients and their caregivers provided informed consent. The study was approved by an institutional review board before the initiation of the study. The inclusion and exclusion criteria were as follows:

Inclusion criteria:

1. Patients diagnosed with muscular dystrophy,

2. Those who can read and write Turkish.

Exclusion criteria:

1. Patients diagnosed with anxiety disorder,

2. Patients who lacked the mental capacity to participate.

After collecting demographic and clinical information, questionnaires were administered to the patients. Patients were given a questionnaire that included limitations in rehabilitation, limitations in physical activity and social life, and acceleration of clinical worsening. Patients were also asked about their symptoms, severity, and activities of daily living. The fear of the COVID-19 scale was also applied to the participants. If the participants were >12 years old, they answered the questions themselves, and if they were younger, their primary caregiver provided the answers.

Functional ambulation classification (FAC): FAC is an observational assessment that can be made by the investigator without requiring a device to evaluate mobilization. FAC is a scale that evaluates the physical support needed during walking (between 0 and 5) on 6 different scores[10].

Katz's activities of daily life index (ADL): ADL consists of six questions containing information about bathing, dressing, toilet use, movement, excretion, and feeding activities[11]. Depending on the independence of the activities mentioned, the subject receives a score ranging from 0 to 6, with higher scores indicating more independence.

Fear of the COVID-19 scale: The fear of the COVID-19 scale was developed by Ahorsu et al.[12] to assess patients' fears regarding the coronavirus pandemic. It consists of seven items. Using a 5-point Likert-type rating system (1: Strongly disagree and 5: Strongly agree). It was observed that the scale was self-consistent and that there was a positive and significant relationship between the total score of the scale and depression, anxiety, perceived contagiousness, and germ avoidance. The validity and reliability of the scale were made by Bakioğlu et al.[13].

Statistical Analysis

The data were analyzed using descriptive statistical methods. The groups were compared using the Mann-Whitney U test. Categorical variables were analyzed using chi-square tests, and Spearman's rank correlation test was used for correlation analysis. Statistical significance was set to $p<0.05$.

Results

One hundred and five participants were included in the study. The demographic and clinical characteristics of the patients are given in Table 1. Eighty percent of the patient population consisted of <20 years. Dystrophinopathies (Duchenne and Becker muscular dystrophy) formed the majority of the patients (54.3%), and as these pathologies are X-linked, 62.9% of the patients were male.

The inquiry about the changes in their participation in rehabilitation and their daily lives revealed that more than half of the patients had problems with their access to physical therapy, rehabilitation, and overall healthcare services. Moreover, more than half of the participants strongly agreed that their physical activity and social activities were reduced during the pandemic. Although not clear as these changes, 45.7% of the participants agreed or strongly agreed that their disease progression was faster during the pandemic. These results are presented in Table 2.

The results of the correlation analysis were performed to reveal whether the levels of fear of COVID-19 were associated with the issues that our participants stated. Fear of COVID-19 was found to be associated with restrictions in physical activity/exercise, social lives, access to physical therapy and rehabilitation, access to healthcare services, and more severe subjective disease progression ($p<0.01$) (Table 3). The correlation analysis between fear of COVID-19 and activities of daily life, and fear of COVID-19 and FAC were found to be insignificant ($R=-0.01$ and $p=0.84$, $R=-0.02$ and $p=0.79$, respectively). None of the patients stated a history of COVID-19 on the day they were referred.

Discussion

The results of this study have shown that the COVID-19 pandemic resulted in affected patients with muscular dystrophy with reductions in physical activity, social interactions, physical therapy/rehabilitation, and access to healthcare services. Moreover, patients stated that their conditions worsened during the pandemic even without contracting COVID-19. These reductions were associated with

Table 1. Socio-demographic and clinical characteristics of the patients [n% or mean (SD)]	
Age group (yrs)	
0-9	44 (41.9%)
10-19	40 (38.1%)
20-29	18 (17.1%)
30-39	3 (2.9%)
Gender	
Female	39 (37.1%)
Male	66 (62.9%)
Occupation	
None	43 (41%)
Worker	9 (8.6%)
Civil servant	18 (17.1%)
Student	35 (33.3)
Self-employed	6 (5.7%)
Education	
None	6 (5.7%)
Elemantary	37 (35.2%)
High-school	40 (38.1%)
College or higher	22 (21%)
Diagnosis	
Duchenne muscular dystrophy	22 (21%)
Becker muscular dystrophy	35 (33.3%)
Facioscapulohumeral muscular dystrophy	11 (10.5%)
Limb-girdle muscular dystrophy	22 (21%)
Myotonic dystrophy	15 (14.3%)
Therapies	
Pharmacologic therapy	51 (48.6%)
Physical therapy	81 (77.1%)
Surgical ıntervention	5 (4.7%)
Other	17 (16.2%)
FAC	
0	28 (26.7%)
1	12 (11.4%)
2	5 (4.8%)
3	39 (37.1%)
4	39 (37.1%)
5	18 (17.1%)
Orthoses and use of medical equipment	
AFO	32 (30.5%)
KAFO	3 (2.8%)
Wheelchair	28 (26.7%)
Spinal brace	2 (1.9%)
Activities of daily life index (Katz)	**4.26 (1.76)**
Pain	**49 (46.7%)**
Respiratory problems	**13 (12.4%)**
Cardiac problems	**19 (18.1%)**
Gastrointestinal problems	**34 (32.4%)**
Fear of COVID-19 scale	**15.4 (7.2)**
Activities of daily life index (Katz)	4.26 (1.75)

FAC: Functional ambulation classification, SD: Standard deviation, COVID-19: Coronavirus disease-2019

their fear of COVID-19, which may result in overprotective actions.

The coronavirus pandemic that spread throughout the world in the early months of 2020 resulted in a year like not other. Although the exact starting moments differed across countries, the first case of coronavirus in Turkey emerged in March 2020[14]. With the expanding numbers, the outbreak resulted in rapid measures quarantines, and lockdowns[15]. Either due to these regulations, fear of infection, or avoidance, the lifestyles of the people changed, which included decreased physical activity, social isolation, remote working, or postponing their needs or their desires[16].

Patients with neuromuscular disorders, including muscular dystrophies, were no exception. It was shown that in the earlier few months of the pandemic, the physical activity of patients with neuromuscular diseases was already significantly reduced[17]. Many experts and organizations have published plans or recommendations for the management of this population in the age of the pandemic[18]. Most of the opinions aimed to plan their management in a case of coronavirus infection, or how to prevent a possible infection. Still, some of them also focused on how to alleviate the effects of isolation, quarantines, and lockdowns, which may also potentially harm patients with neuromuscular disorders[19]. In parallel with these studies, patients reported delays, postponement, and even cancelation of their appointments, both due to regulations and fear. It is reasonable to protect these patients from a possible infection because it can be more threatening than the general population because they are susceptible to pneumonia with their impaired pulmonary clearance[20,21].

Still, there are also reports on the fact that COVID-19 may not be as severe as it is feared in children with neuromuscular diseases[22]. these patients benefit from physical therapy and

Table 2. The problems that the patients encountered during the pandemic (n%)	
I couldn't get physical therapy, I couldn't go to rehabilitation, or my visits decreased during the pandemic.	
Strongly disagree	14 (13.3%)
Disagree	8 (7.6%)
Undecided	10 (9.5%)
Agree	14 (13.3%)
Strongly agree	59 (56.2%)
Although I tried, I could not get healtcare service during the pandemic.	
Strongly disagree	11 (10.5%)
Disagree	10 (9.5%)
Undecided	12 (11.4%)
Agree	16 (15.2%)
Strongly agree	56 (53.3%)
During the pandemic, my physical activity and exercise frequency decreased.	
Strongly disagree	9 (8.6%)
Disagree	9 (8.6%)
Undecided	15 (14.3%)
Agree	11 (10.5%)
Strongly agree	61 (58.5%)
During the pandemic, my social activities were restricted, I was able to meet less people and do activities together.	
Strongly disagree	9 (8.6%)
Disagree	7 (6.7%)
Undecided	8 (7.6%)
Agree	15 (14.3%)
Strongly agree	66 (62.9%)
During the pandemic, I think that my disease progressed faster and that my condition is worse than before.	
Strongly disagree	23 (21.9%)
Disagree	14 (13.3%)
Undecided	20 (19%)
Agree	9 (8.6%)
Strongly agree	39 (37.1%)

rehabilitation, and a lifelong adherence to these programs and routine controls for this dynamic process is crucial for its effectiveness[4]. Although it differs among individuals, stages, and types of the disease, a home-based rehabilitation program is a viable option for an important fraction of patients. Even in home-based programs, most patients opt to get help from doctors and therapists on a routine basis, and some require more. Therefore, overprotective behavior from the fear of infection can also harm these patients, just as the risk of infection does.

The pandemic severely affected these patients' ability to receive rehabilitation care, potentially leading to disease progression, functional worsening, and psychological distress. furthermore, COVID-19 could significantly worsen functional outcomes in these patients in the context of several respiratory and musculoskeletal sequelae, including mild cases in home isolation[18]. A study that was conducted on Danish children found that the pandemic harmed biopsychosocial health and quality of life of children with neuromuscular diseases[23]. Similar to our population, there are reports from around the world that claim that home isolation resulted in restrictions on physical therapy, schooling, and access to healthcare during a pandemic in patients with neurological disabilities, including cerebral palsy[24]. A study from Turkey also focused on access to healthcare services and fear of COVID-19 during the pandemic in children with cerebral palsy and found severe limitations in attending their routine check-ups. The authors also claimed that telemedicine can be a viable option for such scenarios[25]. The results of our study support these reports and recent findings. Likewise, we found that patients with neuromuscular disorders also had difficulties in their hospital appointments, physical therapy, and social activities. Moreover, they stated that their physical activity also decreased during the pandemic. However, while excessive physical activity may deteriorate the functioning in neuromuscular diseases, a healthy dose of activity must remain functional and preserve the muscles.

We proposed that fear of COVID-19 may have affected the restrictions that our patients experienced. While

Table 3. The correlations between the fear of COVID-19 and the problems encountered during the pandemic						
		Reductions in physical therapy/ rehabilitation	**Reduction in visits to the healthcare centers**	**Reductions in exercises**	**Reductions in social activities**	**Percecption of disease/ physical limitations getting worse**
Fear of COVID	Rho	0.320**	0.352**	0.289**	0.360**	0.312**
	p	0.001	0.000	0.003	0.000	0.001
COVID: Coronavirus, COVID-19: Coronavirus disease-2019, **: Denotes statistical significance						

this population has never been a focus for the former studies, studies regarding healthcare and chronic patients proposed that a high fear of COVID-19 was present in these populations[13,26]. Moreover, this fear was associated with more problems in reaching the healthcare that they need.

Study Limitations

Our analyses also showed that increased fear of COVID-19 was associated with more severe limitations and troubles during the pandemic. Moreover, we also performed analyses to show whether disease severity and disability status affected this fear, as more severe disease or worse disability status may have had an effect, and found no correlations. These results show that fear of COVID-19 may be an important factor for these patients to avoid behavior and face restricting consequences. It is imperative to weigh the pros and cons of these restrictions and let the patients have the healthcare access, physical therapy, physical activity, and social activity they require while protecting them from the infection itself. Addressing the fear of COVID-19 and proper patient education can help with the solution of the problem, as well as telemedicine and telerehabilitation when in need, as proposed by Cankurtaran et al.[25].

This is the first study in Turkey to study the effects of the pandemic on patients with muscular dystrophy. With the inclusion of different types of these disorders and broad age groups, the results of this study may be generalized to this population. However, it has some limitations. Greater numbers of participants could provide more reliable results from a broader population. While we subjectively questioned their habits, such as physical activity, we could not use a validated and structured outcome measure, such as IPAQ. Moreover, we did not have such a measure before the pandemic, which was unexpected and resulted in a drastic change. However, there is a lack of outcome measures for physical activity for these patients, which differs from the healthy population. Because they have many items that require activities they are unable to perform, novel studies should aim to create or modify these measures for this special group of patients.

Conclusion

The pandemic of COVID-19 has resulted in major changes worldwide. Patients with muscular dystrophy were no exception, and it caused changes in their physical activity, participation in rehabilitation, problems with accessing healthcare services, and social problems. These problems were associated with their fear of COVID-19. Although protection of this sensitive population from infection is a must, both patients and health professionals should keep the potential harm of restrictions and fear in mind and strive for optimal solutions.

Ethics

Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, İzmir Tepecik Education and Training Hospital (number: 2020/14-36, date: 23.12.2020).

Informed Consent: All patients and their caregivers provided informed consent.

Authorship Contributions

Surgical and Medical Practices: G.T., M.Y.K., B.T., F.B., Concept: G.T., F.M.S., Design: G.T., F.M.S., Data Collection or Processing: G.T., M.Y.K., B.T., F.B., Analysis or Interpretation: G.T., F.M.S., M.Y.K., B.T., F.B., Literature Search: G.T., F.M.S., Writing: G.T., F.M.S., M.Y.K., B.T., F.B.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Suicide Attempts Evaluated in the Emergency Department

Acil Serviste Değerlendirilen Özkıyım Girişimleri

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Abstract

Objective: Suicide attempts and related processes are a serious problem worldwide. Initial evaluation of patients who have attempted suicide is usually performed in the emergency department (ED). In this study, we examined the characteristic features of these cases.

Methods: The study was conducted with patients aged 18 years who were evaluated for suicide attempt over a one-year period in the ED of a comprehensive urban hospital. The data of the cases were retrospectively scanned through the electronic medical record system. The data obtained for each patient were systematically recorded in report forms and analyzed at the end of the study.

Results: In the study, 241 suicide attempt cases with a mean age of 30 (interquartile range: 22-37) were examined, and 167 (69.3%) of them were women. Of the patients, 170 (70.5%) were between the ages of 18 and 35, and 113 (46.9%) had primary education. Of the suicide attempts, 81.7% were self-poisoning with multiple drug ingestion. It was determined that 41.5% of the applications were made between 18:00 and 00:00. Of the patients, 142 (58.9%) were discharged after ED follow-up. ED follow-up could not be completed for 67 (27.8%) patients who refused treatment. Of the remaining patients, 15 (6.2%) were transferred to the intensive care unit and 14 (5.8%) to the inpatient service. A total of 3 (1.3%) patients who died after a suicide attempt were male and used the hanging method.

Conclusion: Most patients who attempted suicide were young women who were primary school graduates and poisoned by ingesting multiple drugs. Most suicide attempts are unsuccessful, but mortality is quite high in those who use the hanging method. Because patients who attempt suicide tend to leave the ED before their follow-up is completed, precautions should be taken.

Keywords: Emergency department, suicide, self-poisoning, hanging

Öz

Amaç: Özkıyım girişimi ve ilişkili süreçler dünya genelinde önemli bir sorundur. Özkıyım girişimi olan hastaların ilk değerlendirmesi genellikle acil servislerde yapılmaktadır. Çalışmada, bu olguların karakteristik özelliklerinin incelenmesi amaçlandı.

Yöntem: Araştırma kapsamlı kentsel bir hastanesinin acil servisinde bir yıllık bir periyotta özkıyım girişimi sebebiyle değerlendirilen 18 yaş ve üstündeki hastalar ile gerçekleştirildi. Olgulara ait veriler hastane elektronik medikal kayıt sistemi üzerinden geriye dönük olarak tarandı. Her bir hasta hakkında elde edilen veriler olgu rapor formlarına sistematik olarak kaydedildi ve çalışma sonunda analiz edildi.

Bulgular: Araştırmada yaş ortalaması 30 (çeyrekler arası aralık: 22-37) olan toplam 241 intihar girişimi olgusu incelendi ve bunların 167'si (%69,3) kadındı. Hastalardan 170'i (%70,5) 18-35 yaş aralığındaydı ve 113'ünün (%46,9) ilköğretim düzeyinde eğitimi vardı. İntihar girişimlerinin %81,7'si aşırı dozda çoklu ilaç kullanımı şeklinde kendini zehirleme idi. Başvuruların 100'ünün (%41,5) 18:00 ile 00:00 saatleri arasında yapıldığı tespit edildi. Hastalardan 142'si (%58,9) acil servis izlemi sonrasında taburcu edildi. Önerilen tedavileri reddeden 67 (%27,8) hastanın acil servis takibi tamamlanamadı. Geriye kalan hastalardan 15'i (%6,2) yoğun bakıma ve 14'ü (%5,8) yataklı servise nakledildi. Özkıyım girişimi sonrası hayatını kaybeden (özkıyım eylemi gerçekleşen) toplam 3 (%1,3) hasta aşı yöntemini kullanan erkek hastalar idi.

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Öz

Sonuç: Özkıyım girişiminde bulunan hastaların çoğunluğunu yüksek dozda ilaç içen ilköğretim mezunu genç kadınlar oluşturmaktadır. İntihar girişimlerinin çoğu başarısız olmakta ancak aşı yöntemini kullananlarda mortalite oldukça yüksektir. Özkıyım girişiminde bulunan hastalar takipleri tamamlanmadan acil servisi terk etme eğiliminde olduklarından buna yönelik önlemler alınmalıdır.

Anahtar Kelimeler: Acil servis, özkıyım, kendini zehirleme, aşı

Introduction

The World Health Organization (WHO) defined suicide in 1974 as the act of self-harm with varying degrees of lethal purpose, conscious of one's purpose[1]. In recent years, the WHO has classified suicide into two groups: Suicidal acts and suicide attempts. The act of suicide results in death. Suicide attempt, on the other hand, includes all voluntary attempts of the patients to destroy, harm, or poison themselves, which do not result in death[2]. Suicide is a serious public health problem, and what needs to be done to prevent it is a prioritized global problem. Globally, more than 700,000 people die every year. There are many more suicide attempts for every suicide act[1].

According to the Turkish Statistical Institute (TÜİK) data, the number of people who committed suicide in 2019 was 3406, of whom 2626 were men and 780 were women. According to the TÜİK data, the number of suicides has increased gradually since 2009. When the average age-specific suicide rates from 2009 to 2019 are compared, the highest age with a range of 6.84 is 75 years and over, followed by 20-24 and 15-19 age groups, respectively. The age group 0-15 had the lowest mean suicide rate. In addition, the average suicide rate of all age groups except this age group is above Turkey's average[3]. These data show that the suicide problem is increasing in our country and has reached levels that will affect public health.

The first WHO World Suicide Report published in 2014 "Preventing Suicide: A Global Mandatory" aims to raise awareness of the public health importance of suicide and its initiatives and to make suicide prevention a high priority on the global public health agenda. It also encourages and support countries in developing or strengthening comprehensive suicide prevention strategies in a multisectoral public health approach[1]. To define, develop, and implement the required measures to prevent suicide attempts, it is necessary to understand the socio-demographic characteristics of the individuals in the risk group and the factors that lead them to commit suicide. The first examination of patients who attempt suicide is usually performed in the emergency department (ED). Therefore, our study aimed to retrospectively examine the socio-demographic characteristics and clinical results of patients who applied to the ED of our hospital with a suicide attempt over a one-year period.

Materials and Methods

This cross-sectional observational study was conducted in an education and research hospital with approximately 180,000 ED admissions annually. Comprehensive health service is provided 24 h a day in the ED of this hospital, which is located in the city center. Ethics committee approval was obtained before starting the study. Ethical approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, İzmir, Turkey (decision no: 2021/06-16, date: 15.06.2021) and all study procedures were performed in accordance with the Declaration of Helsinki. The data of patients aged 18 years who applied to the ED due to a suicide attempt between January 1 and December 31, 2019, were retrospectively scanned through the hospital's electronic medical record system. Patients with missing data were excluded from the study.

Age, gender, marital status, educational status, history of psychiatric illness, and whether or not they had similar attempts before were recorded in the case report forms of the patients included in the evaluation. In addition, the methods used in the suicide attempt, the time of day the attempts were made, the units where patients were followed, and the clinical outcomes of the cases were also questioned. The data obtained were classified at the end of the study and evaluated statistically.

Statistical Analysis

All analyses were performed using IBM® SPSS 22.0 (SPSS Inc., Chicago, Illinois, USA). Whether the data were normally distributed or not was evaluated with the Kolmogorov-Smirnov test. Qualitative variables are expressed as the number of observations and percentage. The median and interquartile range (IQR) are given with their minimum

and maximum values for quantitative data. Pearson's chi-square test was used for analyzing nominal variables, and the Mann-Whitney U test was used for ordinal variables. Analyses were performed at 95% confidence intervals (95% confidence interval). A p-value of 0.05 was set as significant.

Results

After excluding four patients because of missing data, the study was conducted with 241 patients. Patients who attempted suicide were 0.14% of patients admitted to the ED within one year. The median age of our study patients was 30 (IQR: 22-37, min: 18, max: 87), and 167 (69.3%) were female ($p<0.05$). There was no significant difference between the median ages according to the gender of the patients. The median age of male patients was 30 (IQR: 23-39, min: 18, max: 87), whereas that of females was 29 (IQR: 22-36, min: 18, max: 71). Patients of 170 (70.5%) who attempted suicide were between the ages of 18 and 35 ($p<0.05$). Patients of 113 (46.9%) had primary education. In addition, 75 (31.1%) of the patients had a known psychiatric disease diagnosis, and 38 (15.8%) patients had similar attempts before (Table 1).

Table 1. Characteristics of patients who attempted suicide

Parameter	Sub parameters	n	%
Gender	Male	74	30.7
	Female	167	69.3
Age	18-35	170	70.5
	36-50	57	23.7
	51-65	8	3.3
	>65	6	2.5
Marital status	Married	102	42.3
	Single	124	51.5
	Divorced	8	3.3
	Widowed	3	1.3
	Not specified	4	1,6
Educational status	Illiterate	8	3.3
	Literate	15	6.2
	Primary school graduate	113	46.9
	High school graduate	62	25.7
	University graduate	25	10.4
	Not specified	18	7.5
History of psychiatric illness	Yes	75	31.1
	No	166	68.9
Previous suicide attempt	Yes	38	15.8
	No	203	84.2

Suicide attempts of 197 (81.7%) were self-poisoning with multiple drug ingestion (Table 2). It was determined that 100 (41.5%) suicide attempts were made between 18:00 and 00:00 (Figure 1). Patients 142 (58.9%) were discharged after ED follow-up, and 67 (27.8%) could not complete ED follow-up (32 of them signed a record of refusing the recommended treatment, and 35 left the ED without permission). Of the remaining patients, 15 (6.2%) were taken to the intensive care unit, and 14 (5.8%) were followed up in the inpatient service. Of the patients, 3 (1.3%) admitted to the ED after the suicide attempt with the hanging method, who were all male and aged 27, 28, and 30 years, died in the early period. All other patients were discharged without sequelae at the end of the follow-up period.

Discussion

Since suicide attempts are a serious cause of mortality and morbidity, they are frequently the subject of research worldwide. The main purpose of these studies is to identify the current situation and its potential reasons and to make suggestions accordingly, thus preventing new attempts. We

Table 2. Methods used in suicide attempts

Method	n	%
Self-poisoning with multiple drug ingestion	197	81.7
Self-poisoning with street drugs	30	12.4
Drinking corrosive substances	4	1.7
Taking rat poison	4	1.7
Hanging	3	1.3
Jumping from a high place	2	0.8
Try to burn his/herself	1	0.4
Total	241	100

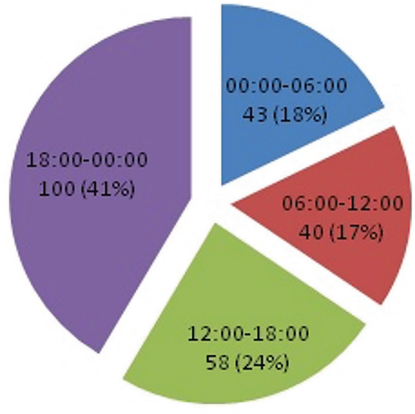

Figure 1. Time intervals of the suicide attempts

believe that our research results will contribute to improving and performing social protection programs for individuals in risk groups.

When suicides were analyzed according to provinces in TÜİK data, 196 suicides were committed in İzmir, among the first three provinces with the highest number of cases, and 157 (80%) were men[3]. In the literature review, Canpolat et al.[4] found that 69.5%, Sahin et al.[5] 63.3%, and Atli et al.[6] 78%, found that women frequently attempted suicide. Similarly, in the studies conducted by Akar et al.[7] and Mert et al.[8], it was stated that the frequency of attempted suicide was higher in women and that the frequency of death due to suicide was higher in men. In our study, consistent with these results, 74 (30.7%) of the 241 patients who attempted suicide were male, 167 (69.3%) were female, and all death cases were male. This result shows that female patients are more likely to attempt suicide, whereas males commit suicide more frequently.

In their studies, Canpolat et al.[4] (44.3%) and similarly, Atli et al.[6] 57% found the most common suicide attempt age range to be 15-24 years. In these studies, patients who attempted suicide were married at a rate of 50% and 51%, respectively[4,6]. According to the suicide data of our country, the most common suicide attempt is in the 19-35 age group[3], which is similar to the age group of the patients in our study. According to TÜİK data, while 48.1% of the patients who committed suicide in our country were married, 48.5% of the patients who attempted suicide in our study were married[3].

In a meta-analysis examining the suicide methods preferred by suicide cases who applied to the ED, it was stated that self-poisoning with multiple drug ingestion was frequently used as the suicide method with a rate of 52%[9]. In the study of Canpolat et al.[4], 93.6% of suicide attempts were found to be drug and toxic substance intake. In the study by Atli et al.[6], the most common suicide method was self-poisoning with multiple drug ingestion at a rate of 93.4%. Similar to these studies, 87.1% of our patient population attempted suicide by self-poisoning with multiple drug ingestion. We believe that this is because patients have easier access to drugs. According to TÜİK data[3], consistent with our study, the most common method of suicide resulting in death was hanging.

According to TÜİK suicide data, 35% of the suicide cases between 2000 and 2019 were carried out by primary school graduates[3]. Consistent with this, in the literature review, suicide attempts were frequently performed by primary school graduates[4-6,10]. These data were found to be compatible with the results of our study. This result can be interpreted as people with higher education levels having more knowledge about asking for help, seeking help, and finding solutions.

In our study, the rate of patients who attempted suicide for the first time was 84.2%, which is consistent with similar studies in the literature[4-6]. In the study by Sahin et al.[5], 33% of the patients were receiving psychiatric treatment in the last 6 months, whereas 31.1% of the patients in our study had a history of psychiatric illness. In the study of Atli et al.[6], suicide attempt was found most frequently between 16:00 and 24:00 with 49.8%, while in our study, it was found most frequently between 18:00 and 24:00 with 41%.

In the study of Sahin et al.[5], it was determined that 47.5% of the patients left the hospital with treatment refusal or without permission, and 27.8% of the patients in our study left the hospital before the end of their treatment and follow-up periods. These results indicate that patients who attempt suicide tend to leave the hospital before completing their observation period or before their treatment is completed. It would be beneficial for the patients to be asked for psychiatric consultation in the early period and thus psychiatric evaluations of the suicide patients before they leave the hospital.

Study Limitations

The limitations of our study include the retrospective design and the fact that a single-center study with data from one ED may not be representative of the whole country. In addition, in patients with ingestion of multiple drugs, it is unclear which substance was mainly responsible for the clinical manifestations. Furthermore, comorbidities that may affect the prognosis of the patients were excluded from the evaluation.

Conclusion

The majority of patients who attempt suicide are young women who are primary school graduates and poisoned by multiple drugs. Suicide attempts, especially by women, are mostly unsuccessful, but the risk of mortality in individuals who use the hanging method is quite high. Because patients who attempt suicide tend to leave the ED before their follow-up and treatment are completed, precautions should be taken.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, İzmir, Turkey (decision no: 2021/06-16, date: 15.06.2021) and all study procedures were performed in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: H.İ., N.Y.O., D.A.D., Design: H.İ., N.Y.O., D.A.D., Data Collection or Processing: N.Y.O., D.A.D., Analysis or Interpretation: H.İ., Literature Search: H.İ., N.Y.O., D.A.D., Writing: H.İ., N.Y.O.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Evaluation of Elastic Stiffness and Tendon Thickness in the Quadriceps Tendon in Patients Undergoing Chronic Hemodialysis

Kronik Hemodiyaliz Hastalarında Kuadriseps Tendonunda Elastik Sertlik ve Tendon Kalınlığının Değerlendirilmesi

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Abstract

Objective: Spontaneous rupture of the quadriceps tendon is more common in patients with chronic renal failure than in the healthy population. Recurrent microtrauma, hypoxia, hyperparathyroidism, and chronic acidosis are some predisposing factors for spontaneous rupture. This study aimed to evaluate tendon thickness and sonoelastography findings of the quadriceps tendon in patients with chronic renal failure undergoing a dialysis program.

Methods: Forty randomly allocated patients [24 male, 16 female; mean [± standard deviation (SD)] age: 58.18±14.41 years [range: 24-75] with chronic renal failure undergoing dialysis program, and 32 healthy volunteers 10 males, 22 females; mean age (± SD): 54.72±13.84 (range: 31-74)] were included. Measurements of quadriceps tendon thickness and strain elastography were performed in the right knees of all subjects. For the measurement of a strain ratio, two ROIs were placed on the tendon that was 1 cm proximal to the patellar insertion area (ROI A) and the prefemoral fat area (ROI B).

Results: The mean quadriceps tendon thickness values were 6.55±1.77 mm (range: 3.8-9.4 mm) in the chronic renal failure group and 5.81±0.93 mm (range: 4.3-8.3 mm) in the control group. The quadriceps tendons were significantly thicker in the patient group (p=0.03). The mean elasticity scores were 6.88±15.82 in patients with chronic renal failure group and 8.49±15.07 in the control group. Mean strain elastography values showed no statistically significant difference (p=0.66).

Conclusion: Compared with the control cases, the increase in the thickness of quadriceps tendons was found to be significant,but there was no significant difference in sonoelastography findings between the two groups.

Keywords: Chronic renal failure, hemodialysis, musculoskeletal ultrasound, quadriceps tendon, sonoelastography

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Öz

Amaç: Kuadriseps tendonunun spontan rüptürü, kronik böbrek yetmezliği olan hastalarda sağlıklı popülasyona göre daha yaygındır. Tekrarlayan mikrotravmalar, hipoksi, hiperparatiroidizm ve kronik asidoz spontan rüptür için predispozan faktörlerden bazılarıdır. Bu çalışmanın amacı kronik böbrek yetmezliği nedeniyle diyaliz programına alınmış olan hastalarda kuadriseps tendonunun kalınlığını ve sonoelastografik bulgularını değerlendirmektir.

Yöntem: Diyaliz programına giren kronik böbrek yetmezliği olan rastgele seçilmiş 40 hasta [24 erkek, 16 kadın; ort [±(standart sapma (SS) yaş: 58,18±14,41 yıl (dağılım: 24-75)] ve 32 sağlıklı gönüllü [10 erkek, 22 kadın; ort (± SS) yaş: 54,72±13,84 (dağılım: 31-74)] çalışmaya dahil edildi. Kuadriseps tendon kalınlığı ve gerinim elastografisi ölçümleri tüm deneklerin sağ dizlerinde gerçekleştirilmiştir. Gerinim oranının ölçümü için, patellar insersiyon alanının 1 cm proksimalindeki tendon üzerine (ROI A) ve prefemoral yağ alanına (ROI B) iki ROI yerleştirildi.

Bulgular: Ortalama kuadriseps tendon kalınlığı değerleri kronik böbrek yetmezliği olan hasta grubunda 6,55±1,77 mm (dağılım: 3,8-9,4 mm) ve kontrol grubunda 5,81±0,93 mm (dağılım: 4,3-8,3 mm) idi. Kuadriseps tendonları hasta grubunda anlamlı olarak daha kalındı (p=0,03). Ortalama elastisite skorları kronik böbrek yetmezliği olan hasta grubunda 6,88±15,82 iken kontrol grubunda 8,49±15,07 idi. Ortalama strain elastografi değerleri istatistiksel olarak anlamlı farklılık göstermedi (p=0,66).

Sonuç: Kontrol grubu ile karşılaştırıldığında kuadriseps tendon kalınlığındaki artış istatistiksel olarak anlamlı derecede yüksek olamakla birlikte, sonoelastografik bulgularda iki grup arasında anlamlı bir fark saptanmamıştır.

Anahtar Kelimeler: Kronik böbrek yetmezliği, hemodiyaliz, kas-iskelet sistemi ultrasonu, kuadriseps tendonu, sonoelastografi

Introduction

Quadriceps tendon rupture is a relatively uncommon injury predominantly affecting middle- aged males[1]. Disruption of the knee extensor mechanism is a significant disabling injury mostly requiring surgical reconstruction and should thus be diagnosed early. Although spontaneous rupture of the quadriceps tendon tends to occur in older patients with degenerative changes, systemic/metabolic diseases like chronic renal failure also have harmful effects on the tendons. Metabolic acidosis and hyperparathyroidism in patients with chronic renal failure receiving hemodialysis may cause impairment of vascular supply and alter the microstructural properties of the tendon, resulting in spontaneous rupture of the tendon[1-6].

Although most quadriceps tendon ruptures can be easily diagnosed by history and physical assessment, imaging studies are required for the confirmation of the diagnosis and for differentiating complete and incomplete ruptures[1,7]. Imaging studies of suspected quadriceps tendon ruptures should begin with orthogonal plain radiographs. Several diagnostic imaging modalities may be used in addition to standard radiographs to confirm the diagnosis, such as ultrasound and magnetic resonance imaging (MRI). Arthrography was widely used before, but the availability of MRI has reduced its importance. Ultrasonography (US) is a safe method that allows real-time and non-invasive imaging without exposure to ionizing radiation in a short examination time. It also allows comparative examination in the same session and is relatively inexpensive[8,9]. Although its reliability is highly dependent on the experience of the operating radiologist, the advantages of US make it the first imaging method to be chosen after physical examination and plain radiographs[8,9].

Sonoelastography (SE) is an assistive ultrasound technology that enhances the characterization of the lesion by assessing the elasticity of soft tissues. With this method, calculated strain values help effective evaluation of stiffness characteristics of tissues and organs, similar to a more advanced form of palpation with objective data. SE was previously used to evaluate the strain characteristics of superficial soft tissues such as the breast, thyroid gland, lymph nodes, and muscle tissue. Currently, strain analysis of visceral organs has also become applicable[10,11]. There are recent studies concerning the use of SE in musculoskeletal pathologies[12,13]. In particular, in comparative studies with MRI, the reliability of the assessment of the tendinopathy area by SE has been demonstrated[13]. In addition, SE is a useful method in cases where it is difficult to identify tendinopathy by conventional US[12].

Although the number of studies concerning the elastographic evaluation of tendon disorders has increased in recent years, studies assessing the elastographic characteristics of the quadriceps tendon in patients with chronic renal failure are very limited[2]. The objective of this study was to analyze the diagnostic efficacy of SE in tendinous injuries by evaluating the elastrographic characteristics of the quadriceps tendon using SE in patients with chronic renal failure undergoing a hemodialysis program.

Materials and Methods

Subjects

Our study group included 40 patients (24 males, 16 females; mean age: 58.18±14.41, range: 24-75 years) who were undergoing hemodialysis (three times a week) with a diagnosis of chronic renal failure at our institution from May 2018 to June 2019. The control group consisted of 32 healthy individuals (10 males, 22 females; mean age: 54.72±13.84, range: 31-74 years). Measurements were performed on the right knees of all subjects. The age, gender, body height, and weight of all subjects were recorded. Patients with a history of knee surgery, tendon rupture, other systemic and/or inflammatory diseases, and systemic and/or intraarticular use of corticosteroids were excluded. All measurements were performed by the same blinded radiologist (experienced 4 years in real-time SE) who did not know the clinical preliminary diagnosis. A written informed consent form was obtained from all patients. This study was approved by the Clinical Research Ethical Committee of Başkent University (ref no: KA-19/21).

US and Real-time SE

US and real-time SE were performed using a linear-array 13.5-MHz high- resolution transducer (Hitachi Arietta V70, Japan). The examinations were performed in the supine position with the hips and knees in 45° flexion and the feet on the examination table. Initially, all patients underwent standard ultrasound examination. Tendon thickness and elastographic measurements were performed 1 cm proximal to the patellar insertion of the quadriceps tendon. Tendon thickness values were recorded by measuring the anteroposterior diameters along the longitudinal axis (Figure 1).

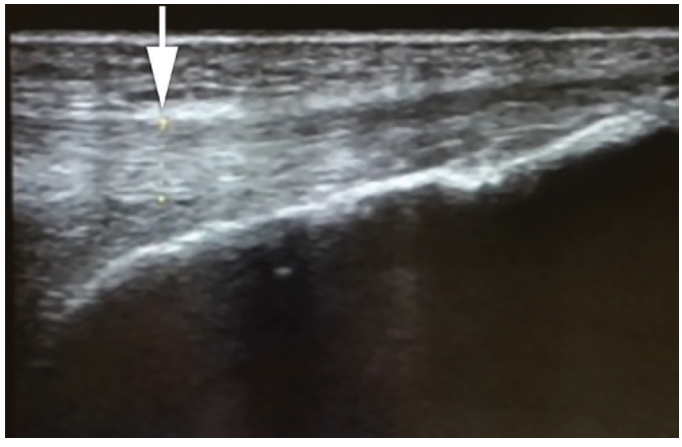

Figure 1. Measurement of quadriceps tendon thickness in Sagittal B-mode display

SE images were obtained by applying repeated compression loads to the quadriceps tendon area with the probe. A real-time image was displayed on the original gray-scale ultrasound image, and the sonoelastogram was displayed in overlay mode within the selected ROIs as a color and numerically coded real-time image. The color scale ranged from red for tissues with the greatest strain (softest areas) to blue for tissues with no strain (hardest areas). The relative stiffness of the tissues was represented by the ROI ratios on the sonoelastogram. To measure the strain ratio, two ROIs were placed on the tendon 1 cm proximal from the patellar insertion area (ROI A) and the prefemoral fat pad area (ROI B). The strain ratios (B/A) were calculated by the elastography software of the US device using these two areas (B/A) (Figure 2). ROI areas were used in standard sizes in all measurements. Patients' identities were not revealed, and all data were automatically stored in the US device memory. The demographic data of all patients were also recorded. Standard descriptive statistics of demographic data and SE measurements were also performed using gender distribution with standard deviations. Mean elastographic strain ratio values were calculated for gender groups (as males and females) and for the combined group.

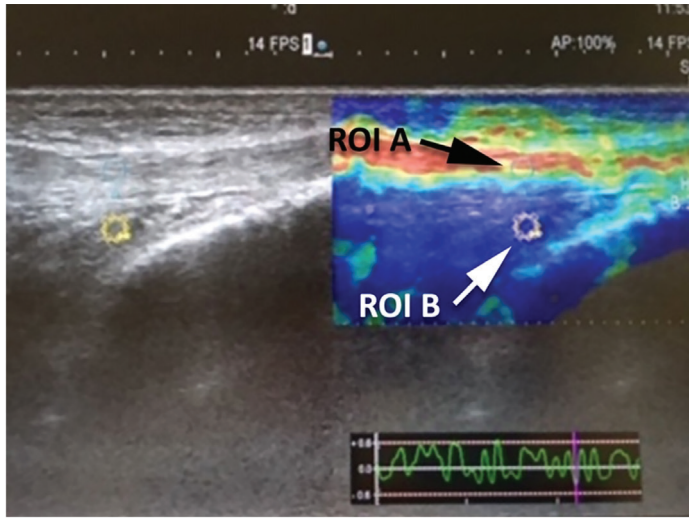

Figure 2. Location of the two ROIs 1 cm proximal from patellar insertion area. Selected quadriceps tendon area (ROI A) and the prefemoral fat pad area (ROI B). Strain elastography ratios (B/A) were calculated by the elastography software of the ultrasonography device

Table 1. Data distribution of study and control groups

Parameter	Control group		Study group		"p"
	Value	Min-max	Value	Min-max	
Age	54.72±13.84	26-74	58.18±14.41	24-85	0.310¥
Height	163.22±10	147-190	166.68±9.4	150-187	0.140π
Weight	71±10.67	50-92	83.8±98.72	50-115	0.470π
BMI	26.72±3.32	18.55±33.26	30.16±3.98	21.15±38.66	0.232
QT	5.81±0.93	4.3-8.3	6.55±1.77	3.6-10.4	**0.030*π**
F/Q	8.49±15.07	0.02-51.67	6.88±15.82	0.01-59.33	0.660¥

Data distribution of study (chronic renal failure patients, n=40) and control groups (n=32) according to age, height, body weight, BMI: Body mass index, QT: Quadriceps tendon thickness, F/Q: Strain value ratio of prefemoral fat pad (F)/quadriceps tendon (Q)*: p<0.05; π: Student's t-test, ¥:Mann-Whitney U test

Statistical Analysis

The results of the tests were expressed as the number of observations (n), mean ± standard deviation, median and min-max values (Table 1). The results of the homogeneity (Levene's test) and normality tests (Shapiro-Wilk) were used to decide which statistical methods to apply in the comparison of the study groups. Normally distributed and with homogeneous variances groups were compared using Student's t-test (two groups). According to these test results, parametric test assumptions were not available for some variables; therefore, non-parametric comparisons of two and three independent groups were performed by Mann-Whitney U test. Categorical data were analyzed using Fischer's Exact test and chi-square test. In cases with expected frequencies of less than 25%, "Monte Carlo Simulation Method" was used for inclusion analysis. SPPS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) software was used for the calculations.

Results

In the study group, 40 randomly allocated patients [24 male (70.6%) and 16 female [42.1%], mean [± standard deviation (SD)] age: 58.18±14.41 years (range: 24-75)] with chronic renal failure undergoing a dialysis program 3 days a week were included. The mean quadriceps tendon thickness values in the chronic renal failure group were (mean ± SD: 6.55±1.77 mm, range: 3.6-10.4 mm) significantly higher than those in the control group (mean ± SD: 5.81±0.93 mm, range: 4.3-8.3 mm) (p=0.030; Student's t-test, Table 1). Comparison of the mean elasticity scores between the study group (mean ± SD: 6.88±15.82) and the control group (mean ± SD: 8.49±15.07) showed no statistically significant difference (p=0.660; Mann-Whitney U test, Table 1).

Discussion

In this study, the mean elasticity scores from the SE evaluation of patients with chronic renal failure revealed no statistically significant difference compared with the control group (p=0.660). However, compared with healthy controls, mean quadriceps tendon thickness values were found to be significantly higher in patients with chronic renal failure (p=0.030).

Quadriceps tendon rupture is a relatively uncommon injury predominantly affecting middle- aged males[1,14]. The inherent structural and biomechanical properties of the extensor mechanism allow the quadriceps tendon to sustain loads up to 17.5 times body weight without failure; however, the low-energy pattern of injury reported in the majority of cases suggests a weakened area of tendon tissue[1]. Age-related changes in the tendon tissue, such as fatty and myxoid degeneration, sclerosis, and decreased tendon thickness with muscular atrophy, may result in changes in the type and cross-linking of collagen fibers of the quadriceps tendon, predisposing to rupture[1]. In addition, several systemic/metabolic diseases have been shown to affect the quadriceps tendon and muscle, including renal failure, diabetes, hyperparathyroidism, rheumatoid arthritis, systemic lupus erythematosus, gout, osteomalacia, infection, steroid use, and obesity[1,4,15-17]. These metabolic diseases weaken the mechanical strength of the tendons by damaging the vascular supply and/or altering their microstructural properties. In patients with chronic renal failure, long periods of hemodialysis and uremia affect the maturation of collagen and cause quadricep muscle

Atrophy resulting in significant weakening of the tendon. Konrath et al.[18], retrospectively reviewed 51 quadriceps tendon ruptures in 39 patients with bilateral and unilateral quadriceps tendon ruptures and reported a significant

correlation between bilateral simultaneous rupture and systemic disease. Although spontaneous rupture of the quadriceps tendon tends to occur in older patients with degenerative changes or those with systemic/metabolic diseases, there may also be a genetic link implicated in bilateral quadriceps tendon rupture with the *COL5A1* gene, which encodes the protein for type-V collagen and has been previously shown to be associated with Achilles tendon and anterior cruciate ligament ruptures[19]. The most common location of spontaneous rupture of the quadriceps tendon occurs at 1-2 cm proximal to the patella, which corresponds to the most hypovascular part of the tendon[20]. Therefore, we preferred to evaluate this area for SE measurements.

Studies concerning elastrographic evaluation of the quadriceps tendon in patients with chronic renal failure are extremely limited. Teber et al.[2] analyzed SE findings of the quadriceps tendon in 53 patients with chronic renal failure. The authors reported that in patients with chronic renal failure, quadriceps tendons were thinner and had lower elasticity scores than controls. However, our results showed no significant difference in elasticity scores but significantly higher tendon thickness in patients with chronic renal failure.

Study Limitations

This study also has some limitations. The relatively limited number of patients in the study group may have influenced the results. Magnetic resonance correlation with SE findings may be considered; however, a reference standard for comparative evaluation (with SE) of the quadriceps tendon is lacking. Equipment variations and operator experience may also impact the results. In our study, all measurements were performed by the same blinded radiologist (experienced 4 years in SE) using the same equipment. Histopathological validation of tendinous pathology may be considered as another limitation of this study.

Conclusion

In musculoskeletal imaging, RTS provides a completely new perspective and provides further information about soft tissue quality and characteristics by assessing tissue elasticity, thus extending the diagnostic capabilities of B-mode ultrasound. Long-term randomized controlled studies with larger patient numbers are necessary to evaluate the value and efficacy of this new technique.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethical Committee of Başkent University (ref no: KA-19/21).

Informed Consent: A written informed consent form was obtained from all patients.

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Management of Urethral Stone Patients in An Endemic Region: A Single Center Experience

Endemik Bir Bölgede Üretral Taş Hastalarının Yönetimi: Tek Merkez Deneyimi

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Abstract

Objective: Urethral stones are rare among all urinary system stones. There is limited data in the literature on the management of urethral stones. In this study, we aimed to present our experience of patients diagnosed with urethral stone in the light of the literature.

Methods: This retrospective study included 24 consecutive patients diagnosed with urethral stone between January 2017 and December 2020. Demographic data, clinical features, primary treatment approaches, peroperative and postoperative data were analysed.

Results: Twenty-four patients with a mean age of 44±20 years (2-73) were included in the study. The clinical presentation of the patients was acute urinary retention in 14 (58.3%) patients and lower urinary tract symptoms in 10 (41.6%) patients. The most common stone location was posterior urethra in 13 (54.2%) patients and anterior urethra in 11 (45.8%) patients. The mean stone size was 10±3 (5-15) mm. Fourteen patients had a history of previous stone surgery or stone expulsion. Two patients underwent internal urethrotomy and one patient underwent cystolithotripsy simultaneously. Surgical success stone-free rate (SFR) was 100%.

Conclusion: Urethral stones are rarely seen in urological practice. The management of urethral stone is uncertain and depends on personal experience. Holimum laser lithotripsy with URS which is minimally invasive with minimal damage to the urethral mucosa, should be considered as the first choice.

Keywords: Urethra, urethral stone, lithotripsy, holmium, acute urinary retention, lower urinary tract symptoms

Öz

Amaç: Üretra taşları tüm üriner sistem taşları arasında nadir görülür. Üretra taşlarının yönetimi ile ilgili literatürde sınırlı veri bulunmaktadır. Bu çalışmada üretra taşı tanısı alan hastalarla ilgili deneyimlerimizi literatür ışığında sunmayı amaçladık.

Yöntem: Bu retrospektif çalışmaya Ocak 2017-Aralık 2020 tarihleri arasında üretral taş tanısı konulan 24 ardışık hasta dahil edildi. Demografik veriler, klinik özellikler, primer tedavi yaklaşımları, peroperatif ve postoperatif veriler analiz edildi.

Bulgular: Ortalama yaşı 44±20 yıl (2-73) olan 24 hasta çalışmaya dahil edildi. Hastaların klinik prezentasyonu 14 (%58,3) hastada akut üriner retansiyon ve 10 (%41,6) hastada alt üriner sistem semptomları idi. En sık taş lokalizasyonu 13 (%54,2) hastada posterior üretra ve 11 (%45,8) hastada anterior üretra idi. Ortalama taş boyutu 10±3 (5-15) mm idi. On dört hastada daha önce geçirilmiş taş cerrahisi veya taş düşürme öyküsü vardı. İki hastaya internal üretrotomi ve bir hastaya eş zamanlı sistolitotripsi uygulandı. Cerrahi başarı taşsızlık oranı (SFR) %100 idi.

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Öz

Sonuç: Üretra taşları üroloji pratiğinde nadiren görülmektedir. Üretra taşlarının yönetimi belirsizdir ve kişisel deneyime bağlıdır. Üretral mukozaya minimal hasar veren minimal invaziv URS ile birlikte holimum lazer litotripsi ilk seçenek olarak düşünülmelidir.

Anahtar Kelimeler: Üretra, üretral taş, litotripsi, holmiyum, akut idrar retansiyonu, alt idrar yolu semptomları

Introduction

Urethral stones are quite rare and constitute less than 1% of all urinary tract stones[1]. Treatment approaches for urethral stones vary depending on many factors, including the experience of the urologist, size and location of the stone, anatomical structure of the urethra, and clinical status of the patient. Different methods such as meatotomy, milking with lidocaine, extracorporeal shock wave lithotripsy, and transurethral lithotripsy after catheter or endoscopic retrograde manipulation of the stone into the bladder are used in treatment[2,3].

Despite all these treatment modalities, there is no certain algorithm for the treatment of urethral stones compared with other urinary stone diseases, and treating them as bladder stones is a common method. To the best of our knowledge, all reports on urethral stones to date are based on retrospective studies and are mostly based on case reports and experiences of some case series[4-12].

In this study, we aimed to present our experience in the management of patients diagnosed with urethral stones in light of the literature.

Materials and Methods

After obtaining the approval of the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (2020-531), the data of 24 consecutive patients operated for urethral stones between January 2017 and December 2020 were retrospectively evaluated. Demographic data and clinical characteristics of the patients [age, body mass index (BMI), American Society of Anesthesiolgy score (ASA), medical history, presenting symptoms, place of presentation), laboratory data (complete urinalysis, urine culture, creatinine), radiological examinations (kidney, ureter, and bladder (KUB) X-ray and/or non-contrast abdominal computed tomography (CT)], primary intervention and final surgery, perioperative and postoperative data (operation time, hospital stay), postoperative data (success rate), and complications were analyzed.

All patients underwent laboratory tests, including blood count, blood electrolytes and biochemistry, coagulation studies, and urine. Patients with urinary tract infection detected by urinalysis and urine culture were treated before elective surgery. A single dose of third-generation cephalosporin was administered prophylactically in patients who underwent urgent intervention.

Surgical Technique

Fragmentation of the stone with a clamp: A thin pointed mosquito clamp was used to gently remove the stones, especially those located in the fossa navicularis and mea. In some stones, the stone was extracted in pieces by fragmentation with a clamp.

Endoscopic lithotripsy: Pethidine HCl (Aldolan ampoule 100 mg/2 mL, Vem, Turkey) 50 mg intramuscularly was injected as premedication locally performed transurethral surgeries. In addition, vital signs and pain levels were monitored by at least one anesthesiologist during local procedures. A single dose of third-generation cephalosporin was administered prophylactically 1 h before the procedure.

In the lithotomy position, 10 cc of 2% lidocaine gel was administered before endourological intervention, and after waiting for 15 min with a penile clamp to prevent its exit from the urethra, the same amount of lidocaine gel was reapplied to the urethra just before entering the anterior urethra with a cystoscope or ureteroscope (URS). All procedures were performed in a sterile environment using a 19-F semi-rigid cystoscope (Karl Storz, Germany) or a 7.5-F semi-rigid URS (Richard Wolf, Knittlingen, Germany or Karl Storz, Tuttlingen, Germany). Urethral anatomy, possible etiological factors, stone sizes, and localization were recorded by cystourethroscopy. After reaching the urethral stones, a Holmium:Yttrium-Aluminum-Garnet (Ho:YAG) laser device (Litho Quanta System, VA, Italy) was used to push the stones into the bladder. Stones that could not be pushed into the bladder were fragmented in the urethra. The laser energy was adjusted as 10-15 Hz, 1.5-2 J and 365 µ fiber was used. Lower laser energy was used during lithotripsy in the urethra. Stone fragments were removed using foreign

body forceps and an evacuator. At the end of the procedure, cystourethroscopy was performed to determine whether there was any stone residue and finally 14-16 Fr foley catheter was placed. The catheter was withdrawn during discharge. The oral antibiotic ciprofloxacin 500 mg/bid was continued for 24 h. The patients were then followed up every 6 months with KUB X-ray and ultrasonography.

Statistical Analysis

Categorical data are presented as numbers and percentages. For continuous variables, data are presented as mean and standard deviation (minimum-maximum). Statistical analysis was performed using the Statistical Package of Social Sciences version 21 (IBM SPSS Statistics; IBM Corp., Armonk, NY).

Results

Twenty-four patients with a mean age of 44±20 years (2-73) were included in the study. The male:female ratio was 22:2. The mean BMI was 22±5 kg/m^2. Four patients had ASA grade ≥III. Fourteen patients had a history of previous stone surgery or stone expulsion. One patient had a history of internal urethrotomy (IU), one had transurethral resection of the prostate (TUR-P), and one had forced catheterization. One patient had bladder stones and five patients had kidney stones simultaneously. The most common place of presentation was the emergency department in 13 (54.2%) patients and the urology outpatient clinic in 11 (45.8%) patients. The clinical presentation of the patients was acute urinary retention (AUR) in 14 (58.4%) patients and lower urinary tract symptoms (LUTS) in 10 (41.6%) patients. Of the 10 patients with LUTS, 5 had hematuria and 3 had penile/pelvic pain. The mean creatinine value was 0.94±0.24 mg/dL. Fifteen (62.6%) patients had infection in the complete urinalysis. The most commonly used radiological examination was CT in 16 (66.6%) patients and KUB X-ray in 8 (33.4%) patients. The most common stone location was the posterior urethra in 13 (54.2%) patients and the anterior urethra in 11 (45.8%) patients. The mean stone size was 10±3 (5-15) mm. The demographic and clinical characteristics of the patients are shown in Table 1.

The most preferred first intervention method was stone fragmentation and extraction in 17 (70.8%) patients (endoscopic lithotripsy in 13 patients, fragmentation and extraction of the stone with clamp in 4 patients). In the first intervention, percutaneous cystostomy catheter insertion was performed in 1 patient, and the stone was pushed into

Table 1. Demographic data and clinical features

Number of patients (n)	**24**
Age (years)	
Mean ± SD	44±20
Median (range)	49 (2-73)
Gender, n (%)	
Male	22 (91.6)
Female	2 (8.4)
BMI (kg/m^2)	
Mean ± SD	23±2
Median (range)	24 (18-27)
ASA	
Mean ± SD	2±1
Median (range)	1 (1-3)
Predisposing factor, n (%)	
History of spontaneous stone passage	10 (41.6)
Endoscopic stones urgery	4 (16.6)
IU	1 (4.2)
TUR-P	1 (4.2)
Traumatic catheter insertion	1 (4.2)
Unknown	7 (29.2)
Concomitant urinary system pathology, n (%)	
Urethral stricture	2 (8.4)
Bladder stone	1 (4.2)
Kidney stone	1 (4.2)
Place of admission, n (%)	
Emergency department	13 (54.2)
Urology outpatient clinic	11 (45.8)
Presenting symptom, n (%)	
AUR	14 (58.4)
LUTS	10 (41.6)
Haematuria	5 (50)
Penile pelvic pain	3 (30)
Preoperative creatinin elevel, n (%)	
Mean ± SD	0.94±0.24
Median (range)	0.89 (0.65-1.46)
Urinary tract infection, n (%)	
None	9 (37.4)
Yes	15 (62.6)
Radiological examination, n (%)	
CT	16 (66.6)
KUB X-ray	8 (33.4)
Stone location, n (%)	
Posterior urethra	13 (54.2)
Anterior urethra	11 (45.8)
Stone size (mm)	
Mean ± SD	10±3
Median (range)	10 (5-15)

SD: Standard deviation, BMI: Body mass index, ASA: American society of anaesthesiology score, IU: Internal urethrotomy, TUR-P: Trans urethral resection of prostate, AUR: Acute urinary retention, LUTS: Lower urinary tracts symptoms, CT: Computed tomography, KUB: Kidney, ureter, and bladder

the bladder with a cathagel and catheter in 6 patients. In definitive surgery, endoscopic lithotripsy was performed in 20 (83.3%) patients. The most preferred method was Ho:YAG laser lithotripsy with URS in 17 patients. In 13 patients, the procedure was performed under local anesthesia. Two patients underwent internal urethrotomy and one patient underwent cystolithotripsy simultaneously. The mean operation time was 23±8 min. The mean length of hospital stay was 18±11 hours No intraoperative complications were observed in any patient. The stone-free rate (SFR) was 100%. In the early postoperative period, two patients had transient fever that was controlled with conservative treatment, and in the late postoperative period, two patients had urethral strictures. They were treated with internal urethrotomy and dilatation. Major complications were not observed in any patient. No recurrent urethral stones were observed in any patient during the follow-up period (Table 2).

Discussion

In Turkey, urinary system stone disease is an endemic disease with a rate of 15% and is observed more frequently in the south and southeast parts of the country[13]. Although urinary system stones can be observed in any part of the urinary tract, they are rare[14]. The prevalence and incidence of stones are increasing in both males and females in different parts of the world[13]. Similar to the study by Scales et al.[15], urethral stones were observed more frequently in male patients (91.6%) than in female patients (8.4%) in our study. In children, isolated urethral stones are relatively common because of the higher prevalence of bladder stones, especially in developing countries[16]. In our series, there were only two female patients and 2 pediatric patients.

Table 2. Operative and post-operative data

First intervention, n (%)	
Emergency operation	17 (70.8)
Insertion a catheter/cystostomy catheter	7 (29.2)
Operation type, n (%)	
Endoscopic lithotripsy	20 (83.3)
URS-LL	17 (85)
Cystoscopy-LL	3 (15)
Removal or fragmentation with clamp	4 (16.7)
Anaesthesia type, n (%)	
General/spinal anaesthesia	11 (45.8)
Local anaesthesia	13 (54.1)
Operation time (minutes)	
Mean ± SD	23±8
Median (range)	23 (12-40)
Length of hospital stay (hour)	
Mean ± SD	18±11
Median (range)	16 (2-48)
Complication, n (%)	
Fewer	2 (8.3)
Urethral stricture	2 (8.3)

URS: Ureteroscopy, LL: Laser lithotripsy, SD: Standard deviation

Patients with urethral stones may present with different symptoms, including AUR, weak stream, frequent urination, hematuria, urethroragia, dysuria, penile mass, and pain in the penile, rectal, or perineal region[2,17]. Another reflection of urethral stones is urinary tract infections[17]. The most common clinical presentation of urethral stone is AUR although it has been reported differently in the series in the literature[2]. The rate of AUR varies between 45.2% and 89% in the literature[4-6,12]. Dysuria, another LUTS, has been reported as the most common reason for presentation in some series[7-9]. In the series of Hemal and Sharma[11] reported perineal and penile pain in all 26 patients. In our study, the most common symptoms were AUR, dysuria, hematuria, and penile pain. In our study, the most common presenting symptom was AUR (63.4%).

In the etiology of urethral stones, many factors that prevent spontaneous passage of the stone are blamed. Previous endourological interventions, neurogenic bladder, infections, foreign bodies, and anatomical disorders of the urethra are the most prominent of these factors[2,7]. Sharfi[7] and Selli et al.[18] reported that 56% of patients with urethral stones had anatomical abnormalities in the urethra. In contrast, Kamal et al.[4] did not notice any anatomical change. Jung et al.[19] In their study in which 221 lower urinary tract stone cases were analyzed, it was reported that 63% of 27 patients with urethral stones had concomitant upper urinary tract stones. Similarly, in a study in which 300 patients were analyzed, stones in the upper urinary system were found in 57.9% of 27 patients with urethral stones[19,20]. In our series, no anomaly in the urethra was found in any patient except urethral stricture in two patients, and five patients had concurrent kidney stones and one patient had bladder stones. In addition, 14 patients had a history of endoscopic stone surgery or spontaneous stone expulsion, 1 patient had a history of forced catheterization, 1 patient had a history of internal urethrotomy, and 1 patient had a history of TUR-P.

Different localizations have been reported in the literature regarding the most common location of the urethral stone.

Ahmed and Saeed[10] reported that the anterior urethra was the most common localization (71.4%). On the contrary, Kamal et al.[4] found the most common stone localization in the posterior urethra with a rate of 88%. Most of the urethral stones in our study (54.1%) were located in the posterior urethra, as reported for isolated urethral stones in support of a previous series[4,7,10].

Many factors, including the patient's age, gender, anatomical status of the urethra, clinical presentations of the patients, general health status, and size and location of the stone, are effective in selecting the correct surgical method for urethral stones[7,21]. The first preferred option in the treatment algorithm of AUR due to urethral stone is placement of a suprapubic cystostomy catheter, which was reported by Amin in 1973[5]. With this first intervention, AUR will be treated rapidly. However, today, less minimally invasive methods may be preferred with technological advances and miniaturization in endoscopic devices. First, retrograde manipulation of the bladder is the most common procedure for posterior urethral stones. However, it may be dangerous to use a catheter or dilator blindly. However, the procedure is safer under endoscopic vision[22]. In our series, stones were most commonly pushed into the bladder by endoscopic visualization.

The most commonly preferred endoscopic lithotripsy is Ho:YAG laser lithotripsy. There are very few studies in the literature on the use of lasers in urethral stones[3,12]. Maheshwari and Shah[2] reported 100% success and no intraoperative complications when they performed Ho:YAG laser lithotripsy in the urethra in 18 patients who could not undergo retrograde manipulation in their study of 42 patients with urethral stones. Kamal et al.[4] reported a success rate of 86% in patients who underwent retrograde manipulation and 80% in patients who did not undergo retrograde manipulation for treating posterior urethral stone. Similarly, Walker and Hamilton[23] presented two pediatric patients with impacted urethral stones and reported that holmium laser lithotripsy in the urethra was an effective and reliable method. In our study, URS - Ho: YAG Ho:YAG lithotripsy was frequently preferred for treating posterior urethral stones and was 100% successful. The reason for frequent use of URS is that if the stone cannot be pushed into the bladder in the narrow urethral lumen, it is aimed to fragment the stone with small manipulations without damaging the urethral mucosa.

Meatotomy or urethroplasty is the preferred treatment method for stones located in the navicular fossa and mea, especially for stones that reach large sizes or have luminal impaction[4,8]. For smaller stones, careful forceps removal or milking with a cathagel can be used. Similarly, it is dangerous to extract the stone with forceps and milking in anterior urethral stones to avoid damage to the urethral mucosa. Care should be taken in protruding and large stones[4,22]. First, El-Sherif and El-Hafi[24] reported a success rate of 77.8% with intraurethral application of 2% lidocaine gel in 18 patients with urethral stones smaller than 10 mm in anterior urethral stones. In a study conducted in our country, Kilciler et al.[8] reported the success rate of this approach for treating anterior urethral stone as 88.2%. In our series, only four patients had mea-located stones removed by clamping. Milking with gel was not performed in any patient. No patient in our series required open surgery.

HO:YAG laser lithotripsy under local anesthesia in patients with comorbidities who cannot receive anesthesia has come to the forefront and has been investigated in limited studies[25]. Kara et al.[26] performed transurethral cystolithotripsy under local anesthesia in 13 patients with bladder stones with a mean size of 3.6 cm and reported a success rate of 100%. Similarly, bladder stones have been successfully and safely removed under local anesthesia with a Ho: YAG laser[27,28]. Atılgan et al.[12] reported the results of urethral stone fragmentation with a Ho: YAG laser under local anesthesia in 31 male patients over 65 years of age. They obtained stone-free results in all patients. They reported hematuria shorter than 24 h and not requiring blood transfusion in seven patients, urethrorrhagia in two patients and urinary tract infection in one patient, and they did not observe grade 3 or higher complications[12]. Our present results are comparable with those reported in other series. Two patients had fever in the early period, which resolved with conservative treatment, and one patient had a urethral stricture in the late period. In our series, no recurrent urethral stone was observed at the 6-month follow-up. In addition, 7 of 13 patients who could not receive anesthesia due to various comorbidities in our series were successfully fragmented with Ho:YAG laser under local anesthesia.

It is necessary to create an algorithm for urethral stones. If AUR fossa navicularis, it may be tried to extract it gently with a clamp without damaging the mucosa. If the stone cannot be seen, retrograde manipulation of the stone into the bladder with a cathagel and catheter may be attempted. If it cannot be passed, a percutaneous suprapubic cystostomy

catheter can be inserted. If urethral stones are in any part of the urethra and are small in size or if there is no primary pathology in the urethra, gentle removal with endoscopic intervention may be considered. Stones in the posterior urethra can be pushed into the bladder with lidocaine or endoscopically and fragmented retrogradely. If there is a large stone, if it is thought to remain for a long time, or if it is protruding and completely obstructive, milking should not be preferred because of mucosal damage. In elderly patients and patients with comorbidities, fragmentation with holmium laser under local anesthesia is a safe and effective method and should be considered.

Study Limitations

Our study has some limitations. The first is the retrospective design. The second is the small number of patients. The strengths of our study are the presentation of the experiences of patients of all sexes, ages, and surgical methods.

Conclusion

This study demonstrated that transurethral endoscopic Ho:YAG laser lithotripsy can be used effectively and safely for treating urethral stone randomized, large-scale and prospective studies are needed to establish a common approach for the treatment of urethral stone disease.

Ethics

Ethics Committee Approval: After obtaining the approval of the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (2020-531), the data of 24 consecutive patients operated for urethral stones between January 2017 and December 2020 were retrospectively evaluated.

Informed Consent: Written informed consent was obtained from all patients for inclusion in this study.

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Analysis of Scientific Videos Explaining Continuous Renal Replacement Therapies Applied in Intensive Care Units on YouTube Channel

YouTube Kanalında Yoğun Bakım Ünitelerinde Uygulanan Sürekli Renal Replasman Tedavilerini Açıklayan Bilimsel Videoların Analizi

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Abstract

Objective: Continuous renal replacement therapy (CRRT) is a critical alternative among hemodialysis options in intensive care patients. Healthcare professionals provide access to health-related information using social media. Our aim in this study is to investigate the accuracy and effectiveness of their presentations on the international video sharing site YouTube.

Methods: A video scan was performed on the "www.YouTube.com" website on 21-22 April 2022 using the "CRRT" scan key without any filter. The quality, reliability and accuracy of the videos was determined by the "global quality score" (GQS), "Journal of American Medical Association (JAMA) quality test" and "Modified DISCERN" questionnaire, respectively.

Results: When the quality of the videos was evaluated with the GQS score, 81% of the videos were found to be low quality, 16% medium and 3% high quality according to the GQS results. When videos are analyzed according to their source, it has been determined that only 3% of the academically sourced videos are of high quality. Statistically significant correlation was found between the source of the videos and the results of the quality, reliability and accuracy scale GQS (p=0.026), JAMA (p=0.010), and modified DISCERN (p=0.003).

Conclusion: Our study determined that most of the YouTube videos about CRRT application in intensive care units contain poor quality and insufficient data. High-quality videos were found to be longer and academically sourced videos. However, low quality or erroneous videos should always be checked for accuracy and reliability before being used as educational and training material, as they may harm users.

Keywords: E-learning, YouTube, intensive care unit, continuous renal replacement therapy

Öz

Amaç: Sürekli renal replasman tedavisi (CRRT), yoğun bakım hastalarında hemodiyaliz seçenekleri arasında kritik bir alternatiftir. Sağlık çalışanları sosyal medyayı kullanarak sağlıkla ilgili bilgilere erişim sağlamaktadır. Bu çalışmadaki amacımız, uluslararası video paylaşım sitesi YouTube'daki sunumlarının doğruluğunu ve etkinliğini araştırmaktır.

Yöntem: 21-22 Nisan 2022 tarihlerinde "www.YouTube.com" internet sitesinde herhangi bir filtresiz "sürekli renal replasman tedavisi" tarama anahtarı kullanılarak video taraması yapılmıştır. Yoğun bakımda çekilen ilk 100 CRRT videosu listelendi. Görüntülenme, beğeni, beğenmeme, yorum, yüklenen kaynak,

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Öz

kaynak ülke ve kıta sayıları belirlendi ve içerik analizleri yapıldı. Videoların kalitesi, güvenilirliği ve doğruluğu sırasıyla "global quality score" (GQS), "Journal of American Medical Association (JAMA) quality test" ve "Modified DISCERN" anketi ile belirlendi.

Bulgular: Videoların kalitesi GQS puanı ile değerlendirildiğinde, GQS sonuçlarına göre videoların %81'i düşük, %16'sı orta ve %3'ü yüksek kalitede bulunmuştur. Videolar kaynağına göre incelendiğinde akademik kaynaklı videoların sadece %3'ünün yüksek nitelikli olduğu tespit edilmiştir. Videoların kaynağı ile kalite, güvenilirlik ve doğruluk ölçeği GQS (p=0,026), JAMA (p=0,010) ve modifiye DISCERN (p=0,003) ve sonuçları arasında istatistiksel olarak anlamlı bir ilişki bulundu.

Sonuç: Çalışmamız, yoğun bakım ünitelerinde CRRT uygulaması ile ilgili YouTube videolarının çoğunun kalitesiz ve yetersiz veri içerdiğini belirledi. Yüksek kaliteli videoların daha uzun ve akademik kaynaklı videolar olduğu tespit edildi. Bu nedenle, ücretsiz olarak sunulan YouTube videolarını öğretim materyali olarak kullanmak mümkündür. Ancak, düşük kaliteli veya hatalı videolar, kullanıcılara zarar verebileceğinden, eğitim ve öğretim materyali olarak kullanılmadan önce her zaman doğruluk ve güvenilirlik açısından kontrol edilmelidir.

Anahtar Kelimeler: Uzaktan eğitim, YouTube, yoğun bakım ünitesi, sürekli renal replasman tedavisi

Introduction

The incidence of acute renal failure (ARF) in intensive care patients varies between 15-25%, and this rate rises to 90% in cases of multi-organ failure[1]. The incidence of ARF requiring renal replacement therapy (RRT) in the intensive care unit (ICU) is reported to be 4-6%. The mortality rate in these patients varies between 4 and 70%[2]. In the case of renal failure that does not respond to medical treatment, choosing the most appropriate method for the right patient at the right time among the RRT options is life-saving[3].

Continuous renal replacement therapy (CRRT) has been used as an alternative to intermittent dialysis renal replacement therapy in intensive care patients in recent years[1]. In intensive care patients, CRRT is a substantial alternative, especially in patients with hypotensive and septic shock, who are hypersensitive to volume reduction, and who are started on high inotropic support[4]. However, preparing the set and seeing the CRRT indication as medically suitable for a patient is essential. Manual medical procedures are best learned under the supervision and guidance of an experienced instructor. An essential step in developing gifted medical students involves observing procedures on dummies or patients after they have been learned through a textbook or a professional health educator[5]. Unfortunately, a limited number of experts may not have enough time for training[6]. Also, since education has become more difficult due to the ongoing Coronavirus disease-2019 (COVID-19) pandemic, multimedia materials can improve learning outcomes among medical students[7]. Therefore, there is a need for freely accessible, quality, and accurate videos that meet the needs of students and teachers. In addition, medical students, educators, general practitioners, resident doctors, allied health personnel, and even patients can often view online visual documents and videos on websites to visually learn and interpret medical conditions[8].

Social media and video-sharing sites such as YouTube are becoming a part of daily life, and the number of health-related videos is increasing daily. YouTube; as considering its popularity and ease of access, it seen as an essential audio-visual education platform for sharing health care information[8]. Freely available video streaming sites such as YouTube are popular sources of information, with more than 100 million daily viewers[7]. However, the quality of the medical information in these videos is very heterogeneous, and inaccurate and misleading information may spread, leading to misdiagnosis and treatment[9].

For this reason, this study aims to analyze the quality of scientific videos on the YouTube website describing CRRT applied in the intensive care unit, according to the sources the videos are uploaded to, the number of views, like-dislikes, comments, and video durations. Thus, it is aimed to evaluate the reliability and effectiveness of learning through video.

Materials and Methods

Search Strategy

Our research, planned as a cross-sectional study, was conducted on April 21st and 22nd 2022, after obtaining approval from the Non-Interventional Ethics Committee of Dokuz Eylül University Faculty of Medicine (ethics committee decision no: 2021/26-14, date: 22.09.2021).

A search was conducted on the YouTube website (www.youtube.com, YouTube, LLC, San Bruno, USA) using the keywords "CRRT" and "CRRT". The first 100 videos with

medical content were analyzed without using any filtering. The first 100 videos, the number of views and their duration, the number of likes and dislikes, and the number of comments were recorded. A similar method was followed for the analysis used in previous studies[10,11]. Two independent researchers (Ö.Ö and V.H) viewed and analyzed all videos. The difference between the authors was resolved by review and consensus. In order to avoid any interaction before the scan and not affect the research results, the computer internet browser and YouTube history and cookies were deleted. Signed out of Google and YouTube accounts[10,11]. Videos of continuous renal replacement therapies in the intensive care unit; video interaction features (number of views, like-dislikes, number of comments, and video durations), the year they were published, video sources (Academic, Doctor, Association/ Professional Organization, Health-related website, and State institution) animation content, high definition (HD) feature, from which country they were loaded and from which continent they were loaded were recorded.

Exclusion Criteria

Only videos in English were included in our study. The analysis excluded videos unrelated to CRRT, duplicate videos, music videos, and videos without sound. Exclusion criteria were established under the guidance of previous studies[10,11].

Data Collecting

Since the search results may change on different days, a playlist was created from the detected videos, and the search result was saved. The source locators (URLs) of the videos were recorded. The intelligibility of the videos was evaluated using the Materials Appropriateness Assessment (MAA)[12]. User engagement metrics were taken for each video. There is no verified scoring system available for videos; The educational content in each video was assessed by the presence/absence of the following factors.

1- Are the indications and contraindications of "continuous renal replacement therapies" explained?

2- Is the type of approach chosen to perform the procedure specified?

3- Is there a clear description of the targeted anatomical region?

4- Is information about anatomical signs given?

5- Have possible complications been explained?

6- Is the information given about the needle/catheter used?

7- Is appropriate monitoring done?

8- Is sufficient information given about sterilization and local anesthesia?

Evaluation of the educational value of videos in terms of reliability and quality:

Global Quality Score (GQS):

The GQS is a five-point Likert scale that indicates website quality, ease of use, and flow[13]. GQS of 5: Excellent quality and excellent flow, very beneficial for patients; 4: Good quality and generally good flow are beneficial for patients; 3: Moderate quality, sub-optimal flow, somewhat beneficial for patients 2: Generally poor quality and poor flow for minimal use for patients; it is scored as 1: Poor quality, poor flow of the site, not useful at all for patients[14].

Journal of American Medical Association (JAMA) Quality Testing Criteria

JAMA quality criteria, online videos, and resources; examines them under 4 criteria: Authorship, attribution, explanation, and timeliness. In the JAMA score; "Authority (1 point): Authors and contributors, their links and relevant credentials must be provided; Citation (1 point): References and sources should be listed for all content; Disclosure (1 point): Conflicts of interest, funding, sponsorship, advertising, endorsement, and video ownership must be fully disclosed; Currency (1 point): The dates on which the content was published and updated should be stated"[15]. JAMA is used to evaluate video accuracy and reliability. The rater gives 1 point for each criterion set in the video, and the final score ranges from 0 to 4. Four points indicate the highest quality[15].

Modified DISCERN Survey

It is a scoring tool consisting of 5 yes/no questions developed to evaluate the quality and reliability of publications related to health information[16]. The score of this questionnaire varies between 0 and 5 points, and the total score is obtained by summing up the yes scores (yes=1 point, no=0 points). The questions included in the survey are: éDoes the video address areas of controversy/ambiguity?", "Are additional sources of information listed for patient reference?", "Is the information provided balanced and unbiased?", "Cite valid sources? (valid studies, doctors)", "Is the video clear, concise and understandable?"[16].

Statistical Analysis

The obtained data were analyzed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) 24.0 package program. Data with continuous values were shown as mean ± standard deviation, and data indicating frequency were shown as numbers (n) and percentages (%). The chi-square test was used in the analysis of frequency data, the Kruskal-Wallis test was used in the analysis of data with continuous values, and the Pearson correlation test was used in correlation analysis. A p-value less than 0.05 was accepted as a significant difference.

Results

In our study, the first 100 videos with medical content related to RRT in the intensive care unit were viewed by typing the keywords "CRRT" and "CRRT" on the YouTube search engine on April 21st and 22nd 2022, were examined.

A total of 42 hours, 27 minutes, and 12 seconds of footage was viewed. The longest of the videos is 1 hour 51 minutes, and the shortest is 16 seconds. The video with the most likes got 2.613 likes, and the video with the least likes got 0 likes. The most watched video was watched 1.227,547 times, and the least watched the video was 12 times. The video with the most comments received 499 comments, and the video with the least comments received 0 comments.

The average number of views per video is 23093.13±124630.68, the average number of likes is 177.09±493.31, the average number of dislikes is 2.02±5.98, the average number of comments is 14±54.95, and the average video duration is 1528.34 It was observed as ±1484.69 seconds.

When the videos are separated according to their dates, it has been determined that 51 (51%) of the videos on the YouTube platform were published before 2020, and 49 (49%) were published after 2020 (Table 1). It was determined that 70 (70%) of the videos contain animation and 48 (48%) HD videos (p= 0.009). The dislike of the videos after 2020 was found to be 2.43±5.78, statistically significant (p=0.049). It was determined that 37 (37%) of the videos were from the United States, 13 (13%) from India, 9 (9%) from Italy, and 41 (41%) from other countries. When the continents where the videos were uploaded were evaluated, it was determined that 43% of the videos were uploaded from the Americas, 24% from the Asian continent, 23% from the European continent, 6% from the African continent, and 4% from the countries located in the Australian continent.

When the sources of the videos were evaluated, it was determined that 64% were health-related sites, 21% were academic sites, 8% were commercial sites, 5% were doctors, and 2% were government sites.

The medical content of the videos related to CRRT; 51% indication, 3% contraindication, 57% explanation of application, 34% explanation of different techniques, 21% coagulation, 19% complications, 2% infectious transmission, 19% timing, 17% solution properties, 8% application termination (Table 1).

When the quality of the videos was evaluated with the GQS score, according to the GQS results, it was determined that 81% of the videos were of low quality, 16% of them were of medium quality, and only 3% of them were of high quality. When the quality of the videos was evaluated with the JAMA score, 76% of the videos were found to be inadequate, 23% partially sufficient, and only 1% entirely sufficient. When the videos were classified according to the modified DISCERN questionnaire, 74% were rated with 1 point, 23% with 2 points, and 3% with 3 points.

No statistically significant difference was found between the sources of the videos and the number of views, likes, dislikes, and comments (p=0.539, p=0.438, p=0.344, and p=0.191), respectively (Table 2).

When the videos were examined according to their sources, it was determined that only 3% of the academic videos were of high quality. A statistically significant correlation was found between the sources of the videos and the results of GQS (p=0.026), JAMA (p=0.010), and modified DISCERN (p=0.003) (Table 3).

There is a weak positive correlation between video durations and GQS (r=0.365, p<0.01) and JAMA (r=0.322, p<0.01) results. Accordingly, videos with higher quality and reliable data have longer durations (Table 4). However, no significant relationship was found between the video sources and the duration of the videos (p=0.086) (Table 3).

There was no statistically significant difference between the stanzas where the videos were uploaded and the number of video views (p=0.291), likes (p=0.370), dislikes (p=0.237), comments (p=0.202), and duration (p=0.193).

Discussion

In our study, in which the content, quality, reliability, and user participation of the videos on YouTube about CRRT in the ICU were evaluated, we evaluated the quality and reliability of the

Table 1. Video content analysis by years

Video content/years		<2020, n (%)	≥2020, n (%)	p-values
HD video	**Exists**	18 (35.3%)	30 (61.2%)	**0.009**
	DNE	33 (64.7%)	19 (38.8%)	
Animation	**Exists**	32 (62.7%)	38 (77.6%)	0.106
	DNE	19 (37.3%)	11 (22.4%)	
Indication	**Exists**	24 (47.1%)	27 (55.1%)	0.421
	DNE	27 (55.1%)	22 (44.9%)	
Contraindication	**Exists**	0 (0%)	3 (10%)	0.114
	DNE	51 (52.6%)	46 (47.4%)	
Explanation of the application	**Exists**	26 (51%)	18 (36.7%)	0.215
	DNE	25 (49%)	31 (63.3%)	
Explanation of the technical detail	**Exists**	14 (41.2%)	20 (58.8%)	0.158
	DNE	37 (72.5%)	29 (43.9%)	
Explanation of the coagulation	**Exists**	7 (13.7%)	14 (66.7%)	0.068
	DNE	44 (86.3%)	35 (44.3%)	
Explanation of infection risk	**Exists**	1 (2%)	1 (2%)	0.742
	DNE	50 (98%)	48 (98%)	
Time description	**Exists**	10 (19.6%)	9 (18.4%)	0.874
	DNE	41 (80.4%)	40 (81.6%)	
Solution features	**Exists**	7 (13.7%)	10 (20.4%)	0.374
	DNE	44 (86.3%)	39 (79.6%)	
Termination features	**Exists**	2 (3.9%)	6 (12.2%)	0.122
	DNE	49 (96.1%)	43 (87.8%)	
	DNE	16 (94.1%)	38 (88.4%)	
Source of the video	Academic (n=21)	12 (23.5%)	9 (18.4%)	0.618
	Doctor (n=5)	2 (3.9%)	3 (6.1%)	
	Health site (n=64)	31 (60.8%)	33 (67.3%)	
	Commercial site (n=8)	4 (7.8%)	4 (8.2%)	
	Government (n=2)	2 (3.9%)	0 (0%)	
JAMA	Inadequate (1 point)	38 (74.5%)	38 (77.6%)	0.509
	Somewhat adequate (2/3 points)	13 (25.5%)	10 (20.4%)	495
	Adequate (4 points)	0 (0%)	1 (2%)	500
GQS	Low quality (1/2 points)	42 (82.4%)	39 (79.6%)	0.817
	Mid quality (3 points)	8 (15.7%)	8 (16.3%)	505
	High quality (4/5 points)	1 (2%)	2 (4.1%)	510
Modified DISCERN	1 point	39 (76.5%)	35 (71.4%)	0.637
	2 points	10 (19.6%)	13 (26.5%)	
	3 points	2 (3.9%)	1 (2.0%)	

HD: High definition, GQS: Global quality score, JAMA: Journal of American Medical Association

Table 2. Video interaction characteristics according to evaluation criteria and different years

Years	Number of views Mean ± SD	Likes Mean ± SD	Dislikes Mean ± SD	Comments Mean ± SD	Duration (second) Mean ± SD
<2020 (n=51)	33465±171606	65.6±115.9	1.62±6.2	12.5±69.8	1434.6±1486.7
≥2020 (n=49)	12297±33576	293±678	2.43±5.78	15.4±33.8	1625.9±1491.6
p-values	0.087	0.074	0.**049**	0.058	0.057
Video source					
Academic (n=21)	5837±14123	39.8±62.9	0.19±0.68	0.62±1.07	1972±1743
Doctor (n=5)	12015,65±29510,75	164.36±518.97	5.77±12.57	7.95±26.62	1203.2±904.4
Site about health (n=64)	13666±31892	252±602.8	2.27±5.79	13.05±30.3	1513.3±1441.5
Commercail site (n=8)	23093.1±124630.6	177±493.3	2.02±5.98	14±54.95	1528.3±1484.6
Government (n=2)	889	9570±0.70	0.50±0.707	1.5±2.12	1109±1055
p-values	0.539	0.438	0.344	0.191	0.086
GQS (1-5 point)					
Low quality (1/2 points) (n=81)	13472.91±30536.004	221.53±558.519	2.51±6.78	11.45±76	1249.4±1329.6
Mid quality (3 points) (n=16)	3926.8±5116.6	61.4±78	1.44±3	2.75±4.79	2781±1464.5
High quality (4-5 points) (n=3)	854±619.9	19.7±22.14	1±1.7	0.33±0.57	2374.7±2348.1
p-values	0.866	0.676	0.396	0.688	**<0.001**
JAMA score (0-4 points)					
Inadequate data (n=76) (1 point)	13472.9±30536	221.53±558.519	2.51±6.78	11.45±26.13	1222.87±1170.10
Somewhat sufficient data (n=23) (2/3 point)	55819.17±255457.07	36±56.79	0.39±0.89	23±103.81	2383.7±1895.88
Adequate data (4 points)	1531	45	3	1	5070.00
p-values	0.611	0.533	0.197	0.243	**0.001**
Modified DISCERN score (0-5 points)					
1 point (n=74)	11693.24±29739.67	156.9±429.03	1.74±5.53	7.27±17.71	1363.7±1507.4
2 points (n=23)	62104.76±254733.4	254.1±689.2	2.87±7.63	37.2±108.7	2068±1404.3
3 points (n=3)	5201±4599.96	82±69.87	2.33±1.15	2±1.73	1452±349.8
p-values	0.644	0.531	**0.029**	0.810	**0.019**

n: Number of videos, SD: Standard deviation, GQS: Global quality score, JAMA: Journal of American Medical Association

videos according to GQS and JAMA. We modified DISCERN scores, where more videos were uploaded before 2020. Results were found to contain low-quality and insufficient data. In addition, although it was determined that the videos with high video quality and reliability scores were longer, a significant relationship could not be determined between the sources and the duration of the videos.

YouTube is not limited to patient education but also can potentially train healthcare professionals to a significant extent[17]. Especially during the COVID-19 pandemic, the disruption of face-to-face education practices caused healthcare providers to consider internet and video-based education applications, and education shifted in this direction[7,8]. Although YouTube offers invaluable opportunities for disseminating medical knowledge, unfiltered, poor-quality, unscientific content can be misleading or harmful[18].

For this reason, we aimed to investigate the accuracy and reliability of the visual presentations on YouTube, which we think has a vital role in health education.

Table 3. Evaluation according to video source

		Academic	Doctor	Health site	Commercial site	Government	p-values
GQS (1-5 points)	Low quality (1/2 points) (n=81)	13 (16%)	5 (6.2%)	54 (66.7%)	8 (9.9%)	1 (1.2%)	**0.026**
	Mid quality (3 points) (n=16)	5 (31.3%)	0 (0%)	10 (62.5 %)	0 (0%)	1 (6.3%)	
	High quality (4/5 points) (n=3)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
JAMA score (0-4 points)	Inadequate data (1 points) (n=76)	9 (11.8%)	4 (5.3%)	54 (71.1%)	8 (10.5%)	1 (1.3%)	**0.010**
	Somewhat adequate data (2/3 points) (n=13)	11 (47.8%)	1 (4.3%)	10 (43.5%)	0 (0%)	1 (4.3%)	
	Adequate data (4 points) (n=3)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Modified DISCERN score (0-5 points)	1 points (n=74)	12 (16.2%)	4 (5.4%)	49 (66.2%)	8 (5.4%)	1 (1.4%)	**0.003**
	2 points (n=23)	9 (39.1%)	(4.3%)	13 (56.5%)	0 (0%)	0 (0%)	
	3 points (n=3)	0 (0%)	0 (0%)	2 (66.7%)	0 (0%)	1 (33.3 %)	

GQS: Global quality score, JAMA: Journal of American Medical Association

Table 4. Correlations between quality variables and interaction parameters

	GQS	JAMA	Modified DISCERN	Number of views	Number of like	Number of dislike	Number of comments	Video duration	Year of upload
GQS	1	**0.707****	0.731	0.027	0,001	0.017	0.043	**0.365****	0.088
JAMA	**0.707****	1	**0.635****	0.078	-0.142	-0.104	0.031	**0.322****	0.073
Modified DISCERN	**0.731****	**0.635****	1	0.124	0.048	0.070	0.164	0.157	0.052
Number of views	0.027	0.078	0.0124	1	0.136	0.029	0.920	-0.093	**-0.228***
Number of like	0.001	-0.142	1	0.136	1	**0.465****	0.377**	-0.136	0.170
Number of dislike	0.017	-0.104	0.070	0.029	**0.465****	1	0.205*	-0.135	0.131
Number of comments	0.043	0.031	0.164	**0.920****	**0.377****	**0.205***	1	-0.110	-0.113
Video duration	**0.365****	**0.322****	0.157	-0.093	-0.136	-0.135	-0.110	1	0.107
Year of upload	0.088	0.073	0.052	**-0.226***	0.170	-0.131	0.113	0.107	1

**p<0.01 Pearson correlation test,

* p<0.05 Pearson correlation test,

GQS: Global quality score, JAMA: Journal of American Medical Association

Past studies evaluate YouTube videos' content, quality, and reliability; deficiencies in the content are emphasized[7]. Zengin and Onder[5] evaluated the videos describing musculoskeletal system ultrasonography training and found the video to be of low quality with a rate of 59%. Rodriguez-Rodriguez et al.[19] found that most cancer rehabilitation training videos were low-quality. The mean modified DISCERN, JAMA, and GQS scores in the study were 2.14, 2.03, and 2.78, respectively. Similarly, Boztaş et al.[20] evaluated the anterior abdominal wall blocks and determined that 58% of the videos were inadequate. Tolu et al.[21] pointed out that videos uploaded by doctors, academic sources, and professional organizations offer higher-quality content.

Pamukcu and Izci Duran[22] evaluated the quality of videos describing the self-injection methods of anakinra according to GQS. They found that 21.6% of the videos were of low quality, 35.3% were of medium quality, and only 43.1% were of high quality. In another study examining the technical data of YouTube videos about percutaneous tracheostomy in the intensive care unit, it was found that most of them (49%, 70%) shared personal experiences, and medical equipment companies uploaded some (10.3%) for advertising purposes[23].

When we questioned how accurate and reliable the contents of YouTube videos, especially for teaching medical information, were, we saw that the result was unfortunately not very promising. Based on this situation, we sought an answer to the question, "Can the videos have different reliability according to their sources"[22]. In a study investigating videos teaching ultrasonography-guided brachial plexus blocking techniques in the literature, academic videos contained higher accuracy and precision than other sources[24]. In another study evaluating videos that still examined frailty syndrome, videos with doctor uploaders had the highest average DISCERN and average GQS scores[25]. Consistent with the literature, higher GQS and JAMA scores were found in academic videos in our study. This statistical difference can be explained by the fact that academically sourced videos are higher quality and more reliable. Similarly, Arslan et al.[26], found that even on vital issues such as endotracheal intubation in the operating room and intensive care COVID-19 patients, YouTube videos do not provide sufficient and comprehensive educational information.

Similarly, videos describe the operating room's regional anesthesia and procedure technique. A report evaluating the quality of the videos found that half of the videos were of low quality[27]. Besides quality scores, video interaction data should also be considered when evaluating YouTube videos, but the relationship between them is unclear. In a study investigating the reliability of YouTube videos on self- injection of anti-TNF agents, while half of the videos examined taught safe and appropriate injection techniques with accurate and unbiased information, misleading information was detected in the other half[21]. However, the good news in the same study was that videos that were most likely to attract viewers had high-reliability values in viewer interaction parameters (daily views and likes). Similarly, Delli et al.[28] found that 51% of the videos about Sjögren's syndrome were applicable. In their study, Singh et al.[29] found that 54.9% of YouTube videos about rheumatoid arthritis were helpful, while 30.4% were misleading. In another study evaluating anterior abdominal wall blocks, they determined a weak positive correlation between the quality levels of the videos and the number of views, likes, dislikes, and comments[22]. However, in another study in which he evaluated YouTube videos about oral care in Parkinson's patients, it was found that videos originating from low-quality television channels had a high number of views, likes, and dislikes[30]. In the study we presented, no statistically significant difference was found between the sources of the videos and the number of views, like-dislikes, comments, and the duration of the video. This shows that YouTube users cannot distinguish between reliable and quality videos and videos with potentially low quality and insufficient content when choosing videos. Thus, although the reliability and quality scores of the videos describing CRRT, academic and long-term, were high, this situation was not significant in the audience selection and was not reflected in the video interaction data. It is also essential to enable the YouTube audience to critically evaluate the information hosted in the presentations when trying to learn medical knowledge.

Video duration is among the criteria that show the quality and usefulness of video content[10]. A study investigating the quality of COVID-19 vaccines and informational videos during the pandemic process found that high-quality videos were of longer duration[17]. In our research, we have found that videos with high reliability and quality have longer video durations. This situation can also be interpreted as needing more time while presenting quality video content. Based on this situation, we think that while designing the video duration, it should be aimed to provide quality information without distracting the audience but without missing the necessary information in the content.

Our study analyzed English-language YouTube videos about CRRT in the intensive care unit. Many of the videos included in the study were rated as having poor quality, low reliability, and insufficient data scores. Although it was determined in our study that the videos with high quality and reliability were academically sourced and of longer duration, they were not reflected in the video interaction data. For this reason, we think that watching the visual presentations that mediate the learning and dissemination of medical information without making source, quality, and accuracy analysis may lead to objectionable results.

Study Limitations

Since we included the first 100 videos in the study, our sample size may be limited. Secondly, we only included videos with English content in our study. Since we could not include non-English videos, we could not include knowledge and experience of other nationalities in our work. However, considering that English is the world's most widely spoken language, we think this limitation will not affect our study too much.

Conclusion

In our research, we have found that videos with high reliability and quality have longer video durations. This situation can also be interpreted as needing more time while presenting quality video content. Based on this situation, we think that while designing the video duration, it should be aimed to provide quality information without distracting the audience but without missing the necessary information in the content.

Our study analyzed English-language YouTube videos about CRRT in the intensive care unit. Many of the videos included in the study were rated as having poor quality, low reliability, and insufficient data scores. Although it was determined in our study that the videos with high quality and reliability were academically sourced and of longer duration, they were not reflected in the video interaction data. For this reason, we think that watching the visual presentations that mediate the learning and dissemination of medical information without making source, quality, and accuracy analysis may lead to objectionable results.

Ethics

Ethics Committee Approval: Our research, planned as a cross-sectional study, was conducted on April 21st and 22nd 2022, after obtaining approval from the Non-Interventional Ethics Committee of Dokuz Eylül University Faculty of Medicine (ethics committee decision no: 2021/26-14, date: 22.09.2021).

Informed Consent: Since the research was not conducted on patients, informed consent forms were not obtained.

Authorship Contributions

Concept: Ö.Ö., V.H., Design: Ö.Ö., V.H., Data Collection or Processing: Ö.Ö., V.H., Analysis or Interpretation: Ö.Ö., V.H., Literature Search: Ö.Ö., V.H., Writing: Ö.Ö., V.H.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Risk Factors for Tuberculosis Co-infection in People Living with HIV: A Single-center Retrospective Cross-sectional Study

HIV'le Yaşayan Bireylerde Tüberküloz Ko-enfeksiyonu için Risk Faktörleri: Tek Merkezli Retrospektif Kesitsel Bir Çalışma

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Abstract

Objective: Tuberculosis (TB) remains a leading cause of morbidity and mortality among people living with HIV (PWH). The coexistence of HIV and TB mutually enhances their pathogenicity and disrupts immunological functions. This study aims to analyze the biopsychosocial risk factors predicting HIV-TB co-infection in our center.

Methods: A retrospective cross-sectional cohort study was conducted using the records of PWH followed between 2019 and 2022 at the Infectious Diseases and Clinical Microbiology Clinic of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital. Logistic regression analysis was employed to examine factors influencing the development of TB. Results were considered statistically significant when the p-value was less than 0.05.

Results: Among the 73 individuals living with HIV in the study, 22 (30.1%) had TB co-infection, with a median age of 40 years (32-50). Multivariate logistic regression analysis identified baseline BMI and the number of people living in the household as independent risk factors for TB co-infection in PWH. Each increase in baseline BMI was associated with a 0.73-times reduced risk of developing TB (0.57-0.94, p=0.016), while each additional person in the household increased the risk of TB co-infection by 1.16 times (1.00-1.35, p=0.047).

Conclusion: TB is influenced by various social factors, and this study demonstrates that PWHs with specific characteristics are at a higher risk of TB co-infection. Therefore, multicenter studies are needed to identify the risk factors predicting HIV-TB co-infection.

Keywords: HIV, co-infection, risk factors, tuberculosis

Öz

Amaç: Tüberküloz (TB), HIV ile yaşayan bireyler (PWH) arasında morbidite ve mortalitenin önde gelen nedenlerinden biridir. HIV ve TB birlikteliği birbirlerinin patojenitesini güçlendirir ve immünolojik fonksiyonları bozar. Bu çalışmanın amacı, merkezimizde HIV+TB birlikteliğini öngören biyopsikososyal risk faktörlerini analiz etmektir.

Yöntem: Sağlık Bilimleri Üniversitesi, İzmir Tepecik Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği'nde 2019-2022 arasında takipli PWH'lerin kayıtları kullanılarak kesitsel retrospektif bir kohort çalışması yürüttük. TB gelişmesine etki eden risk faktörlerinin incelenmesinde de lojistik regresyon analizi kullanıldı. Sonuçlar, p-değerinin 0,05'ten küçük olduğunda istatistiksel olarak anlamlı kabul edildi.

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Öz

Bulgular: Çalışmadaki 73 HIV'le yaşayan bireyin 22'sinde (%30,1) TB birlikteliği mevcut olup yaş medyanı 40 (32-50) idi. Çok değişkenli lojistik regresyon analizinde başlangıç vücut kitle indeksi (VKİ) ve evde yaşayan kişi sayısının PWH'de TB ko-enfeksiyonu açısından bağımsız risk faktörleri olduğu belirlenmiştir. Başlangıç VKİ değerindeki her bir artışın 0,73 kat TB gelişmesini azalttığı görülürken (0,57-0,94, p=0,016), evde yaşayan kişi sayısındaki her bir kişilik artış TB gelişmesini 1,16 kat artırdığı görülmüştür (1,00-1,35, p=0,047).

Sonuç: TB çeşitli sosyal faktörlerin belirlediği bir hastalıktır. Bu çalışma, belirli özelliklere sahip PWH'lerin TB geliştirme riskinin daha yüksek olduğunu göstermektedir. Bu yüzden HIV+TB birlikteliğini öngören risk faktörlerini belirlemek için çok merkezli çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: HIV, ko-enfeksiyon, risk faktörleri, tüberküloz

Introduction

Tuberculosis (TB) is one of the leading causes of morbidity and mortality among people living with HIV (PWH). The co-existence of HIV and TB mutually reinforces their pathogenicity and disrupts their immunological functions. *Mycobacterium tuberculosis* accelerates the progression of AIDS in individuals with HIV[1].

Globally, it has been reported that in 2022, there will be 7.5 million newly diagnosed TB cases, leading to an estimated 1.3 million deaths, with 167.000 of them occurring in HIV-positive individuals[2]. In our country, TB incidence (12.000 cases) ranks first in Europe in terms of HIV-TB co-infection and mortality[2,3]. Although TB incidence in our country has decreased by 25% between 2015 and 2022, the incidence among HIV-positive individuals has increased by 0.22%. Furthermore, while TB mortality has decreased by 37% among HIV-negative individuals from 2015 to 2022, it has increased 2.5 times among HIV-positive individuals[2,4]. TB remains a primary cause of mortality among HIV-positive individuals in our country[3].

In Turkey, the rate of people diagnosed with TB who are known to be HIV-positive is 1.6%, and this rate has doubled in the last 5 years. Despite an increase in the rates of requesting HIV tests for known TB patients, it is observed that we lag proportionally behind when considering the estimated co-existence[5]. Of the individuals with HIV-TB co-infection in Turkey, 82% are under treatment for TB, and treatment success has been achieved in 62% of them[2,6].

Despite all available data, the rate of individuals living with HIV who underwent latent TB testing is determined to be 45%, and it is estimated that the rates of latent TB are higher in our country; however, there is insufficient data on the actual numbers[2,7].

TB is influenced by various social factors. When examining general risk factors for TB; smoking, alcohol consumption, diabetes, and HIV incidence are increasing in our country and worldwide. Among the risk factors, poverty has shown the most striking increase, having tripled in the last 5 years[8]. Due to the high incidence and mortality in our country, the co-infection of TB in individuals living with HIV is a worthwhile topic to investigate; however, there are relatively few studies available.

The aim of this study was to analyze the biopsychosocial risk factors predicting HIV-TB co-infection in our center.

Materials and Methods

Study Setting and Design

We conducted a retrospective cross-sectional cohort study using the electronic medical records of individuals with HIV followed up between 2019 and 2022 at the Infectious Diseases and Clinical Microbiology Clinic of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital. The inclusion criteria for the case group were confirmed HIV diagnosis, age 18 years and older, and inclusion of patients with bacteriologically confirmed TB coinfection[9]. For the selection of the control group, patients with confirmed HIV diagnosis, aged 18 years, with no known or suspected TB diagnosis, and patients in whom TB was excluded by microscopic/molecular/pathological or bacteriological methods were included. Subsequently, patients with no available data in the control group or those who were lost to follow-up were eliminated through secondary screening.

Study Definitions and Variables

The diagnosis of TB was based on clinical manifestations (fever, night sweats, weight loss), laboratory findings (acid-fast staining, adenosine deaminase), imaging results, pathological results (necrotic granulomatous reaction), and the positivity of Xpert MTB/RIF TB polymerase chain reaction or culture results (bacteriologically confirmed TB).

Subclassifications of clinical TB diagnoses were made in accordance with national/international guidelines[9,10].

Pulmonary TB: Used for TB affecting the lung parenchyma or the tracheobronchial tree.

Extrapulmonary tuberculosis (EPTB): Patients showing extrapulmonary organ involvement with demonstrated acid-fast bacilli (AFB) in samples taken from organs outside the lung parenchyma, along with histological and clinical evidence compatible with TB, fall into this category. Miliary TB is considered to be both pulmonary and EPTB. In the case of TB lymphadenitis in the mediastinum or hilum, it is designated as EPTB[9,10].

Variables included demographic data (gender, age, education level, marital status, monthly income level, household crowding, number of cohabitants), baseline weight and body mass index (BMI), smoking, alcohol consumption, drug use status, presence of comorbidities, tuberculin skin test (TST) results, history of latent TB prophylaxis, history of BCG vaccination, nadir and baseline $CD4^+$ T-lymphocyte count/percentage, and baseline HIV RNA results. The term "nadir $CD4^+$ T-lymphocyte" refers to the individual's measured lowest $CD4^+$ T-lymphocyte level. The education level was classified into five categories: Illiterate, primary school, secondary school, high school, and undergraduate and above. TST was performed using purified protein derivative, and the results were categorized as anergic (0 mm), 0-5 mm, 6-14 mm, and 15 mm and above. The monthly income level was categorized as 0-499 US dollars (USD), 500-999-USD, and 1000 USD and above. The term "Household crowding" was used for situations such as prisons, military barracks, refugee camps, and situations where three or more people live in the same room[11].

Statistical Analysis

Patient data collected within the scope of the study were analyzed using IBM Statistical Package for the Social Sciences (SPSS) for MacOS 29.0 (IBM Corp., Armonk, NY). Frequency and percentage were provided as descriptive values for categorical data, whereas median (interquartile range) was used for continuous data. The "Mann-Whitney U test" was employed for intergroup comparisons, and the "chi-square or Fisher's Exact test" was used for comparing categorical variables. Logistic regression analysis was used to examine the risk factors influencing the development of TB. Results were considered statistically significant when the p-value was 0.05.

The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee on May 4, 2023, with approval number 2023/03-19.

Results

Among the 73 individuals living with HIV included in the study, 22 (30.1%) had TB coinfection, with a median age of 40 years (32-50). Of the sample group, 26% were married. The average baseline BMI value for the patients was 22.9. Among the cases, 52.1% smoked and 43.8% consumed alcohol. Substance abuse was observed in 12.3% of cases, with marijuana and methamphetamine being the most commonly used. Comorbidities were present in 30.1% of the cases, with the most common being psychiatric disorders (9.6%), hyperlipidemia (6.8%), diabetes mellitus (5.5%), and hypertension (5.5%). When examining the social variables of our cohort, it was found that 38.4% had completed primary school education, the average number of cohabitants was 3.8 (min-max: 1-24), 12.3% lived in crowded households, and 87.7% had a monthly income below 1.000 USD.

In terms of clinical data, it is noteworthy that 69.9% of the cohort did not undergo the TST, 5.5% had results above 5 mm, and latent TB prophylaxis treatment was given to this group. In addition, 89% of our cohort had a history of BCG vaccination. Descriptive statistics for nadir/basal $CD4^+$ T-lymphocyte and baseline HIV RNA results and all other variables are detailed in Table 1.

HIV-infected individuals with TB coinfection were clinically subclassified, with pulmonary TB being the most common (77.3%). The frequencies are presented in Table 2 in descending order.

Univariate analysis revealed that low BMI at the time of diagnosis in HIV-infected individuals had a statistically significant effect on the presence of TB coinfection risk (odds ratio: 0.73, $p<0.001$). Furthermore, as the number of people living in the same household increased, the probability of TB presence increased by 1.08 times (0.97-1.21, $p=0.011$). When examining the $CD4^+$ T-lymphocyte levels of the cases, it was statistically significant that the decrease in the number of nadir $CD4^+$ T-lymphocytes and baseline $CD4^+$ T-lymphocytes increased the risk of TB/HIV coinfection in the univariate model (Table 3).

Table 1. Demographics and clinical findings of the patients

Variables	Total (n=73)	No tuberculosis (n=51)	Tuberculosis (n=22)	p-value
	n (%) or median (IQR)	n (%) or median (IQR)	n (%) or median (IQR)	
Gender				1.000
Male	66 (90.4)	46 (90.2)	20 (90.9)	
Female	7 (9.6)	5 (9.8)	2 (9.1)	
Age (years)	40 (32-50)	38 (31-50)	43 (32-52)	0.463
Baseline BMI	22.9 (20.7-25.6)	**24.1 (21.7-26.6)**	**19.4 (17.5-22.9)**	**<0.001**
Marital status				0.565
Married	26 (35.6)	18 (35.3)	8 (36.4)	
Single	38 (52.1)	28 (54.9)	10 (45.5)	
Divorced	9 (12.3)	5 (9.8)	4 (18.2)	
Education level				0.944
Primary school	28 (38.4)	19 (37.3)	9 (40.9)	
Secondary school	13 (17.8)	10 (19.6)	3 (13.6)	
High school	13 (17.8)	9 (17.6)	4 (18.2)	
University	19 (26)	13 (25.5)	6 (27.3)	
Number of households	2 (1-4)	**2 (1-3)**	**4 (2-6)**	**0.011**
Household crowding	9 (12.3)	5 (9.8)	4 (18.2)	0.439
Monthly income level (USD)				0.250
0-499	25 (34.2)	15 (29.4)	10 (45.5)	
499-999	39 (53.4)	28 (54.9)	11 (50)	
1000 and above	9 (12.3)	8 (15.7)	1 (4.5)	
Smoking	38 (52.1)	26 (51)	12 (54.5)	0.980
Alcohol consumption	32 (43.8)	23 (45.1)	9 (40.9)	0.941
Drug use	9 (12.3)	6 (11.8)	3 (13.6)	1.000
Comorbidity	22 (30.1)	13 (25.5)	9 (40.9)	0.299
DM	4 (5.5)	3 (5.9)	1 (4.5)	1.000
HT	4 (5.5)	3 (5.9)	1 (4.5)	1.000
Latent TB prophylaxis	4 (5.5)	2 (3.9)	2 (9.1)	0.579
PPD (mm)				0.458
Unknown	51 (69.9)	37 (72.5)	14 (63.6)	
0-5	18 (24.7)	12 (23.5)	6 (27.3)	
6-14	1 (1.4)	1 (2)	0 (0)	
≥15	3 (4.1)	1 (2)	2 (9.1)	
BCG vaccination	65 (89)	47 (92.2)	18 (81.8)	0.232
Nadir $CD4^+$ T-lymphocyte (cell/mm^3)	390 (119-602)	**448 (219-660)**	**164.5 (46-427)**	**0.004**
Baseline $CD4^+$ T- lymphocyte (cell/mm^3)	408 (168-620)	**448 (250-656)**	**172 (46-436)**	**0.009**
Baseline HIV RNA ($x10^3$) (copies/mm^3)	69.9 (18.3-343)	62.1 (5.21-261)	166.5 (40-545)	0.069

IQR: Interquartile range, BMI: Body mass index, BCG: Bacillus Calmette-Guérin, PPD: Purified protein derivative, USD: United States dollar, DM: Diabetes mellitus, HT: Hypertension, TB: Tuberculosis, *: p-value ≤0.05 is considered statistically significant

Table 2. Distribution of tuberculosis classes	
Tuberculosis diagnosis	**n (%)**
Pulmonary	17 (77.3)
Extra-pulmonary	10 (45.4)
Lymph node	4 (18.2)
Ileum	1 (4.5)
Renal	1 (4.5)
Pleura	2 (9.1)
Miliary	2 (9.1)
In one patient with diagnoses of renal, ileal, and lymph node tuberculosis, there was a co-occurrence of pulmonary tuberculosis	

Table 3. Examination of risk factors affecting tuberculosis coinfection in PWHs				
Variables	**Univariate**		**Multivariate**	
	Odds ratio (95% CI)	**p-value***	**Odds ratio (95% CI)**	**p-value***
Baseline BMI	0.73 (0.61-0.88)	<0.001	0.73 (0.57-0.94)	**0.016**
Number of households	1.08 (0.97-1.21)	0.011	1.16 (1.00-1.35)	**0.047**
Nadir $CD4^+$ T lymphocytes (cell/mm^3)	0.997 (0.995-0.999)	0.010	0.99 (0.98-1.00)	0.065
Baseline $CD4^+$ T lymphocytes (cell/mm^3)	0.998 (0.996-1.000)	0.038	1.01 (1.00-1.02)	0.070
CI: Confidence interval, BMI: Body mass index, PWH: People living with HIV, *: p-value ≤0.05 is considered statistically significant				

The distribution of risk factors affecting the development of TB in the multivariate logistic regression analysis within the scope of the study is presented in Table 3. Baseline BMI and the number of people living in the same household were independent risk factors for TB coinfection. While each increase in baseline BMI value reduced the development of TB by 0.73 times (0.57-0.94, p=0.016), each increase in the number of people living in the same household increased the development of TB by 1.16 times (1.00-1.35, p=0.047).

Discussion

In our study, the predictive variables for the development of TB in individuals living with HIV were identified as low BMI at the time of diagnosis and more people living in the same household.

When evaluated in terms of gender and age, no significant difference in the risk of TB infection was observed among HIV-positive individuals in our cohort. This finding is consistent with similar studies conducted in different settings worldwide[12]. However, there are also studies indicating that male gender and increased age contribute to the incidence of HIV-TB co-infection[13,14]. It is worth noting that the incidence of TB in the regions where these studies were conducted is several times higher than that in our country. Social and cultural dynamics may contribute to prolonged exposure and movement within the community, increasing exposure to the TB bacillus.

A study conducted among prisoners living in crowded conditions revealed that contrary to our study, alcoholism, smoking, and drug addiction are risk factors for TB/HIV coinfection. Our cohort did not include individuals with alcoholism. Moreover, the presence of these risk factors may be associated with increased vulnerability due to factors such as overcrowded prisons, insufficient food, high alcohol and drug consumption, and inadequate access to health services.

Similar to our study, recent findings from a study by Hanifa et al.[15] and another study by Suwanpimolkul et al.[13] have shown, respectively, that having a BMI below 18 and an initial weight below 50 kg significantly increases the risk of TB coinfection. Additionally, a research study with a methodology similar to ours demonstrated that each increase in BMI by 1 kg/m^2 reduces the development of TB coinfection by 0.9 times[16].

A large-scale meta-analysis suggested that conditions creating social vulnerability, such as low monthly income and many people living in the same household, increase the risk of HIV-TB co-infection[17]. In our study, only 12% of the study population had a monthly income above USD 1000, and it is possible that poverty did not create a difference

because this condition, which increases social vulnerability, was present in most of our cohort. However, as expected, many studies, including ours, concluded that an increase in the number of people in the household, which is a social situation that increases bacillus exposure, is a risk factor for HIV-TB co-existence.

Univariate analysis revealed that $CD4^+$ T lymphocyte levels, which are important for the individual's immune monitoring and immune system, increase the risk of TB coinfection. However, multivariate analysis showed that the immunological and virological status of the individual, including $CD4^+$ T- lymphocyte and HIV RNA levels, did not alter the risk of TB coinfection. Although this relationship was not significant in the multivariate analysis, studies suggest that individuals with suppressed immune systems are at a higher risk of developing TB[13,16,18]. This result could be attributed to the fact that our unit has extensive experience in HIV health services and has been successful in accessing and using the available resources. Furthermore, this discrepancy in the results among studies may be caused by unequal access to healthcare between countries.

Latent TB infection progresses to active TB disease more rapidly with suppressed immunity[19]. Despite the proven effectiveness of latent TB prophylaxis in reducing the risk of TB infection among people with HIV and the general population, our study did not observe any impact on the prevention of TB. The limited number of individuals receiving latent TB prophylaxis in our study may account for this result. In contrast to this study, other studies conducted in different geographical settings have indicated a significant impact on preventing TB coinfection[20,21].

The strength of this study lies in its execution within an experienced HIV healthcare clinic, which is co-located on the same campus as an actively managed TB sanatorium. This co-location contributes to high rates of HIV-TB co-infection.

Study Limitations

The study is cross-sectional and single-centered, potentially limiting the generalizability of the results due to constraints in the case set. Our research design is retrospective and relies on existing clinical records; thus, the results may be influenced by the possibility of undocumented additional clinical factors. In addition, the retrospective nature of the study prevented the screening of patients' family history of TB.

Conclusion

Given the high incidence and mortality rates of TB in our country, it remains a significant issue. Numerous studies indicate that TB is the leading cause of death among individuals living with HIV in our country. TB is influenced by various social factors. This study demonstrates that PWHs with specific characteristics are at a higher risk of developing TB. Among the individuals living with HIV, access to healthcare and individual's social opportunities influence the outcomes of our study. Considering all these data, multicenter studies from different regions predicting HIV-TB co-infection and interventions addressing it is needed.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee on May 4, 2023, with approval number 2023/03-19.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: İ.A., İ.Ö., E.D.Ö., S.A., Concept: İ.A., F.D., S.A., Design: İ.A., İ.Ö., E.D.Ö., F.D., S.A., Data Collection or Processing: İ.A., E.D.Ö., Analysis or Interpretation: İ.A., İ.Ö., F.D., Literature Search: İ.A., İ.Ö., E.D.Ö., Writing: İ.A., İ.Ö., F.D., S.A.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Ethical Perspective on Planned Clinical Trials; Non-interventional Local Ethics Committee Observation

Planlanan Klinik Araştırmalara Etik Bir Bakış Açısı; Girişimsel Olmayan Yerel Etik Kurulu Gözlemi

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Abstract

Objective: Clinical trials are an important tool for determining the efficacy and safety of medical treatments. They are scientific studies involving human volunteers and are conducted under the supervision of ethics committees. In recent years, many regulations and guidelines have been published to regulate clinical trials and set ethical standards for research.

Methods: In this study, the applications made to the Ethics Committee for Non-drug Clinical Research of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital were retrospectively analyzed. The general characteristics of the applications made to the Ethics Committee, approval and rejection rates, problems and criticisms frequently encountered during the review of the applications were evaluated and the data were analyzed using SPSS.

Results: It was found that most of the files reviewed were approved, but were subject to significant criticism. During the 4 years studied, it was found that the number of files submitted to the ethics committee and the rate of approved files increased each year. It was noted that most of the applications were single-center studies, but the budget requests were low and the scientific basis of the investigators was inadequate.

Conclusion: The findings suggest that investigators should pay more attention to methodology and improve the informed consent process. By addressing these deficiencies, clinical trials can be conducted according to ethical and scientific standards.

Keywords: Ethics committees, informed consent, research

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Öz

Amaç: Klinik araştırmalar, tıbbi tedavilerin etkinliği ve güvenilirliğinin belirlenmesi için önemli bir araçtır. Bu çalışmalar, gönüllü katılımcıların dahil olduğu bilimsel çalışmaları kapsar ve etik kurulların denetimi altında yürütülür. Son yıllarda, klinik araştırmaları düzenleyen birçok yönetmelik ve kılavuz yayımlanmıştır, bu da araştırmaların etik standartlarını belirlemiştir.

Yöntem: Bu çalışmada, Sağlık Bilimleri Üniversitesi, İzmir Tepecik Eğitim ve Araştırma Hastanesi İlaç Dışı Klinik Araştırmaları Etik Kurulu tarafından yapılan başvurular retrospektif olarak incelenmiştir. Etik kurula yapılan başvuruların genel özelliklerini, onaylanma ve reddedilme oranlarını, başvuruların incelenmesi sırasında sıkça karşılaşılan sorunları ve eleştirileri değerlendirilmiş ve veriler SPSS kullanılarak analiz edilmiştir.

Bulgular: İncelenen dosyaların çoğunun onay aldığı ancak önemli eleştirilere maruz kaldığı tespit edilmiştir. İncelenen 4 yıl boyunca etik kurula başvuran dosya sayısında ve onay alan dosya oranında her yıl artış olduğu belirlenmiştir. Başvuruların çoğunun tek merkezli çalışmalar olduğu, ancak bütçe taleplerinin az olduğu ve araştırmacıların bilimsel dayanaklarının yetersiz olduğu belirlenmiştir.

Sonuç: Bulgular, araştırmacıların metodolojiye daha fazla önem vermesi ve aydınlatılmış onam sürecini iyileştirmesi gerektiğini göstermektedir. Bu eksikliklerin giderilmesiyle, klinik araştırmaların etik ve bilimsel standartlara uygun olarak yürütülmesi sağlanabilir.

Anahtar Kelimeler: Etik kurullar, aydınlatılmış onam, araştırma

Introduction

Clinical trials are scientific studies involving voluntary participants to obtain medical knowledge and determine the safety and efficacy of new drugs, medical devices, and treatment methods[1-3]. These studies are conducted to develop potential new treatment methods and understand the effects and side effects of existing treatments. Participants can participate in clinical trials with their personal or legal permission. These trials are usually conducted with the permission of the Ministry of Health and the approval of institutional ethics committees in Turkey[4].

Recently, many guidelines and regulations on clinical trials have been published. In particular, the "Regulation on Pharmaceutical Research" published in 1993 and the "Good Clinical Practice Guide" published by the Ministry of Health in 1995 have been important guidelines for ethics committees[5,6]. Regulations issued in subsequent years have clarified the procedures for conducting and supervising clinical trials.

The main purpose of ethics committees is to protect the rights, safety, and welfare of clinical trial participants. According to the Declaration of Helsinki, these committees review the submitted research from an ethical and scientific perspective, follow the standards, and ensure compliance with the relevant legislation[7].

The "Ethics Committee for Non-drug Clinical Research" at the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital has been operating effectively since 2009. The committee acts in accordance with international ethical principles to support researchers and increase the speed of scientific studies[8-10].

In this study, a retrospective evaluation of applications to the ethics committee, determination of research tendencies of hospital staff, and presentation of relevant statistical data will be performed. This evaluation is intended to provide feedback to researchers and the international scientific community.

Materials and Methods

In this retrospective study, the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Non-drug Clinical Research Ethics Committee retrospectively evaluated 652 studies with a final decision between May 2014 and December 2017. The "file screening information form", which inquiries about the characteristics of the application files, was used as the data collection tool. The conduct and ethical aspects of the study were approved by the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital on September 17, 2018, with decision number 2018/08-14.

Statistical Analysis

SPSS 22 software (IBM Corporation, Armonk, New York, USA) was used for data analysis. Descriptive statistical measures, such as frequency and percentage distribution, were used to analyze the data. The authors' demographic information was categorized by specialty and the purpose of referral. All studies were classified and statistically evaluated according to eligibility, revision, unapproved, or refusal rates.

The data obtained from these methods were evaluated and statistically interpreted using number and percentage calculations. The results obtained in this manner were used to test the aim and hypotheses of the study.

Results

This study reviewed 652 files that met our ethics committee's criteria for file requests. All criteria were detailed by year (2014-2017) (Table 1). It was determined that 71.1% of the files did not have a budget request, 78.6% were single-center studies, 42.5% were retrospective file studies, and 23.1% were academic studies with survey content. When the distribution of the files submitted to the committee was analyzed according to the characteristics of the results, 74.3% of the files were accepted with approval (approval in the first application or approval after revision), while 22.1% were rejected. The rates of approval, rejection, revision, and unapproved applications by years are shown in Figure 1.

When the approved files were examined, it was found that 60.5% (395 files) of all files were approved in the first application and 90 (13.8%) of the 112 files that went to revision received re-revision or direct approval (Table 2). When the reasons for rejection were examined, it was observed that the method of the planned study was not appropriate due to the application of out-of-scope studies to the ethics committee and there was an inconsistency between the method and informed consent.

The analysis of the criticisms resolved by the ethics committee is presented in Table 3, and 79.5% of the criticisms were method-related. Among the method-related criticisms, 27% were related to inadequate statistical analyses, 19.6% to sampling errors, 15.9% to inadequate explanations in the conduct of the study, 11.6% to insufficient information about data collection tools (e.g., assessment of validity and reliability of scales), and 10.2% to insufficient understanding of the method. In the same table, 68.4% of the criticisms were related to the content of the informed consent. It was observed that 13.9% of the criticisms related to the content of the informed consent included incorrect explanations, 12% excluded sufficient explanations about the surveys, applications, and procedures to be performed, 11.3% included explanations that were in the informed consent given to the participants but were not related to the study, and 9.2% used too many medical terms in the information. It was found that 15.9% of the files did not clearly explain the contribution of the study to science, its purpose, scientific basis, originality, and significance. When evaluated under some technical deficiencies, 10.6% of the files did not properly collect and submit the training approved forms, data collection forms, and commitment and consent control forms of the research unit (Table 3).

Table 1. Characteristics of the files submitted to the committee

		2014			2015			2016			2017			Total	
		n	%	Year %	n	%	Year %	n	%	Year %	n	%	Year %	n	%
Research levels (center/ discipline)	Single center-single discipline	**30**	37.5	17.1	**48**	44.4	27.4	**42**	31.3	24	**55**	33.7	31.4	**175**	**36.1**
	Single center-multidisciplinary	**46**	57.5	22.2	**41**	38	19.8	**68**	50.7	32.9	**52**	31.9	25.1	**207**	**42.7**
	Multi-centered-single discipline	**3**	3.7	7.9	**11**	10.1	28.9	**10**	7.5	26.3	**14**	8.6	36.8	**38**	**7.8**
	Multicenter-multidisciplinary	**1**	1.3	1.8	**8**	7.4	14.5	**14**	10.4	25.5	**32**	19.6	58.1	**55**	**11.3**
Research technique	Survey	**24**	30	21.4	**30**	27.7	26.8	**18**	13.4	16.1	**40**	24.5	35.7	**112**	**23.1**
	Scanning files	**41**	51.3	19.9	**51**	47.2	24.8	**67**	50	32.6	**47**	28.8	22.8	**206**	**42.5**
	Sample collection (Blood-urine-tissue, etc.)	**9**	11.3	6.5	**22**	20.4	15.8	**43**	32.1	30.9	**65**	39.9	46.8	**139**	**28.7**
	Nursing practices	**6**	7.5	21.4	**5**	4.6	17.9	**6**	4.5	21.4	**11**	6.7	39.3	**28**	**5.8**
Type of research	Academic	**71**	88.8	16.4	**97**	89.8	22.4	**124**	92.5	28.6	**141**	86.5	32.6	**433**	**89.3**
	Postgraduate	**9**	11.3	17.3	**11**	10.1	21.1	**10**	7.5	19.2	**22**	13.5	42.3	**52**	**10.8**
Research budget	Demanding	**21**	26.3	15	**30**	27.7	21.4	**47**	35.1	33.6	**42**	25.8	30	**140**	**28.9**
	No demand	**59**	73.8	17.1	**78**	72.2	22.6	**87**	65	25.2	**121**	74.2	35.1	**345**	**71.1**
	Total	**80**	100	16.5	**108**	100	22.3	**134**	100	27.6	**163**	100	33.6	**485**	**100**

Discussion

This study presents a retrospective evaluation of 652 applications submitted to the Ethics Committee for Non-drug Clinical Research of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital between 2014 and 2017. The results include the general characteristics of the applications submitted to the Ethics Committee, approval and rejection rates, problems frequently encountered during the review of the applications, and criticisms.

According to the results of our study, most files reviewed were single-center, retrospective, or survey-based academic studies without budget requests. This result shows that researchers reveal their preferences in terms of easier academic work in our country. In addition, it may be related to the fact that academics in our country have to provide health services during most of their daily working hours and that academic budget support is insufficient[11,12].

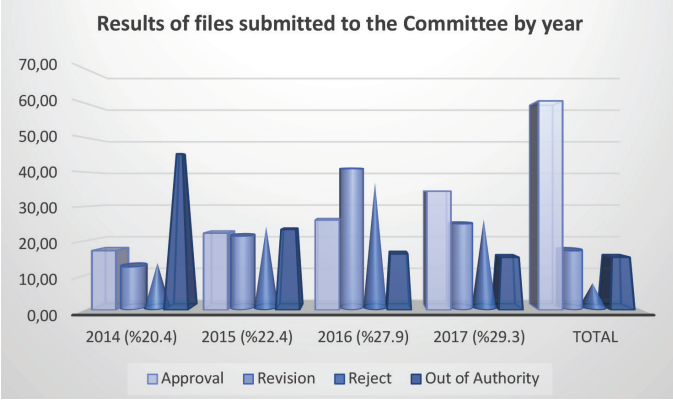

Figure 1. Results of files submitted to the committee by year

Table 2. Follow-up of files with revision decision

	n	%
Re-revision	32	28.8
Reject	22	19.2
Approval	58	51.7
Total	112	100

The majority of applications submitted to the ethics committee were accepted, but the number of rejected applications was also significant. Among the reasons for rejected applications, ethical and methodological problems, such as inappropriate methodology of the study and inconsistency between informed consent and methodology, come to the fore. In addition, an examination of the criticisms resolved by the ethics committee showed that methodological criticisms were in the majority, and a significant proportion of these criticisms included issues such as inadequacy of statistical analyses, faulty sampling, and inadequate explanations in the conduct of the research. These findings underscore the need to increase the level of methodological and statistical knowledge among researchers[9,13].

The study found that a significant proportion of the files had an inadequate scientific basis and that the importance of the study was not clearly indicated by its title and content. In addition, technical deficiencies such as the lack/inadequacy of the study's data collection forms should also be addressed. This suggests that researchers did not sufficiently prepare and review scientific resources during the planning stages of their studies. The difficulty of free access to scientific resources for conducting research may have led to these results[14,15].

The informed consent process is also an important part of the study and has often been criticized. In particular, problems such as inadequate explanations in the informed consent documents and lack of accurate information to participants

Table 3. Classification of file review

Reviews	Prominent review*	n	%
Respect for the field of expertise	Lack of expert involvement in data interpretation	32	26.2
Purpose	The purpose statement does not reflect the study	25	20.5
Budget	Inadequate budget disclosure, lack of funding	21	17.2
Study title	Unintentional, long title	16	13.1
Survey	Lack of clarity of the questionnaires, inadequacy in filling time	14	11.5
Research timeline plan	Inconsistency in study start and end dates, insufficient time	8	6.6
Study group plan	Lack of randomization, bias	6	4.9
Total		122	100

*: Files received multiple review

have come to the fore. The importance of this issue has been emphasized in many similar studies and sources[16,17].

The strength of this study is that evaluating the activities of the ethics committee for non-drug clinical trials is an important step to ensure that clinical trials comply with ethical and methodological standards. Our findings suggest that more attention should be paid to the training needs of investigators and ethical regulations. Thus, clinical trials can be conducted by ethical and scientific standards.

Study Limitations

A limitation of our study was that the reasons for criticism of the studies could not be evaluated from the investigators' perspectives. The research motivations and reasons for criticism/shortcomings could not be detailed. In addition, the lack of similar studies in our country limits our ability to make local comparisons.

Conclusion

Most of the files reviewed by the ethics committee were accepted, but there were some important criticisms. Researchers should pay more attention to the methodology and manage the informed consent process more carefully.

Ethics

Ethics Committee Approval: In this retrospective study, the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Non-drug Clinical Research Ethics Committee retrospectively evaluated 652 studies with a final decision between May 2014 and December 2017. The "file screening information form", which inquiries about the characteristics of the application files, was used as the data collection tool. The conduct and ethical aspects of the study were approved by the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital on September 17, 2018, with decision number 2018/08-14.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: İ.A., Concept: İ.A., B.G.S., F.D., Design: İ.A., Ş.K., Data Collection or Processing: İ.A., F.D., Analysis or Interpretation: İ.A., Ş.K., B.G.S., Literature Search: İ.A., Ş.K., B.G.S., F.D., Writing: İ.A., Ş.K., B.G.S., F.D.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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FIB-4 Index: Potential Predictor of Mortality in COVID-19 Patients

FIB-4 İndeksi: COVID-19 Hastalarında Potansiyel Ölüm Öngörücüsü

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Abstract

Objective: To evaluate the predictive value of the fibrosis-4 (FIB-4) index for mortality among patients with Coronavirus disease-2019 (COVID-19).

Methods: This retrospective study included 325 patients diagnosed with COVID-19 via reverse transcription-polymerase chain reaction at a tertiary care hospital from January 2021 to January 2022. We calculated the FIB-4 index using age, aspartate aminotransferase, alanine aminotransferase, and platelet count. Data on demographics, clinical characteristics, comorbid conditions, and outcomes were analyzed.

Results: Patients were categorized into survivors (56.6%, n=184) and non-survivors (43.4%, n=151). The median FIB-4 index was significantly higher in non-survivors [4.02 interquartile range (IQR) 2.48-8.62)] than in survivors [2.57 (IQR 1.69-3.95)], p<0.001. ROC analysis showed that the FIB-4 index had a moderate predictive accuracy for mortality (area under the curve =0.693). A FIB-4 index cut-off of >3.80 provided the best balance between sensitivity (53.90%) and specificity (74.46%).

Conclusion: The FIB-4 index serves as a reliable predictor of mortality in patients with COVID-19, surpassing traditional liver function tests in prognostic accuracy. It offers a practical tool for the early identification of patients at higher risk of adverse outcomes.

Keywords: COVID-19, FIB-4 index, mortality

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) hastalarında fibrozis-4 (FIB-4) indeksinin mortalite açısından öngörücü değerini değerlendirmek.

Yöntem: Bu retrospektif çalışmaya Ocak 2021 ile Ocak 2022 arasında üçüncü basamak bir hastanede gerçek zamanlı-polimeraz zincir reaksiyonu ile COVID-19 tanısı konan 325 hasta dahil edildi. FIB-4 indeksi yaş, aspartat aminotransferaz, alanin aminotransferazve trombosit sayısı kullanarak hesaplandı. Demografik özellikler, klinik özellikler, komorbid durumlar ve sonuçlara ilişkin veriler analiz edildi.

Bulgular: Hastalar hayatta kalanlar (%56,6, n=184) ve hayatta kalmayanlar (%43,4, n=151) olarak kategorize edildi. Medyan FIB-4 indeksi hayatta kalanlarda [4,02 (çeyrekler arası aralık (ÇAA) 2,48-8,62)], hayatta kalanlara [2,57 (ÇAA 1,69-3,95)] kıyasla anlamlı derecede yüksekti, p<0,001. ROC analizi, FIB-4 indeksinin mortalite için orta düzeyde bir tahmin doğruluğuna sahip olduğunu gösterdi (eğri altında kalan alan =0,693). FIB-4 indeks kesme noktası >3,80, duyarlılık (%53,90) ve özgüllük (%74,46) arasındaki en iyi dengeyi sağladı.

Sonuç: FIB-4 indeksi, prognostik doğruluk açısından geleneksel karaciğer fonksiyon testlerini geride bırakarak, COVID-19 hastalarında mortalitenin güvenilir bir tahmincisi olarak hizmet vermektedir. Olumsuz sonuç riski daha yüksek olan hastaların erken tespiti için pratik bir araç sunar.

Anahtar Kelimeler: COVID-19, FIB-4 indeksi, mortalite

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Introduction

The Coronavirus disease-2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has posed unprecedented health challenges globally[1-3]. Since its emergence in late 2019, the virus has led to significant morbidity and mortality, requiring the medical community to identify reliable predictors that can guide patient management and improve outcomes[4,5]. Among the predictors investigated, the severity of infection and mortality rates have shown marked variability, influenced by a host of demographic, clinical, and biological factors[6-8].

Various scoring systems have been employed to predict outcomes in patients with COVID-19, underlining the necessity for accurate prognostic tools in managing the disease[9-11]. Among these, liver function, as reflected in parameters like fibrosis scores, has emerged as a critical element. The Fibrosis-4 (FIB-4) index, originally developed to assess liver fibrosis in patients with hepatitis C, has gained attention for its potential utility in other clinical settings[12]. This index, which incorporates age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count, offers a practical tool to assess liver fibrosis. Recent studies have suggested that FIB-4 could also serve as a significant prognostic marker in patients with COVID-19, potentially correlating with disease severity and mortality[13].

The current study aimed to evaluate the predictive value of the FIB-4 index for mortality among COVID-19 patients.

Materials and Methods

This retrospective cohort study was conducted at a tertiary care hospital's emergency department from January 2021 to January 1, 2022. This study was approved by the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (number: 2023/514/255/4, date: 09.08.2023). The study encompassed all patients aged 18 years who presented to the emergency department and were diagnosed with COVID-19 based on a positive reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2. Eligible participants included all patients who tested positive for COVID-19 via reverse transcription-polymerase chain reaction during the study period. The exclusion criteria were patients under the age of 18, patients with liver disease, and those without complete medical records available for review.

Data were retrospectively collected from the hospital's electronic health records. The variables extracted included demographic information (age and gender), laboratory results, comorbid conditions, admission to intensive care units, and in-hospital mortality. These data elements were used to assess the severity of the disease and its outcomes in the study population.

The FIB-4 index was calculated for each patient using the following formula:

$$(age \times AST) / (platelets \times \sqrt{(ALT)})$$

Statistical Analysis

Statistical analyses were performed using SPSS software for Windows (Version 29, Chicago, IL, USA). Descriptive statistics will be used to summarize the demographic and clinical characteristics of the patients. The primary outcome of this analysis will be to assess the predictive power of the FIB-4 index for in-hospital mortality. To further evaluate the diagnostic performance of the FIB-4 index, receiver operating characteristic (ROC) curve analysis will be conducted. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the FIB-4 index at optimal cut-off values determined from the ROC analysis will also be reported. A p-value of 0.05 will be considered statistically significant.

Results

After applying the inclusion and exclusion criteria, the study was completed with 325 participants. The patients were divided into two groups: Survivors (56.6%, n=184) and non-survivors (43.4%, n=151). Various characteristics of the patients are summarized in Table 1. There was no statistically significant difference in median age between survivors [73.3 (interquartile range (IQR) 68-81)] and non-survivors [75 (IQR 68.4-81)] (p=0.379). No significant differences were observed in gender ratios between the groups (p=0.184).

While no significant difference was noted in median systolic blood pressure between the groups (p=0.598), a statistically significant higher median diastolic blood pressure was observed in the survivor group [72 (IQR 70-80) mmHg] compared with the non-survivor group [70 (IQR 65-80) mmHg] (p=0.019). The survivor group exhibited a significantly lower median pulse rate [83 (IQR 75-91) beats per minute] than the non-survivor group [95 (IQR 79-105) beats per minute (p<0.0019). Oxygen saturation was also significantly lower in the non-survivor group [92 (IQR 85-96) %] compared to the survivor group [95 (IQR 92-97) %] (p<0.001). No significant difference was found in the median body temperature between the groups (p=0.072).

Table 1. Comparison of various characteristics between the groups			
	Survivors (n=184)	**Non-survivors (n=141)**	**p-value**
Age (years)	73.3 (68-81)	75 (68.4-81)	0.379
Gender (man)	90 (50%)	81 (57.4%)	0.184
Systolic blood pressure (mmHg)	120 (110-135.25)	129 (110-144)	0.598
Diastolic blood pressure (mmHg)	72 (70-80)	70 (65-80)	0.019
Pulse (beats/min)	83 (75-91)	95 (79-105)	<0.001
SpO_2	95 (92-97)	92 (85-95)	<0.001
Body temperature (°C)	36.7 (36.2-37.2)	36.8 (36.4-37.5)	0.072
Chronic obstructive pulmonary disease	17 (9.2%)	17 (12.1%)	0.411
Diabetes mellitus	61 (33.2%)	38 (27%)	0.229
Hypertension	83 (45.1%)	53 (37.6%)	0.173
Congestive heart failure	12 (6.5%)	21 (14.9%)	0.013
Chronic renal failure	7 (3.8%)	19 (13.5%)	0.001
White blood cells (10^9/L)	6.3 (5-8.7)	8.4 (6.3-12.4)	<0.001
Neutrophil (10^3/uL)	4.5 (3.2-6.8)	6.8 (4.7-10.4)	<0.001
Lymphocite (10^3/mm^3)	1 (0.6-1.4)	0.8 (0.6-1.2)	0.034
Hemoglobin (g/dL)	12.5 (11.5-13.4)	11.8 (9.9-13.1)	0.005
Platelet (10^9/L)	195 (152-264)	217 (171-288)	0.023
Blood urea nitrogen (mg/dL)	44 (31-57)	64 (43-93)	<0.001
Albumin (g/dL)	34 (30-37)	32 (29-36)	<0.001
Aspartate aminotransferase (IU/L)	29 (22-41)	52 (36-97.5)	<0.001
Alanine aminotransferase (IU/L)	19 (12-33)	20 (13-33)	0.833
Creatinine (mg/dL)	0.87 (0.71-1.06)	1.11 (0.8-1.82)	0.004
Intensive care unit admission	19 (10.3%)	82 (58.2%)	<0.001
Fib-4 score	2.57 (1.69-3.95)	4.02 (2.48-8.62)	<0.001

When evaluating comorbid conditions, no significant differences were observed between the groups in the prevalence of chronic obstructive pulmonary disease, diabetes mellitus, hypertension, and coronary artery disease (respectively; p=0.411, p=0.229, p=0.173, p=0.447). However, the incidence of chronic kidney disease and congestive heart failure was significantly higher in the non-survivor group (respectively; p=0.013, p=0.001).

The non-survivor group had significantly higher median values of white blood cell count, neutrophils, platelets, urea, AST, and creatinine compared with the survivor group (respectively; p<0.001, p<0.001, p=0.023, p<0.001, p<0.001, p=0.004). Conversely, median lymphocytes, hemoglobin, and albumin were significantly higher in the survivor group (respectively; p=0.034, p=0.005, p<0.001). No significant difference was observed in the median ALT levels between the groups (p=0.833).

The median FIB-4 score was significantly lower in the survivor group [2.57 (IQR 1.69-3.95)] than in the non-survivor group [4.02 (IQR 2.48-8.62)] (p<0.001) as shown in Figure 1.

The area under the receiver operating characteristic curve for the FIB-4 score predicting mortality was 0.693 [95% confidence interval (CI) 0.640-0.743] (p<0.001). At the optimal cut-off value for the FIB-4 score (>3.80) based on the Youden index, the sensitivity was 53.90 (95% CI 45.3-62.3), specificity was 74.46 (95% CI 67.5-80.6), PPV was 2.11 (95% CI 1.58-2.82), and NPV was 0.62 (95% CI 0.51-0.75) as depicted in Figure 2, Table 2).

Discussion

The FIB-4 index, as demonstrated in this study, offers significant predictive value for mortality among COVID-19 patients. This aligns with the growing body of literature suggesting the role of liver function metrics in

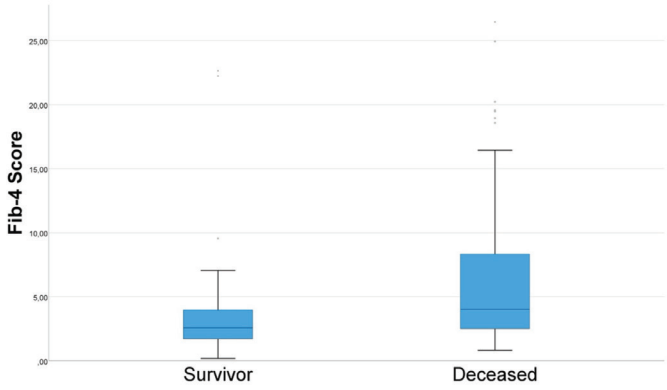

Figure 1. Comparison of Fib-4 scores between the groups

Fib-4: Fibrosis-4

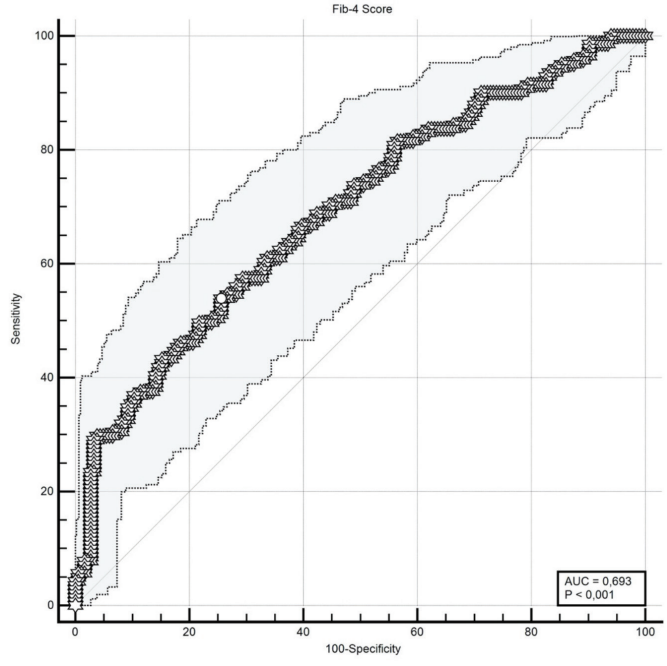

Figure 2. Area under the curve (AUC) analysis of the Fib-4 score in mortality prediction

Fib-4: Fibrosis-4

understanding the progression and outcomes of COVID-19. The pathophysiological linkage between liver dysfunction and COVID-19 may be attributed to the direct cytopathic effects of SARS-CoV-2 and systemic inflammation, leading to hepatocyte injury and altered liver enzyme levels.

Recent studies have reinforced this association. For instance, Pranata et al.[14] in their meta-analysis reported a strong correlation between higher FIB-4 scores and increased mortality rates in COVID-19 patients, with a calculated odds ratio significantly indicating worse outcomes. Similarly, Bucci et al.[15] found that a FIB-4 score greater than 3.25 was significantly associated with increased mortality, underscoring its utility over traditional liver transaminases and the AST-to-platelet ratio index for mortality prediction in emergency settings.

These findings are pivotal, considering the high prevalence of abnormal liver tests observed in COVID-19 patients, which has been widely reported as a marker of severe disease. For example, elevated levels of AST and ALT, which are components of the FIB-4 calculation, have been consistently linked with poor outcomes in these patients. The mechanism likely involves the systemic inflammatory response triggered by the virus, which not only impacts lung tissue but also affects the liver. This systemic inflammation, often referred to as a "cytokine storm," can intensify underlying liver conditions, thereby increasing the FIB-4 score[16-18].

However, the literature also presents some variability in the predictive accuracy of FIB-4 across different cohorts and settings. This variability can be partly attributed to differences in patient demographics, baseline liver health, and stage of COVID-19 at presentation. For instance, in settings with a high prevalence of underlying chronic liver diseases, the predictive value of FIB-4 may differ, as shown by studies that specifically looked at patients with conditions like non-alcoholic fatty liver disease[19].

Given the significant role of liver dysfunction in COVID-19 prognosis, FIB-4 serves not only as a tool for assessing liver fibrosis but also as a broader indicator of patient vulnerability

Table 2. Predictive performance of the Fib-4 score in terms of severity in COVID-19 patients

AUROC (95% CI)	Youden J	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
0.693 (0.640-0.743)	0.283	>3.809	53.9 (45.3-62.3)	74.46 (67.5-80.6)	2.11 (1.58-2.82)	0.62 (0.51-0.75)

AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, AUROC: Area under the receiver operating characteristic, CI: Confidence interval, COVID-19: Coronavirus disease-2019, Fib-4: Fibrosis-4

to severe outcomes. This dual utility makes the FIB-4 index a valuable component of the clinical assessment tool in managing COVID-19, particularly in stratifying patients based on risk and optimizing resource allocation.

Study Limitations

This study, while comprehensive, is not without limitations. The retrospective nature and single-center design may limit the generalizability of the findings. In addition, the inherent biases associated with retrospective data collection and the potential for missing data could affect the accuracy of the FIB-4 scores and subsequent analyses. Future studies should validate these findings in a larger, multicenter cohort with a prospective design to mitigate these limitations.

Conclusion

The FIB-4 index is a robust predictor of mortality in COVID-19 patients, offering a simple, non-invasive measure of liver dysfunction and overall disease severity. This index could be particularly useful in emergency departments and other acute care settings to rapidly identify patients at a higher risk of severe outcomes, thereby guiding more targeted interventions and supportive care strategies.

Ethics

Ethics Committee Approval: This retrospective cohort study was conducted at a tertiary care hospital's emergency department from January 2021 to January 1, 2022. This study was approved by the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (number: 2023/514/255/4, date: 09.08.2023).

Informed Consent: Written informed consent was not necessary because no patient data have been included in the manuscript.

Authorship Contributions

Surgical and Medical Practices: G.A.U., Concept: G.A.U., Design: G.A.U., Data Collection or Processing: İ.U., Analysis or Interpretation: İ.U., Literature Search: İ.U., Writing: G.A.U., İ.U.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Identification of Corin and Procalcitonin in Endometrial Flushing Fluid Between Women with Polycystic Ovary Syndrome, Endometrioma, Unexplained Subfertility, and Fertile Healthy Women

Polikistik Over Sendromu, Endometrioma, Açıklanamayan Subfertilite ve Fertil Sağlıklı Kadınlarda Endometriyal Yıkama Sıvısında Corin ve Prokalsitonin Belirlenmesi

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Abstract

Objective: Endometrial receptivity is a critical factor in achieving successful implantation; however, the precise molecular mechanisms underlying this process remain unclear. This study aimed to assess and compare the levels of corin and procalcitonin in the endometrial flushing fluid among women with unexplained infertility, polycystic ovary syndrome (PCOS), endometrioma, and fertile healthy women in relation to endometrial receptivity.

Methods: A study was undertaken on a cohort of women aged 20 to 40 from January 2013 to June 2015. The study cohort comprised 20 women diagnosed with unexplained subfertility, 20 women diagnosed with PCOS, and 20 women diagnosed with endometrioma. Additionally, a control group of 20 healthy fertile women was included. Corin and procalcitonin levels were assessed in endometrial flushing fluid from all patients during the implantation window, and compared between the different groups.

Results: Mean levels of corin (ng/mL) were 0.45, 0.54, 0.46, and 0.49 for PCOS, unexplained subfertility, endometrioma, and control groups, respectively (p=0.341). Mean levels of Procalcitonin (pg/mL) were 76.79, 112.21, 75.57, and 90.41 for PCOS, unexplained subfertility, endometrioma, and control groups (p=0.098). The corin and procalcitonin levels were seen to be lower in the PCOS and endometriosis groups in comparison to the control group. Nevertheless, this difference did not achieve statistical significance.

Conclusion: Understanding the molecular and biochemical aspects of endometrial receptivity can provide valuable insights for diagnosis and treatment. Further research is needed to elucidate the underlying mechanisms and establish the clinical relevance of corin and procalcitonin for endometrial receptivity.

Keywords: Corin, endometrial receptivity, procalcitonin, polycystic ovary syndrome, unexplained subfertility

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Öz

Amaç: Endometrial reseptivite, başarılı implantasyonun sağlanmasında kritik bir faktördür; ancak bu sürecin altında yatan kesin moleküler mekanizmaları belirsizliğini korumaktadır. Bu çalışma, açıklanamayan infertilitesi, polikistik over sendromu (PKOS), endometrioma ve fertil sağlıklı kadınlarda endometrial reseptivite ile ilişkili olarak endometrial yıkama sıvısındaki corin ve prokalsitonin düzeylerini değerlendirmeyi ve karşılaştırmayı amaçlamıştır.

Yöntem: Ocak 2013 ile Haziran 2015 tarihleri arasında 20-40 yaş arası kadınlardan oluşan bir kohorta çalışma yapıldı. Çalışma grubu açıklanamayan subfertilite tanısı alan 20 kadın, PKOS tanısı alan 20 kadın ve endometrioma tanısı alan 20 kadından oluşuyordu. Ayrıca 20 sağlıklı fertil kadından oluşan bir kontrol grubu da dahil edildi. İmplantasyon penceresi sırasında tüm hastaların endometrial yıkama sıvısında corin ve prokalsitonin seviyeleri değerlendirildi ve gruplar arasında karşılaştırıldı.

Bulgular: Corin düzeyleri (ng/mL) PKOS, açıklanamayan subfertilite, endometrioma ve kontrol gruplarında sırasıyla 0,45, 0,54, 0,46 ve 0,49 idi (p=0,341). PKOS, açıklanamayan subfertilite, endometrioma ve kontrol gruplarında ortalama prokalsitonin düzeyleri (pg/mL) 76,79, 112,21, 75,57 ve 90,41 olarak belirlendi (p=0,098). PKOS ve endometriozis gruplarında corin ve prokalsitonin düzeylerinin kontrol grubuna göre daha düşük olduğu görüldü. Ancak bu fark istatistiksel anlamlı düzeyde değildi.

Sonuç: Endometrial reseptivitenin, moleküler ve biyokimyasal yönlerini anlamak, tanı ve tedavi için değerli bilgiler sağlayabilir. Altta yatan mekanizmaları aydınlatmak ve corin ile prokalsitoninin endometrial reseptivite açısından klinik ilişkisini belirlemek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Croin, endometriyal reseptivite, prokalsitonin, polikistik over sendromu, açıklanamayan subfertilite

Introduction

Infertility is a complex and multifactorial condition affecting the reproductive system of a significant proportion of couples worldwide. According to data gathered worldwide from 1990 to 2021, the World Health Organization approximates that around 1 in 6 people has encountered infertility at least once in their lifetime[1]. The establishment of pregnancy relies on the successful implantation process, which involves a complicated sequence of interactions between different types of cells in the uterus and the blastocyst. Endometrial receptivity is the capacity of the uterine lining to receive and support an early-stage embryo, leading to a viable pregnancy. The synchronization of embryonic development and endometrial differentiation is crucial, thus establishing a distinct and temporary phase during which implantation can occur. This period is usually known as the "implantation window"[2]. Endometrial receptivity refers to the precise coordination of molecular, cellular, and structural changes in the endometrium to create an environment suitable for the implantation of an embryo. Endometrial receptivity is controlled by various variables, including hormone receptors, pro-inflammatory cytokines, and endometrial decidualization-related factors[3]. Understanding the molecular and biochemical aspects of reproductive health can provide valuable insights for diagnosis and treatment.

The uterine microenvironment and its primary constituent, the endometrial fluid, have a significant impact on reproductive success by affecting sperm motility within the uterus and fallopian tubes, as well as embryo development and implantation processes[4]. Understanding the biochemical differences in endometrial flushing fluid may contribute to the development of targeted diagnostic and therapeutic approaches for these conditions.

Corin is a transmembrane serine protease predominantly located in the heart. Its primary role is to convert the precursor peptide pro-atrial natriuretic peptide (ANP) into the active form of ANP. This conversion leads to the stimulation of natriuresis, diuresis, and vasodilation[5]. Corin has been identified in the pregnancy uterus, where it has a significant function in facilitating trophoblast invasion and spiral artery remodeling to provide sufficient uteroplacental perfusion[6]. Uterine artery perfusion in healthy women has been observed to enhance throughout the luteal phase, which aligns with the period of implantation[7]. Based on these studies, it appears that corin may be efficacious during the implantation period and in enhancing endometrial receptivity. Nevertheless, the role of corin as a biomarker in human endometrial receptivity throughout the implantation stage remains undetermined.

Procalcitonin is a 116-amino acid polypeptide that serves as the precursor to the calcitonin hormone. It is secreted by neuroendocrine C-cells in the thyroid gland and K-cells in the lung, as well as several cell types and organs, in reaction to pro-inflammatory stimulation[8]. It acts as a marker for sepsis and bacterial infection[9]. Although there have been studies examining procalcitonin levels in cervicovaginal secretions for preterm rupture of membranes[10,11], no research has been identified regarding the involvement of procalcitonin in endometrial receptivity.

This study aims to explore the levels of corin and procalcitonin in the endometrial flushing fluid of women with unexplained infertility, polycystic ovary syndrome (PCOS), endometrioma, and compare them to fertile healthy women during the implantation window.

Materials and Methods

Study Design

This cross-sectional controlled trial was performed in the infertility outpatient clinic of İzmir Katip Çelebi University, Atatürk Training and Research Hospital, Obstetrics and Gynecology Clinic from January 2013 to June 2015. The study design adhered to the ethical principles of the Helsinki Declaration and appropriate clinical practice, and received approval from the Local Ethical Committee (number: 2013-198).

Participants

All individuals involved in the study provided informed consent, including healthy controls and patients. The study involved 80 participants aged 20-40 years old, split into four groups. The first group comprised 20 patients diagnosed with PCOS based on the ESHRE Rotterdam 2003 criteria. The second group consisted of 20 individuals diagnosed with endometriosis using a clinical interview, physical examination, and transvaginal ultrasound using the Medison Sono Ace X8 from Seoul, South Korea. The third group comprised 20 individuals with unexplained subfertility who had undergone a basic infertility evaluation following the diagnostic criteria of the American College of Obstetricians and Gynecologists. The fourth group, serving as the control group, also consisted of 20 participants[12]. The control group comprised healthy women without any gynecologic problems. They were not utilizing an intrauterine device or hormonal contraception, and they were not consuming any prescription that could impact the endometrium.

Sample Collection

Patients who wished to voluntarily withdraw from the study, were pregnant, smoked, exhibited symptoms of pelvic infection, or had luteal phase serum progesterone levels less than 3 ng/dL were excluded from the research. After ovulation was confirmed by measuring blood progesterone levels during the implantation window, an endometrial fluid sample was obtained using a procedure similar to the saline infusion sonography method in both the study and control groups. A bivalve disposable speculum was introduced into the vagina, followed by the insertion of a menstrual-regulating cannula (4 mm in diameter) into the uterine cavity via the cervical canal. Using a syringe, 5 mL of sterile 0.154 mol/L sodium chloride saline solution was instilled into the uterine cavity. The contents of the uterus were aspirated rapidly. The endometrial fluid samples were collected in a standard microtest tube (Eppendorf, Hamburg, Germany) and the samples were then stored at a temperature of -80 °C. After obtaining endometrial fluid samples from every patient, the concentrations of corin and procalcitonin were determined using BioTek ELISA devices equipped with Eastbiopharm (Hangzhou Eastbiopharm Co. Ltd./China) ELISA kits [Human Procalcitonin (PCT) ELISA Kit and Human Corin (CRN) ELISA Kit]. During the whole collection of data procedure for all patients, the exact same kits were consistently employed for the same markers.

Statistical Analysis

A statistical analysis was conducted utilizing IBM SPSS Statistics 21.0 for Windows (SPSS Inc., Chicago, IL). In contrast with categorical variables, which are denoted by numbers (n) and percentages (%), numeric variables are represented by the median or mean. Shapiro-Wilks and Levene's tests were utilized to assess normality. Parametric MANOVA was not preferred over non-parametric analysis due to the skewed nature of the data. Comparisons of variables between groups were conducted using the Kruskal-Wallis H test. Pairwise comparisons were performed using Mann-Whitney U tests when the differences between groups were deemed statistically significant. Statistical significance was assigned to values less than 0.05.

Results

Table 1 contains the demographic information and serum progesterone levels of the subjects. Although there was no statistically significant distinction between the endometrioma group and the control group, there was a statistically significant distinction in terms of age only between the unexplained subfertility group and the endometrioma group in all other comparisons. The average ages of patients diagnosed with PCOS, unexplained subfertility, endometriosis, and the control group were 29.3, 28.15, 33.15, and 32.15, respectively. The PCOS group had the greatest body mass index (BMI) of 27.15 kg/m^2, whereas the endometrioma group had the lowest BMI of 23.35 kg/m^2. Furthermore, there was no statistically significant disparity in BMI when comparing the three groups with the control group, as well as when comparing any two groups. All

groups exhibited demographic similarity, with the exception of gravidity and parity. The serum progesterone levels (ng/mL) during the mid-luteal phase were similar across the unexplained subfertility (10.1), PCOS (10.06), and control groups (8.75). Nevertheless, the group with endometrioma exhibited notably reduced levels (5.85) (Table 1).

Table 2 presents the distribution of corin and procalcitonin levels in the endometrial flushing fluid across the three groups of gynecologic disorders, as well as the control group. Mean levels of corin (ng/mL) in endometrial flushing fluid were 0,45, 0,54, 0,46, and 0,49 for PCOS, unexplained subfertility, endometrioma, and control groups, respectively (Table 2). Nevertheless, there were no notable disparities that reached statistical significance (p=0.341). Mean levels of procalcitonin (pg/mL) in endometrial flushing fluid were 76,79, 112,21, 75,57, and 90,41 for PCOS, unexplained subfertility, endometrioma, and control groups, respectively. Procalcitonin levels were found to be lower in the PCOS and endometriosis groups compared to the control group; however, this distinction did not reach statistical significance (p=0.098). Furthermore, according to the data presented in Table 3, there was no statistically significant disparity observed in any of the pairwise comparisons when comparing corin levels between the paired groups. For procalcitonin level, this marker was notably lower in the PCOS (76,79) and endometrioma (75,57) patients relative to the unexplained subfertility in pairwise comparisons between all groups (p<0.05) (Table 3).

Discussion

We identified the presence of midluteal corin and procalcitonin expression in the endometrial flushing fluid of all the groups in this prospective and cross-sectional study. While the levels of corin and procalcitonin were found to be lower in the PCOS and endometrioma groups compared to the control group, the difference was not statistically significant.

Infertility is a significant clinical problem observed in patients with unexplained infertility, polycystic ovarian disease, and endometrioma. However, the underlying causes of infertility in these patients have not been fully understood. Nevertheless, the findings indicate that a crucial pathophysiological aspect is the compromised receptivity in the endometrium, which subsequently affects implantation. Various factors contribute to infertility, and understanding the molecular and biochemical aspects of reproductive health can provide valuable insights for diagnosis and treatment. Benign gynecological diseases such as endometriosis,

Table 1. Demographic, laboratory and clinical characteristics of the groups

	PCOS (n=20)	US (n=20)	End (n=20)	Control (n=20)	p-value*
Age (year)	29.3±5.36	28.15±4.56	33.15±6.65	32.15±5.18	**0.012**
BMI (kg/m^2)	27.15±5.55	23.37±3.97	23.35±4.09	24.93±3.67	0.057
Gravida (n)	0.55±0.6	0.5±1	1±1.21	3.75±1.77	**0.000**
Parite (n)	0.4±0.6	0.2±0.52	0.85±1.04	2.9±1.37	**0.000**
Progesteron (ng/mL)	10.06±4.5	10.1±5.25	5.85±3.06	8.75±3.67	**0.003**

Values are presented as mean ± standard deviation, *: Kruskal-Wallis test, BMI: Body mass index, PCOS: Polycystic ovary syndrome, US: Unexplained subfertility, End: Endometrioma

Table 2.The distribution of corin and procalcitonin levels among groups

	PCOS (n=20)	US (n=20)	End (n=20)	Control (n=20)	p-value*
Corin (ng/mL)	0.45±0.2	0.54±0.16	0.46±0.16	0.49±0.18	0.341
Procalcitonin (pg/mL)	76.79±44.94	112.21±58.39	75.57±30.55	90.41±44.63	0.098

Values are presented as mean ± standard deviation, *: Kruskal-Wallis test, BMI: Body mass ındex, PCOS: Polycystic ovary syndrome, US: Unexplained subfertility, End: Endometrioma

Table 3. The comparison of corin and procalcitonin levels between the two groups*

	PCOS vs. control	US vs. control	End vs. control	PCOS vs. US	PCOS vs. End	US vs. End
Corin (ng/mL)	0.534	0.297	0.626	0.133	0.797	0.104
Procalcitonin (pg/mL)	0.304	0.239	0.330	0.029	0.735	0.040

*: Mann-Whitney U test, PCOS: Polycystic ovary syndrome, US: Unexplained subfertility, End: Endometrioma

hydrosalpinx, and PCOS are linked to reduced fertility and altered endometrial receptivity functions[13]. A recent study has demonstrated that individuals with PCOS have changes in endometrial receptivity. This suggests that the presence of hyperandrogenism, as well as insulin resistance and obesity, may contribute to reduced embryo implantation and unfavorable pregnancy outcomes[14]. A study conducted in patients with PCOS revealed that insulin resistance had an impact on both endometrial function and the process of implantation[15]. Following a thorough assessment of infertility, the root cause of infertility remains unknown to around 15% of women[16]. Unexplained infertility may be attributed to disruptions in molecular and cellular indicators that play a role in endometrial receptivity[17]. In a comparable manner, in women affected by these illnesses, infertility may be attributed to issues concerning endometrial receptivity and its capacity to facilitate implantation. Hence, we selected these conditions that could potentially hinder endometrial receptivity while designing our study.

Corin, well known for its role in regulating blood pressure by the activating ANP[6,18,19], was shown to be expressed in the uterus of pregnant mice and humans, which is interesting[20]. Following these discoveries, investigations were initiated to explore the potential roles of corin within the pregnant uterus. Recently, it has been demonstrated that the expression of corin is increased in the uterus during pregnancy. In this context, corin and ANP play a role in enhancing trophoblast invasion and remodeling of spiral arteries[6,21]. Furthermore, in this study, given that corin seems to be exclusive to the secretory phase, its existence in endometrial glands and subsequent secretion into the uterine lumen suggest that corin produced by endometrial glands may contribute to endometrial receptivity and the interaction between blastocysts and the endometrium. Therefore, apart from its putative function in facilitating trophoblast invasion, it may also have a role in the initial phases of gestational implantation[21]. Pregnant mice that lack corin and ANP experience impaired remodeling of spiral arteries, resulting in gestational hypertension and proteinuria, which resemble the phenotype of preeclampsia[6,22,23]. Preeclamptic women have been found to exhibit decreased quantities of corin messenger RNA (mRNA) and protein, as well as harmful corin variations[6,24,25]. Recent transcriptome studies comparing mammalian species indicate that corin is expressed specifically in a group of cells within the endometrial stromal lineage. This expression may play a role in the development of profound placental invasion and significant modification of spiral arteries[26]. Progesterone therapy consistently elevated the expression of corin in ovariectomized mice[27]. Corin and ANP were observed to facilitate a series of molecular and cellular processes in uterine decidualization and spiral artery remodeling, as demonstrated by investigations involving mouse models and cultured human uterine cells[28]. Corin has been found to be present in the endometrium throughout the late secretory phase in non-pregnant individuals, as well as in the implantation sites of early human pregnancies. Additionally, its expression is increased through the process of *ex vivo* decidualization[21]. During the embryonic invasive phase, communication between the uterine stromal cells and trophoblasts may regulate the controlled breakdown of proteins and immune responses. This helps protect both the embryo and the mother from harm[29]. Specifically, the lack of successful trophoblastic invasion into the musculoelastic layer of the spiral arteries has been demonstrated to cause incomplete transformation of the blood vessels and consistently elevated resistance in the uterine arteries[30]. Furthermore, in these studies, given that corin seems to be exclusive to the secretory phase, its existence in endometrial glands and subsequent secretion into the uterine lumen suggest that corin produced by endometrial glands may contribute to endometrial receptivity and the interaction between blastocysts and the endometrium. Hence, apart from its putative function in facilitating trophoblast invasion, it might also play a role in the initial phases of gestational implantation. In our study based on this hypothesis, we detected the presence of corin in the endometrial flushing fluid during the implantation window period. We also found decreased corin levels in two groups with infertility that may cause endometrial receptivity disorders, such as PCOS and endometriosis. However, the lower levels in our collective were not statistically significant. These findings may serve as a starting point for future investigations aimed at elucidating the mechanism by which corin contributes to endometrial receptivity and infertility. Nevertheless, additional investigations on corin biology in implantation and early pregnancy may provide information on potential therapeutics aiming at enhancing implantation quality in early pregnancies. And it could potentially lessen the likelihood of pregnancy issues from poor implantation.

Procalcitonin is the precursor form of calcitonin, a hormone that is predominantly synthesized by the C-cells located in the thyroid gland and is generated by various cell types in response to pro-inflammatory triggers[31]. In addition to infectious diseases, we sought to determine their association

with endometrial receptivity in the context of fertility and reproductive health in the present study. We hypothesized that procalcitonin may play a role in the immune modulation and inflammation associated with the implantation process. Immune factors are crucial in establishing an environment that is favorable for embryo implantation, and procalcitonin may contribute to this immunomodulation. Calcitonin is intermittently secreted by the uterine epithelia throughout the implantation phase[32,33]. Embryo implantation rates in rats are substantially reduced when calcitonin expression is inhibited during the preimplantation phase; furthermore, exogenous calcitonin administration may stimulate implantation subsequent to embryo transfer[34]. Procalcitonin is the precursor form of calcitonin, has not been assessed in the literature as a marker of endometrial receptivity during the luteal phase. During the implantation window, we examined and demonstrated the presence of procalcitonin levels in the endometrial flushing fluid secreted into the uterine lumen. Additionally, procalcitonin levels were found to be lower in the PCOS and endometriosis groups compared to the control group; however, this distinction did not reach statistical significance.

Study Limitations

Recognizing the limits of our research, particularly the comparatively limited number of participants, is crucial. Further investigations involving larger cohorts of patients are crucial in order to enhance the dependability of these measures. Another limitation is the discrepancies in baseline demographic data among groups and the failure to utilize infertility as a criterion for classifying patients into distinct categories of benign gynecological conditions. Unfortunately, the existing constraints make it challenging to establish a clear connection between the levels of these indicators and endometrial receptivity, therefore hindering the acquisition of a conclusive outcome. However, we have not found any studies in the literature examining the relationship between corin and procalcitonin and endometrial receptivity, and conducting research on this subject is among the strengths of our study. Additionally, it is the initial study to demonstrate the existence of corin and procalcitonin in the fluid obtained from the endometrium at the specific time frame of implantation.

Conclusion

Implantation failure is a persistent issue in the field of reproductive medicine and is recognized as a significant factor contributing to infertility in women who are otherwise in good health. The discovery of biomarkers that indicate endometrial receptivity not only yields insights into the molecular processes that govern implantation, but also enables the development of novel therapeutic interventions aimed at enhancing endometrial receptivity. This, in turn, will help mitigate the financial burden and time constraints involved with the treatment of affected women. Although initial findings indicate a possible correlation, additional investigation is required to clarify the fundamental processes at play and establish the clinical significance of corin and procalcitonin in evaluating endometrial receptivity.

Ethics

Ethics Committee Approval: The study received ethical approval from the Local Ethics Committee of İzmir Katip Çelebi University, Atatürk Training and Research Hospital (number: 2013-198).

Informed Consent: Informed consent was obtained from patients who participated in this study.

Authorship Contributions

Surgical and Medical Practices: Z.Ş., S.A., Concept: Z.Ş., S.A., Design: S.A., Z.Ş., S.K., M.D., G.S., Data Collection or Processing: M.D., G.S., F.O.T., Analysis or Interpretation: Z.Ş., S.A., B.Y., F.O.T., Literature Search: Z.Ş., B.Y., M.D, Writing: Z.Ş., S.A., M.D.

Conflict of Interest: The authors affirm the absence of any conflicting interests.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Exploring the Effect of Aspirin on Preeclampsia Clinic: Does It Make Any Difference Even If It Does Not Prevent the Disease?

Aspirinin Preeklampsi Kliniğine Etkisinin Araştırılması: Hastalığı Önlemese Bile Kliniği Hafifletiyor Mu?

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Abstract

Objective: To find out whether there is a benefit in aspirin prophylaxis for alleviating the adverse outcomes of preeclampsia even if it would not prevent the disease. Preeclampsia is one of the major complications of pregnancy, which has life-long consequences for the mother and the baby. For the past few decades, aspirin prophylaxis has taken attention as a prevention method. However, it does not ensure the prevention of the disease. This study investigated whether aspirin still has a beneficial effect in easing the clinic even if it does not prevent the disease.

Methods: This retrospective study includes 541 preeclamptic patients in a tertiary center. The patients were allocated into two groups: Those who took aspirin prophylaxis during pregnancy (study group) and those who didn't (control group). Maternal clinical parameters, complications of preeclampsia, and fetal/neonatal outcomes were compared between the groups.

Results: No significant difference was found in clinical parameters suggesting preeclampsia with severe features. HELLP syndrome was significantly higher in the study group. Maternal complications like eclampsia, renal failure, pulmonary edema, disseminated intravascular coagulation, abruptio placenta, and transfusion of blood products didn't differ between the groups. Neonatal outcomes were significantly worse in the study group.

Conclusion: In this study, aspirin was not found to improve maternal and neonatal outcomes in an already established preeclampsia clinic. However, the imbalance in maternal baseline risk profile remarkably affected the results. Future studies with larger sample sizes and groups with comparable risk profiles should be conducted.

Keywords: Preeclampsia, aspirin, maternal complications, perinatal outcomes

Öz

Amaç: Hastalığı önlemese bile preeklampsinin maternal ve fetal olumsuz sonuçlarını hafifletmede aspirin profilaksisinin bir faydası olup olmadığının araştırılmasıdır. Preeklampsi, anne ve bebek için yaşam boyu sonuçları olan, gebeliğin en önemli komplikasyonlarından biridir. Aspirin, erken preeklampsiyi önlemede etkisi kanıtlanmış bir yöntem olarak klinik uygulamaya girmiştir. Ancak hastalığın önlenmesini garanti etmez. Bu çalışmada aspirinin hastalığı önleyemediği olgularda bile hastalığın maternal ve fetal kliniği iyileştirmede faydalı etkisinin olup olmadığı araştırılmıştır.

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Öz

Yöntem: Bu, üçüncü basamak bir merkezdeki 541 preeklamptik hastayı içeren retrospektif bir çalışmadır. Hastalar gebelikte aspirin profilaksisi alanlar (çalışma grubu) ve almayanlar (kontrol grubu) olmak üzere iki gruba ayrıldı. Gruplar arasında annenin klinik parametreleri ve preeklampsinin komplikasyonları ile fetal/neonatal sonuçlar karşılaştırıldı.

Bulgular: Ciddi özellikler gösteren preeklampsiyi düşündüren klinik parametrelerde anlamlı farklılık saptanmadı. HELLP sendromu çalışma grubunda anlamlı olarak daha yüksekti. Eklampsi, böbrek yetmezliği, akciğer ödemi, yaygın damar içi pıhtılaşma, plasenta dekolmanı, kan ürünleri transfüzyonu gibi maternal komplikasyonlar gruplar arasında farklılık göstermedi. Çalışma grubunda neonatal sonuçlar anlamlı derecede daha kötüydü.

Sonuç: Bu çalışmada, preeklampsi gelişmiş olan hastalarda hastalığın aspirin profilaksisi altında gelişmiş olmasının maternal, fetal, neonatal sonuçları iyileştirdiği bulunamamıştır. Ancak maternal bazal risk profilindeki, ko-morbiditelerdeki dengesizlik sonuçları önemli ölçüde etkilemiştir. Gelecekte eşit risk profiline sahip gruplarla geniş örneklem sayılı çalışmalar yapılmalıdır.

Anahtar Kelimeler: Preeklampsi, aspirin, maternal komplikasyon, perinatal sonuçlar

Introduction

Preeclampsia (PE) is a multisystemic disorder that affects 2-8% of pregnancies, accounting for 10 million pregnant women worldwide per year[1]. It causes significant maternal and perinatal morbidity and mortality. It has lifelong consequences such as chronic hypertension, renal failure, cardiovascular and cerebrovascular diseases for the mother. Additionally, for the baby, the risk of chronic diseases related to prematurity or fetal growth restriction, such as cerebral palsy, neurodevelopmental impairment, respiratory diseases, hypertension, insulin resistance, obesity, cardiovascular diseases, and renal dysfunction, is increased[2]. For many years, numerous studies have been conducted to identify those women who are at risk of PE, and to invent preventative treatments for those women[3]. Despite the algorithms that can detect 96% of the cases who require delivery <34 gestational weeks for preeclampsia, and the well-proved preventative effect of aspirin, which can reduce preterm PE by 62%, the prevalence of the disease has not been changed dramatically for the last few decades[3,4]. This fact raises two main questions: What factors reduce the preventional effect of aspirin? Is there any beneficial effect of aspirin on maternal and perinatal outcomes, even if it cannot prevent the development of preeclampsia?

This study aims to compare the maternal and perinatal outcomes between those patients who develop PE while under treatment with aspirin and those who develop PE while not being treated with aspirin. The second aim is to identify the characteristics of the patients that reduce the effect of aspirin on preventing preeclampsia.

Materials and Methods

This retrospective observational cohort study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Zeynep Kamil Women and Children Diseases Training and Research Hospital (approval date: 10.05.2023, no: 79). It was conducted following the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000. Informed consent stating that the data can be used for scientific purposes has been routinely provided from all the patients who applied to the clinic. It was conducted in the Maternal Fetal Medicine clinic of a single tertiary center. Patients diagnosed with PE in the antepartum, intrapartum, or postpartum period between January 2020 and December 2023 were retrospectively recruited via electronic patient records. Exclusion criteria were as follows: Multiple pregnancies, adolescent pregnant, intrauterine fetal infections, chromosomal or structural fetal anomalies, patients with known heart disease or hemorrhagic diatheses, Coronavirus disease-2019 infection during pregnancy, obstetric complications resulting in preterm delivery irrelevant to PE (preterm premature rupture of membranes, placental insertion or invasion anomalies, cholestasis, uncontrolled diabetes, spontaneous preterm delivery, etc.). Obstetric history, conception method, personal and familial medical history, use of tobacco, alcohol, and other substances, laboratory results, peripartum clinical findings, and peripartum maternal, fetal, and neonatal complications were obtained from the hospital's electronic records and manual patient charts. Regarding the laboratory results, the 24-hour-urine protein level in the last week of the antepartum period, antepartum hemoglobin on the day of delivery, and postpartum count of blood cells, liver, and renal function tests in the first 6 hours of the postpartum period were recorded for the analyses.

Patients were divided into two groups: Those not prescribed aspirin during pregnancy (control group) and those under aspirin prophylaxis (study group). Maternal demographic data associated with risk of PE, clinical data during

the hospital follow-up, peripartum laboratory results, peripartum maternal complications related to PE, and fetal and neonatal outcomes were compared between the two groups.

Statistical Analysis

Categorical variables are expressed as frequency (n) and percentage (%), and continuous variables are expressed as mean, standard deviation, median, minimum and maximum value. Normality behaviors were assessed with the Kolmogorov-Smirnov test. In comparisons between the two groups, the Mann-Whitney U test was used when the normality level was not met, and the Independent Samples t-test (Independent Samples t-test) was used when it was met. Associations between categorical variables were assessed by chi-square/Fisher's Exact analysis. IBM SPSS.25 program was used in all analyses, and $p<0.05$ was accepted as the significance level.

Results

A total of 670 patients with PE were identified, and 541 of them were included. Table 1 demonstrates the demographic and clinical features of the entire cohort. It was remarkable that 38.3% of the cohort had a family history for hypertension, and 14% had chronic hypertension.

Table 2 shows clinical data and complications related to PE in the current pregnancy for the entire cohort.

A total of 157 patients were included in the study group, and 384 cases were included in the control group. Table 3 summarizes the comparison of demographic data and medical history of the two groups. Maternal age, body mass index, artificial reproductive techniques pregnancy, diabetes, chronic hypertension, history of preeclampsia, and history of preterm PE were significantly higher in the study group. Comparison of the laboratory results revealed that there was no significant difference between the groups in terms of antepartum and postpartum hemoglobin levels, decline in the hemoglobin level after the delivery, postpartum thrombocyte, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, uric acid, creatinine level. Twenty-four-hour-urine protein level was higher in patients who were not under aspirin prophylaxis, yet it did not reach statistical significance ($p=0.060$).

Table 4 demonstrates the comparison of clinical data of the current pregnancy and complications associated with preeclampsia. The need for antihypertensive therapy was higher, and the GW at which antihypertensive medications were first administered was earlier in the study group. Antepartum hospitalization was longer in the study group, whereas the postpartum hospitalization period was similar between the groups. None of the clinical criteria suggesting PE with severe features was different between the patients who were under aspirin prophylaxis and those who were not. Except for HELLP and the need for cesarean section (C/S), none of the complications related to PE were different between the groups. HELLP and C/S were significantly lower in the control group. Interestingly, uterine atony bleeding was lower in the aspirin group.

Regarding neonatal outcomes, GW at birth, birth weight, and APGAR score at 1st minute were significantly higher, and the neonatal intensive care unit (NICU) hospitalization period was shorter in the control group. NICU admission and LBW rates were slightly lower in the control group, although not statistically significant. Neonatal mortality was significantly higher in the study group. Composite adverse neonatal outcomes were similar between the groups (Table 5).

Table 1. Demographic data, obstetric and non-obstetric medical history of the entire cohort

	n	Mean ± SD	Median (min-max)
Age	541	31.27±6.11	31.00 (19.00-44.00)
Gravidity	541	2.57±1.70	2.00 (1.00-13.00)
Parity	541	1.04±1.28	1.00 (0.00-9.00)
BMI	541	32.61±5.52	31.60 (19.90-50.70)
	n	**%**	
Tobacco/substance consumption	39	7.2	
Family history of HT	207	38.3	
ART pregnancy	26	4.8	
GDM/DM	99	18.3	
Pregestational DM	22	0.04	
Autoimmune disease/APAS	9	1.7	
Chronic hypertension	75	14	
Chronic renal disease	1	0.2	
History of PE	122	22.6	
History of preterm PE	36	6.7	

BMI: Body mass index, ART: Artificial reproductive techniques, HT: Hypertension, GDM: Gestational diabetes mellitus, DM: Diabetes mellitus, APAS: Antiphospholipid antibody syndrome, PE: Preeclampsia, SD: Standard deviation

Table 2. Clinical data and complications related to preeclampsia in the current pregnancy			
	n	**Mean ± SD**	**Median (min-max)**
MAP (mmHg)*	541	108.83±12.43	106.67 (73.33-147.33)
SBP (mmHg)*	541	144.92±17.75	140.00 (100.00-200.00)
DBP (mmHg)*	541	90.78±11.21	90.00 (60.00-130.00)
Duration of antenatal hospitalization (days)	541	3.42±5.91	1.00 (0.00-41.00)
Duration of postnatal hospitalization (days)	541	3.75±2.01	3.00 (2.00-35.00)
GW at diagnosis	541	34.16±4.22	35.00 (19.00-41.00)
	n		**%**
Antihypertensive medication	252		46.6
Antihypertensive medication before 20 GWs	67		26.6
PE with severe features	402		74.3
SBP ≥160 mmHg	148		27.4
SDP ≥110 mmHg	40		7.4
FGR	171		31.6
Amniotic fluid volume abnormalities	77		14.4
Neurologic symptoms	242		44.8
GIS symptoms	79		14.6
HELLP	39		7.2
Eclampsia	10		1.8
Abruptio placenta	43		7.9
Fetal distress	146		27.0
Fetal demise	14		2.6
Need for transfusion of blood products	31		5.7
Uterine atony	23		4.3
DIC	3		0.6

*: Data on the day of first hospitalization, MAP: Mean arterial pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GW: Gestational weeks, PE: Preeclampsia, FGR: Fetal growth restriction, GIS: Gastrointestinal system, DIC: Disseminated intravascular coagulation, SD: Standard deviation

Discussion

A significant number of studies have been conducted to illuminate the pathophysiology of preeclampsia. A great body of evidence has been accumulated about the prediction of high-risk patients and preventative methods to reduce the incidence of the disease[5-7]. PE can be defined as a syndrome in which multiple overlapping pathways lead to systemic inflammation and endothelial cell activation, resulting in endothelial damage, platelet aggregation, and thrombosis in maternal circulation and placenta[6]. Aspirin has been proposed to block the cascade by selectively inhibiting cyclooxygenase-1, resulting in a reduction of thromboxane A2, which is responsible for activating and aggregating platelets, endothelial damage, and thrombosis[3]. ASPRE trial proved that administration of daily 150 mg aspirin initiated before 16th GW reduced preterm PE by 62% in high-risk patients[8].

It is obvious that aspirin prophylaxis does not prevent all PE cases, and lots of pregnancies are still complicated with PE despite aspirin. In fact, according to a hypothesis that was supported by a secondary analysis of ASPRE, aspirin does not prevent it, but it delays the onset of PE[9].

Looking from a different point of view, in this study, we questioned whether being under aspirin prophylaxis during pregnancy mitigates the severity of the disease, maternal complications, and fetal/neonatal adverse outcomes in the case of preeclampsia, or not. Given the common pathophysiology of PE and placenta-associated adverse outcomes, it was anticipated that even if aspirin could not prevent preeclampsia, the clinic and perinatal complications

Table 3. The comparison of maternal characteristics, medical and obstetric history of the groups

	Control group (n=384) ASA (-)		Study group (n=157) ASA (+)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p
Age[a]	30.83±6.33	30.00 (19.00-44.00)	32.35±5.41	33.00 (19.00-44.00)	0.006
Gravidity[a]	2.44±1.73	2.00 (1.00-13.00)	2.87±1.61	3.00 (1.00-9.00)	<0.001
Parity[a]	1.02±1.34	1.00 (0.00-9.00)	1.11±1.11	1.00 (0.00-4.00)	0.077
BMI[a]	32.18±5.40	31.20 (19.90-50.70)	33.64±5.70	32.95 (22.50-49.40)	0.003
	n	%	n	%	
Tobacco/substance use[b]	30	7.9	9	5.8	0.398
ART[b]	9	2.3	17	10.8	<0.001
Familial history of HT/ PE[b]	141	36.7	66	42.0	0.248
GDM/DM[b]	60	15.6	39	24.8	0.012
Autoimmune disease[c]	6	1.6	3	1.9	0.723
Chronic HT[b]	25	6.6	50	31.8	<0.001
APAS[c]	1	0.3	3	1.9	0.076
Chronic renal disease[c]	0	0.0	1	0.6	0.291
History of PE[b]	54	14.1	68	43.3	<0.001
History of preterm PE[b]	10	2.6	26	16.6	<0.001

BMI: Body mass index, ART: Artificial reproductive techniques, GDM: Gestational diabetes mellitus, DM: Diabetes mellitus, HT: Hypertension, APAS: Antiphospholipid antibody syndrome, PE: Preeclampsia, SD: Standard deviation, [a]: Mann-Whitney test, [b]: Chi-square test, [c]: Fisher's Exact test

of PE should have been mitigated in those preeclamptic patients under aspirin prophylaxis compared to those who are not.

No significant difference was detected in maternal complications and severity of PE except for HELLP syndrome. Unexpectedly, the incidence of HELLP syndrome was higher in the aspirin group despite the expectations in favor of the aspirin group given the mechanism of action, which increases the ratio of endothelial prostacyclin to platelet thromboxane providing better vascular endothelial functions and anti-thrombosis[10]. It can be speculated that the endothelial damage had already begun before the onset of PE in this group because 41.9% required antihypertensive medications before the 20th week of pregnancy or before the pregnancy at all. Moreover, since the long-term negative cardiovascular effect of a previous PE is well-proved in the literature, the higher rate of PE history in the study group supports the above-mentioned "already damaged vascular endothelium" statement[11]. The higher rate of C/S in the study group was a consequence of higher gravidity and higher rate of previous C/S history; therefore, it should not be regarded as a complication of preeclampsia.

The fact that the study group (aspirin group) had a higher maternal age, gravidity, and a higher burden of chronic diseases like obesity, chronic hypertension, and diabetes had an extreme impact on the results. This was expected as the study group mostly consisted of patients who had been prescribed aspirin as they were deemed high-risk for PE due to those underlying co-morbidities in association with vasculopathy.

In a secondary analysis of the ASPRE trial, Shen et al.[12] reported that there was no prophylactic effect of aspirin for preventing preterm PE in high-risk risk patients with chronic hypertension compared to those who did not have chronic hypertension. Thus, they detected that chronic hypertension was strongly associated with the development of preterm PE despite aspirin prophylaxis[12]. In our study group, 31.8% of the patients had known chronic hypertension, and 41.9% needed antihypertensive therapy before the 20th GW, suggesting that a considerable amount of patients in this group had chronic vasculopathy which might have negatively affected the perinatal outcomes via uteroplacental insufficiency, irrespective of PE status. GW at birth, birth weight, APGAR score at 1st minute, NICU admission, and neonatal mortality were significantly higher in the study group despite aspirin prophylaxis. A previous

Table 4. Comparison of clinical data of the current pregnancy and complications related to preeclampsia

Parameters	Control group (n=384) (ASA -)		Study group(n=157) (ASA+)		
	Mean ± SD	**Median (min-max)**	**Mean ± SD**	**Median (min-max)**	**p**
MAP*[a] (mmHg)	108.44±11.83	106.67 (73.33-133.33)	109.77±13.79	110.00 (80.00-147.33)	0.433
SBP*[a]	144.35±17.22	140.00 (100.00-200.00)	146.32±18.99	140.00 (110.00-200.00)	0.491
DBP*[a]	90.49±10.65	90.00 (60.00-120.00)	91.49±12.49	90.00 (60.00 - 130.00)	0.546
Anti-hypertensive medications[b]	147	38.3	105	66.9	<0.001
Anti-hypertensive medications <20 GW[b]	23	15.6	44	41.9	<0.001
Onset of anti-hypertensive medications (GW)[a]	28.50±10.40	32.00 (0.00-40.00)	19.94±11.85	24.00 (0.00-38.00)	<0.001
Antenatal hospitalization duration (days)[a]	2.63±4.71	1.00 (0.00-32.00)	5.36±7.82	2.00 (0.00-41.00)	<0.001
Postpartum hospitalization duration (days)[a]	3.64±1.21	3.00 (2.00-12.00)	4.01±3.21	3.00 (2.00-35.00)	0.671
GW at diagnosis	34.91±3.63	36.00 (24.00-41.00)	32.33±4.97	33.00 (19.00-41.00)	<0.001
	n	**%**	**n**	**%**	
PE with severe features[b]	284	74.0	118	75.2	0.772
SBP ≥160 mmHg	102	26.6	46	29.3	0.517
DBP ≥110 mmHg[b]	25	6.5	15	9.6	0.219
Neurologic symptoms	170	44.3	72	46.2	0.690
GIS symptoms[b]	53	13.8	26	16.7	0.393
Pulmonary edema	5	0.01	2	0.012	1.00
HELLP[b]	22	5.7	17	10.8	0.037
Eclampsia[c]	7	1.8	3	1.9	1.00
Abruptio placenta[b]	32	8.3	11	7.0	0.605
IUFD[c]	12	3.1	2	1.3	0.370
FGR[b]	114	29.7	57	36.3	0.133
Fetal distress[b]	99	25.8	47	29.9	0.323
C/S[b]	313	81.5	147	93.6	<.001
Transfusion of blood products[b]	24	6.3	7	4.5	0.416
Atony[b]	21	5.5	2	1.3	0.028
DIC[c]	3	0.8	0	0.0	0.560

MAP: Mean arterial pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GW: Gestational weeks, PE: Preeclampsia, FGR: Fetal growth restriction, IUFD: Intrauterine fetal demise, GIS: Gastrointestinal system, DIC: Disseminated intravascular coagulation, C/S: Caesarean section, SD: Standard deviation, [a]: Mann-Whitney U test, [b]: Chi-square test; [c]: Fisher's Exact test, *: Mean blood pressure in the day of hospitalization

meta-analysis reported that aspirin prophylaxis initiated before 16 GW reduces the incidence of FGR, perinatal mortality, and PTB compared to no treatment or placebo[13]. ASPRE trial also suggested a reduction in perinatal death rates and LBW[8]. However, the studies either overestimated the intervention's effect size or underpowered for secondary outcomes. To our knowledge, no study in the literature reports the effect of aspirin on perinatal outcomes, excluding the impact of established preeclamptic status. In this study, the earlier GW at birth in the study group was the main reason for worse neonatal outcomes in the aspirin group compared to the control group. Regarding the "delay theory", which suggested that aspirin provided a 4.4 weeks delay in the gestational age at delivery for those who would have been delivered at 24 weeks if not treated with aspirin, we can speculate that aspirin might have provided positive

Table 5. Comparison of neonatal outcomes

	Control group (n=384) ASA (-)		Study group (n=157) ASA (+)		
	Mean ± SD	**Median (min-max)**	**Mean ± SD**	**Median (min-max)**	**p**
GW at birth[a]	35.41±3.35	36.00 (24.00-41.00)	33.87±3.81	35.00 (23.00 41.00)	<0.001
Birth weight[a]	2428.13±866.28	2515.00 (390.00-4430.00)	2175.03±953.42	2150.00 (360.00-4600.00)	0.005
APGAR 1. min[a]	6.99±1.15	7.00 (2.00-9.00)	6.65±1.34	7.00 (2.00-8.00)	0.008
APGAR 5. min[a]	8.38±0.83	9.00 (5.00-10.00)	8.25±0.91	8.00 (4.00-9.00)	0.128
NICU hospitalization (days)[a]	9.16±18.77	0.00 (0.00-150.00)	13.35±23.85	0.00 (0.00-174.00)	0.028
	n	%	n	%	
LBW[b]	141	37.9	72	46.8	0.060
NICU admission[b]	187	50.3	92	59.4	0.057
Composite adverse neonatal outcome[b]	125	34.2	63	42.3	0.086
Neonatal mortality[c]	3	1.1	6	5.9	0.013

[a]: Mann-Whitney U test, [b]: Chi-square test, [c]: Fisher's Exact test, GW: Gestational weeks, NICU: Neonatal intensive care unit, LBW: Low birth weight, ETE: Endotracheal intubation, SD: Standard deviation

effects on perinatal outcomes; however, the imbalance in the risk profiles of the groups led to completely opposite results in perinatal outcomes.

Study Limitations

This study has a major limitation. Due to the retrospective design of the study, the baseline risk status for preterm PE could not be calculated, and the remarkable imbalance between the groups regarding chronic medical conditions had an inevitable impact on the outcomes. Yet, the similarity in the maternal complications despite the significant maternal co-morbidities can be considered a positive protective effect of aspirin in the case of a preeclampsia.

Conclusion

The results of this study show that, in case of a pregnancy complicated with preeclampsia, being under aspirin treatment does not yield better maternal and perinatal outcomes and does not reduce the complications of preeclampsia. Nevertheless, considering there is no difference in maternal complications of PE (except for HELLP) despite a significantly higher burden of co-morbidities like chronic hypertension in the aspirin group, a beneficial effect of aspirin cannot fully be denied with this study. A larger study excluding the patients with chronic hypertension and providing a homogenous distribution of co-morbidities should be designed on this subject.

Ethics

Ethics Committee Approval: This retrospective observational cohort study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Zeynep Kamil Women and Children Diseases Training and Research Hospital (approval date: 10.05.2023, no: 79). It was conducted following the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Informed Consent: Informed consent stating that the data can be used for scientific purposes has been routinely provided from all the patients who applied to the clinic.

Authorship Contributions

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

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CASE REPORT / OLGU SUNUMU

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Liver Transplantation in Crigler-Najjar Syndrome

Crigler-Najjar Sendromunda Karaciğer Nakli

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Abstract

Crigler-Najjar syndrome is a rare, inherited disease that causes unconjugated hyperbilirubinemia. Liver transplantation is a definitive treatment option for Crigler-Najjar syndrome. Two patients with Crigler-Najjar syndrome who received liver transplantation are presented in this case report. The first patient who was misdiagnosed with Gilbert's syndrome was a 15-year-old male. He had speech and gait disturbances that partially recovered after liver transplantation. The second patient was a 22-year-old male. He developed liver fibrosis although he had a mild clinical form of the disease. Liver transplantation was successfully performed for both of these patients without significant morbidity.

Keywords: Liver transplantation, Crigler-Najjar syndrome, liver fibrosis

Öz

Crigler-Najjar sendromu, unkonjüge hiperbilirubinemiye neden olan nadir, kalıtsal bir hastalıktır. Karaciğer nakli, Crigler-Najjar sendromu için kesin tedavi sağlayan bir seçenektir. Bu olgu sunumunda Crigler-Najjar sendromu nedeniyle karaciğer nakli yapılan iki hasta sunuldu. Gilbert sendromu olarak yanlış teşhis konulan ilk hasta 15 yaşında bir erkekti. Var olan konuşma ve yürüme bozukluğu karaciğer nakli sonrası kısmi olarak düzeldi. İkinci hasta 22 yaşında erkekti. Hastalığın hafif bir klinik formuna sahip olmasına rağmen, karaciğer fibrozisi gelişmişti. Karaciğer nakli her iki hastaya da önemli bir morbidite olmaksızın başarıyla uygulandı.

Anahtar Kelimeler: Karaciğer nakli, Crigler-Najjar sendromu, karaciğer fibrozisi

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Introduction

Crigler-Najjar syndrome (CNS) is a rare, autosomal recessive disorder characterized by unconjugated hyperbilirubinemia. A mutation in the *UGT1A1* gene located on chromosome 2 causes partial or complete loss of function of the uridine diphosphate-glucuronosyl transferase enzyme, which provides bilirubin glucuronidation. Therefore, severe unconjugated hyperbilirubinemia occurs in the affected individuals[1]. If the level of unconjugated bilirubin rises above the albumin binding capacity, free circulating bilirubin accumulates in lipophilic tissues. This accumulation is particularly important in the brain because brain damage develops in varying severity[2,3].

Phototherapy (PT) is commonly used in CNS patients to lower bilirubin levels. Although it is effective in the initial years of therapy, its effectiveness diminishes over time[1,4]. Thus, most patients with CNS eventually require liver transplantation (LT) at early ages of their life[2]. The mean and median age at transplantation was reported as 9 years, ranging from 0 to 32 years, in different world registries[5,6].

This paper presents two patients with CNS type I who received LT at a relatively late age due to misdiagnosis and lack of medical care.

Case Reports

Case 1

The first patient was a 15-year-old male. His parents were first-degree cousins. His elder brother died of an undiagnosed disease with similar symptoms.

The patient had icteric sclera since the first year of life. However, he was misdiagnosed with Gilbert's syndrome and received no treatment. He had no other complaints until four months ago. He was admitted with speech and gait disturbance that had been present for four months. Upon sequencing the coding exon 5 of UGT1A1, a homozygous c.1381T>C mutation was detected, resulting in a p. W461R substitution at the protein level. He was diagnosed with CNS type I by genetic analysis. Phenobarbital was given to the patient, but the symptoms worsened. He was then referred for LT.

The patient had severe jaundice, and his serum total bilirubin level was 19.6 mg/dL. During his neurological examination, the patient was stuttering and had trouble choosing the right words when speaking. He was walking in an anteflexed position with his knees slightly flexed. His general orientation was impaired. However, his brain magnetic resonance imaging showed no significant abnormalities.

The donor was his 42-year-old mother. No genetic tests were performed before organ donation. The patient underwent live donor liver transplantation (LDLT) with a right liver lobe graft. The early postoperative period was uneventful. The serum total bilirubin level gradually decreased to 0.7 mg/dL starting from 31 mg/dL in the immediate postoperative period. At the end of the 1-year follow-up, liver function was normal and neurological status improved without complete recovery. While the gait disturbance was completely resolved, he still had troubles with his speech.

Case 2

The second patient was a 22-year-old male. His parents were first-degree cousins, similar to the first case. The family history was otherwise uneventful, with no significant systemic diseases.

He had jaundice from birth; however, he had never consulted a doctor before and hence did not receive any treatment. Because of DNA sequence analysis of this patient, the same genetic mutation was detected as in the first case. In addition, liver fibrosis was detected with imaging studies, and the patient was finally referred for LT. He had no neurological symptoms, unlike the previous patient. The serum total bilirubin level was 21.0 mg/dL.

The patient underwent left lobe LDLT. The donor was his 51-year-old father. The early postoperative period was uneventful. The serum total bilirubin level gradually decreased to 1 mg/dL in the early postoperative period; however, it started to rise again up to 20 mg/dL at the postoperative 10th month. Magnetic resonance cholangiopancreatography revealed stenosis in the biliary reconstruction. Percutaneous transhepatic cholangiography was performed to dilate the stenosis, and bilirubin values returned to normal afterward. At the end of the 1-year follow-up, the liver function and neurological status of the patient were normal.

Discussion

CNS is a rare, inherited disease characterized by hyperbilirubinemia. It was first described as "congenital familial non-hemolytic jaundice" in 1952 by Crigler and Najjar[7]. The initial paper consisted of six children with reported 100% mortality, most of whom perished in the early years of their lives[7]. The development of PT provided these

patients with a longer life without neurological disability[8]. Mortality rates decreased to an impressive 7.1% ratio in patients who received adequate and high standard PT, and most of these patients reached adulthood without any signs of encephalopathy[6].

Genetic analysis plays a pivotal role in diagnosing CNS, as it helps clinicians identify specific mutations in the *UGT1A1* gene, guiding personalized treatment plans, and enhancing our understanding of this rare genetic disorder[9]. Both patients were diagnosed by genetic testing.

The study; using a web-based world registry, which included data from 221 CNS patients, and reported PT as the most common treatment. A total of 75 patients among the 132 patients who were offered PT as a monotherapy failed to receive adequate PT due to lack of infrastructure. The reported mortality rate was 7.1% for patients who had sufficient access to PT as opposed to the mortality rate of 62.7% in patients with insufficient access[6]. These results clearly demonstrate the effectiveness of PT.

However, PT has its own limitations. Its efficacy decreases over time because of skin thickening and decreasing body surface area to weight ratio. In addition, the compliance with the treatment decreases over time, as PT sessions last approximately 10-12 hours a day. Daily therapy duration also limits social life and negatively affects quality of life[5,6,8].

Another issue to be considered for treating CNS is liver fibrosis. Liver fibrosis in patients with CNS type I and II has started to be reported in increasing frequency[10-13]. The cause and consequence of fibrosis are not clear[1,13]. In a recent study, Aronson et al.[6] indicated that all patients with liver fibrosis in the cohort were 7 years or older and had a severe form of CNS. In contrast, Schröder et al.[1] reported varying levels of fibrosis, differing in severity regardless of the type of CNS. Only one patient in the current report developed liver fibrosis, despite having a favorable disease course mild enough to live untreated until the age of 22.

LT is a definitive and effective therapy for CNS[5]. A recent single-center retrospective study including 13 CNS patients who underwent LT showed that the overall survival rate was 100%. The graft survival rate for the first LT was 61.5%. Five patients underwent re-transplantation and one patient underwent a second re-transplantation. At the end of a median follow-up period of 10 years, 12 of 13 patients' graft function was normal[1]. In the aforementioned web-based world registry report, 26 patients underwent LT for CNS. LT was curative for all patients. However, the LT-related complication rate was 54%[6]. According to these results, LT offers a definitive curative treatment option for patients with severe CNS.

This report shows that LT is a curative treatment even in cases where treatment is delayed for various reasons. Because liver fibrosis can develop independently of the severity of the disease and clinical findings, liver fibrosis should be a part of the routine evaluation in the follow-up of CNS patients.

Ethics

Informed Consent: Informed consent was obtained from the patients in this report.

Authorship Contributions

Surgical and Medical Practices: M.K., K.B., K.A., Z.Y., M.A., M.Ab., E.F., A.Y., S.J., S.S., A.P., S.G., H.R., Concept: S.V., Design: S.V., Data Collection or Processing: S.S., Analysis or Interpretation: S.V., Literature Search: S.V., Writing: S.V., M.K., K.B., K.A., Z.Y., M.A., M.Ab., E.F., A.Y., S.J., S.S., A.P., S.G., H.R.

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CASE REPORT / OLGU SUNUMU

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

A Rare Presentation of Anthrax: Preseptal Cellulitis

Şarbon için Nadir Bir Başvuru Şekli: Preseptal Selülit

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Abstract

Anthrax is a rare zoonotic infectious disease caused by *Bacillus anthracis*. Cutaneous anthrax constitutes most of the cases and occurs in exposed skin areas (arms,fingers,etc.). Here we report a case of periorbital cutaneous anthrax infection. An 8-year-old girl presented to our hospital with a necrotic black lesion on the upper left eyelid and swelling around the eye. She had a history of contact with a dead cow. Her father and brother also had necrotic ulcerative lesions on their forearms. Gram-positive rods were detected in the swab Gram strain taken from her lesion. In addition, *Bacillus anthracis* growth in swab culture taken from her father's lesion. She was diagnosed as "Anthrax" and treated with intravenous penicillin-G and topical oxytetracycline for 10 days. She recovered without functional sequelae. Physicians should consider cutaneous anthrax in the differential diagnosis of ulcerative and necrotizing preseptal and orbital infections, particularly in underdeveloped and developing countries.

Keywords: Cutaneous anthrax, periorbital anthrax, preseptal cellulitis, anthrax

Öz

Şarbon, *Bacillus anthracis*'in neden olduğu nadir görülen zoonotik bir enfeksiyon hastalığıdır. Olguların çoğunu deri şarbonu oluşturur ve açıkta kalan deri bölgelerinde (kollar, parmaklar, vb.) meydana gelir. Burada periorbital kutanöz şarbon enfeksiyonu olan bir olguyu sunuyoruz. Sekiz yaşında kız hasta, sol üst göz kapağında nekrotik siyah lezyon ve göz çevresinde şişlik şikayetiyle hastanemize başvurdu. Ölü bir inekle temas öyküsü mevcuttu. Babasının ve erkek kardeşinin de ön kollarında nekrotik ülseratif lezyonlar vardı. Lezyondan alınan sürüntüde Gram-pozitif çomaklar tespit edildi. Babasının lezyonundan alınan sürüntü kültüründe de *Bacillus anthracis* üremesi oldu. "Şarbon" tanısı konan hastaya 10 gün boyunca intravenöz penisilin-G ve topikal oksitetrasiklin tedavisi uygulandı. Fonksiyonel sekel kalmadan iyileşti. Özellikle az gelişmiş ve gelişmekte olan ülkelerde hekimler ülseratif ve nekrotizan preseptal ve orbital enfeksiyonların ayırıcı tanısında kutanöz şarbonu da göz önünde bulundurmalıdır.

Anahtar Kelimeler: Kutanöz şarbon, periorbital şarbon, preseptal selülit, şarbon

Introduction

Anthrax is a zoonotic infectious disease caused by *Bacillus anthracis*. Essentially, anthrax is a disease of animals, but it can be transmitted from domestic animals such as sheep, goats, and cattle to humans. *B. anthracis* is a Gram-positive, aerobic, and facultative anaerobic, endospore-forming bacillus. These spores can remain in nature for a long time. It is transmitted to humans by ingesting infected meats, inhaling spores, or by direct contact with the skin, meat, and wool of infected animals[1]. Although in developing countries it causes animal and human deaths, in most industrialized countries, anthrax is considered a bioterrorism threat[2]. There are three clinical types of anthrax, according to the inoculation of spores into the body: Cutaneous, inhalation,

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and gastrointestinal. Cutaneous anthrax constitutes 95% of the cases, and it mostly occurs in exposed skin areas (face, neck, hands, forearms, etc.)[3,4]. Herein, we report a case of periorbital cutaneous anthrax infection in an 8-year-old girl from Turkey with a brief literature review.

Case Report

An 8-year-old girl presented to our hospital with a black lesion on the upper left eyelid and swelling around the eye. The patient's complaints started two days ago. There was no history of trauma or insect bite. The patient's family had been ranching in the village, and their cow had died suddenly a week ago. She, her father, and her brother had contacted the dead cow's meat and skin. Her father and brother also had necrotic ulcerative lesions on their forearms. On physical examination, her body temperature was 38.7 °C, and other vital signs were normal (heart rate: 90 beats per minute, breath rate: 20/min, oxygen saturation: 99% at room air, blood pressure: 110/70 mmHg, Glasgow-Coma score: 15). There was a black necrotic area, swelling, and redness around the left eyelid (Figure 1). In laboratory evaluation, white blood cell count was 9310/mm^3 (normal range 4500-9500/mm^3) and C-reactive protein was 103 mg/dL (normal range 0-8 mg/dL). She was also evaluated by an ophthalmologist, and the ophthalmological examination showed normal anterior and posterior segments. Orbital magnetic resonance imaging was performed to exclude orbital cellulite. The findings were consistent with preseptal cellulitis (left frontal, periorbital, zygomatic, and molar subcutaneous edematous signal increases). A swab sample was taken from the necrotic lesion in the eyelid, and Gram staining and culture were performed. Gram-positive rods were observed on microscopic examination. Swab culture was negative. In her father's examination, there was a 2x1 cm black, necrotic, ulcerated lesion on the forearm (Figure 2). *Bacillus anthracis* was isolated from the swab culture taken from the lesion on her father's arm. On microscopic examination, Gram-positive rods were also observed in the swab sample of her brother's necrotic lesion on his forearm. Based on all clinical and laboratory findings, the preseptal cellulite in our patient was considered caused by anthrax. Intravenous Penicillin-G and topical Oxytetracycline treatment were initiated. Other family members were also screened for anthrax. On the third day of treatment, edema and redness of the left eyelid began to regress. Penicillin G treatment was completed in 10 days. The necrotic scar tissue on the eyelid did not regress and was followed up (Figure 3). Three months after treatment, it regressed,

Figure 1. Periorbital cellulitis in the left eye and black necrotic area on the lesion at presentation

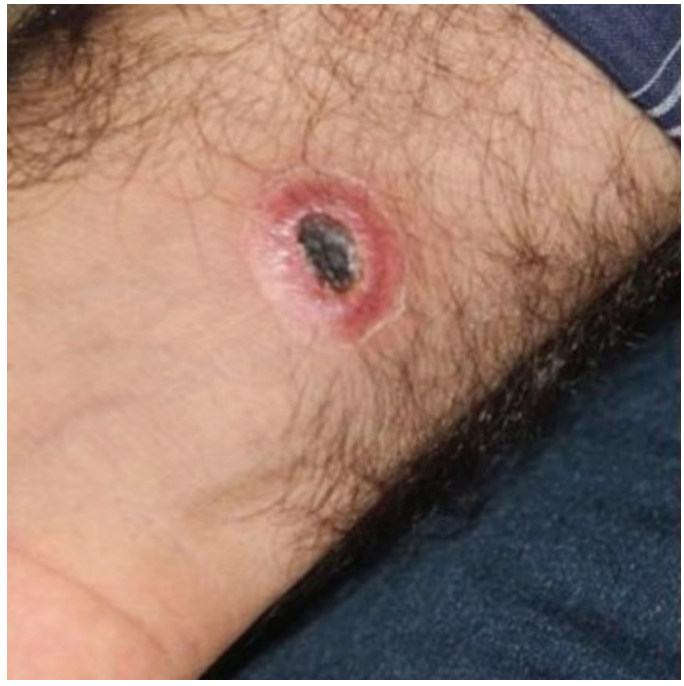

Figure 2. Necrotic lesion on the forearm of the patient's father

and no functional or cosmetic loss occurred in the eyelids (Figure 4).

Discussion

Here we report a case of anthrax with a rare presentation, preseptal cellulitis. Anthrax has not been eradicated worldwide, although its frequency has decreased gradually. Because butchers, veterinarians, shepherds, farmers, and farmworkers are at great risk of exposure to infected substances, anthrax can also be considered an occupational disease, especially in underdeveloped countries. It is a common disease, especially in parts of Asia, Africa, Latin America, and Eastern Europe[5]. In our country, it seems more frequent in Eastern and Southeastern Anatolia areas with intense contact with animals[6]. In 2017, 37 cases were reported from 14 provinces in Turkey, but no cases were reported from Sivas. However, in September 2018, anthrax came back on the agenda due to cases in provinces of Turkey, including Sivas. Anthrax reminds us of a serious and fatal disease that can affect both animals and humans. In Sivas, in three patients from the same family, cutaneous anthrax was defined. Here we present a child with preseptal cellulitis in this family.

Anthrax, which can be observed in all animal species, is transmitted mainly from animals such as cattle, sheep, and goats. *B. anthracis* can be transmitted to humans by contact with the wool or meat of infected animals, by inhalation, or by digestion. Although periorbital cellulitis due to anthrax is a rare disease, it should be considered in the differential diagnosis of patients who have close contact with animals or animal products. In our patient's case, the patient's family had been ranching in the village. Their cow had died suddenly, and then her father, brother, and she had contacted the dead cow's meat and skin. Taking this story is important for diagnosis. Symptoms begin to appear 2-7 days after the bacilli enter the body. It starts with swelling and itching on the skin and turns into a blister filled with water within 1-2 days, and then a black wound occurs in the middle. Overall, the most common locations of cutaneous anthrax are the arm and finger. The incidence of lesions around the face and neck region has been reported to be 20%[7-10]. Facial involvement has been observed in five of seven cutaneous anthrax cases diagnosed between 2017 and 2018 in Turkey. Child and adult anthrax cases causing preseptal cellulitis similar to our patients have been reported in our country and other countries. Bayoğlu et al.[11] reported

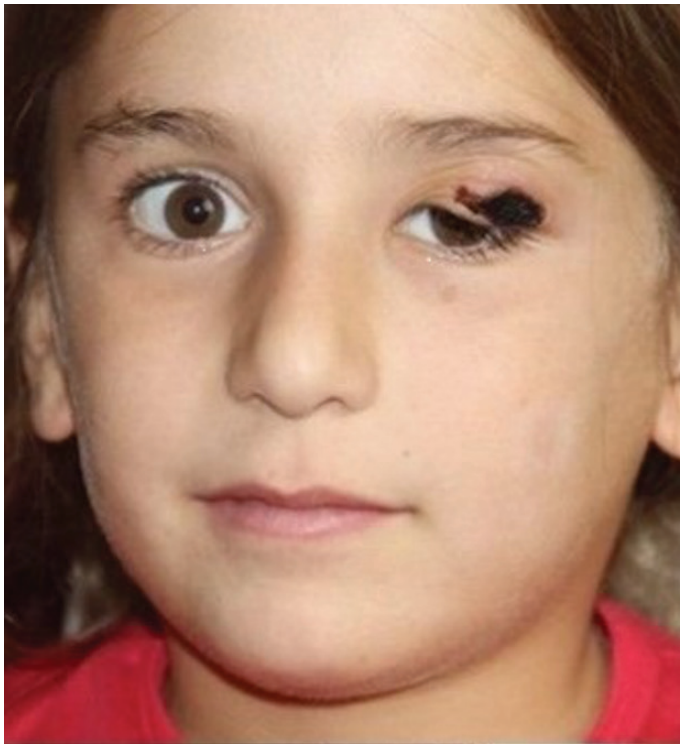

Figure 3. Necrotic scar tissue in the left eye during the first week during discharge

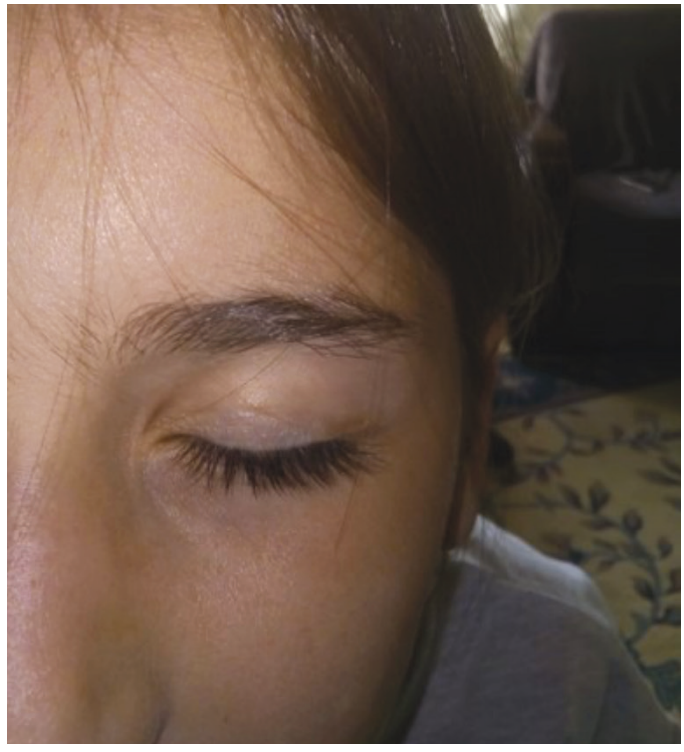

Figure 4. Fully healed image of the patient after 6 months

anthrax on the right eyelid of an 8-year-old patient in 2013, and he healed without complications. In 2016, Gül et al.[12] reported a 14-year-old patient with a preliminary diagnosis of angioedema who noticed a classic necrotic black lesion in the left eye. Gram-positive bacilli were found in this case, and the patient was treated for anthrax, but scar tissue remained. In a study conducted in India, the causes of preseptal and orbital cellulitis were found to be associated with cutaneous anthrax in 5% of pediatric cases and 21% of adult cases[13]. In a previous study, Gelaw and Asaminew[14] reported a case series of three adult patients with periocular anthrax who were seen in Ethiopia from June 2011 to May 2012. In another study, Munteanu et al.[15] reported a 21-year-old patient with palpebral anthrax.

In the differential diagnosis of cutaneous anthrax, carbuncles, erysipelas, necrotizing cellulitis, cutaneous tuberculosis, tularemia, leishmaniasis, primary syphilis lesion, cat scratch disease, necrotic herpes simplex, and tropical ulcers should be considered[7,16,17]. Anthrax can be diagnosed by detecting bacillus by Gram staining of a swab from the lesions, positive culture, and clinical and laboratory findings. Diagnosis can be rapidly made also by polymerase chain reaction or enzyme-linked immunosorbent assay testing techniques[18].

Delay in treatment or misdiagnosis can lead to varying complications ranging from local complications to death, including ectropion (47%), lagophthalmos (19%), and corneal scars (9.5%) in periorbital anthrax cases[19-23]. The biggest anthrax epidemic in the past few years was the Zimbabwe epidemic, which affected 9.711 people in the late 1970s[24]. Reported cases from Zimbabwe continue to be reported. In 2015, a 3-year-old patient similar to our case was reported to have cutaneous anthrax diagnosed on the left upper eyelid, and the lesion had occurred 2 weeks after eating dead antelope meat[25]. It was reported that the patient was reconstructed with a skin graft at the end of the treatment and developed mild lagophthalmos. Celebi et al.[26] reported that a 4-year-old child developed cicatricial ectropion on the upper eyelid despite anthrax treatment with high-dose penicillin. Similarly, there have been reported pediatric and adult periorbital anthrax cases resulting from ectropion and corneal scars despite appropriate treatments[20,22,27,28]. Unfortunately, the youngest reported case was a 4-month-old baby among these cases[22]. Dinc et al.[29] reported a 36-year-old farmer patient who was clinically and bacteriologically diagnosed with cutaneous anthrax with a necrotic lesion on the left eyelid and facial edema. There were no sequelae, except for bilateral pterygium, after 10-day penicillin-G treatment[29]. In another study, Bozpolat et al.[30] reported a 13-year-old female patient with cutaneous anthrax in her left eyelid. After 14 days of penicillin treatment, tissue grafting was performed on the lesion area with tissues taken from the postauricular areas. Devrim et al.[5] presented a case of a 13-year-old boy who developed eyelid anthrax after contact with a sheep carcass, resulting in eyelid anthrax and cicatricial ectropion.

In underdeveloped and developing countries, physicians should consider cutaneous anthrax in the differential diagnosis of ulcerative and necrotizing preseptal cellulitis and orbital infections, especially in patients with a history of close contact with animals. Recognition of the signs and symptoms by physicians is very important for early and effective treatment. Sequelae development can be prevented in this way. With this article, we also want to highlight the presence and importance of the infectious zoonotic disease "Anthrax" for public health, especially in underdeveloped and developing countries. Therapeutic and preventive measures should be taken.

Ethics

Informed Consent: We obtained written informed consent from the patient's parents for this report.

Authorship Contributions

Surgical and Medical Practices: A.K.T., A.K.A., A.V.Ö., Concept: A.K.T., A.K.A., A.V.Ö., Design: A.K.T., A.K.A., Data Collection or Processing: A.K.T., A.K.A., Analysis or Interpretation: A.K.T., Literature Search: A.K.T., A.K.A., Writing: A.K.T.

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