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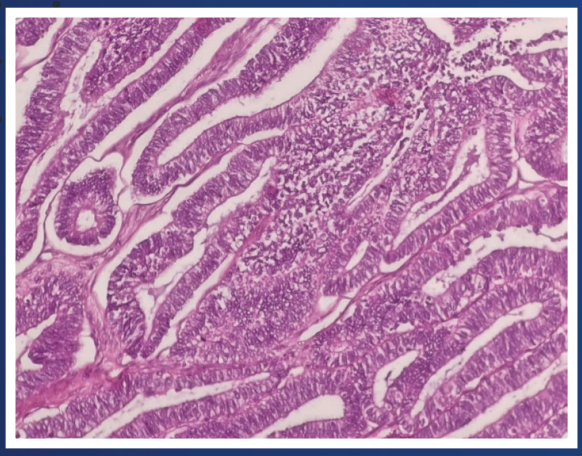

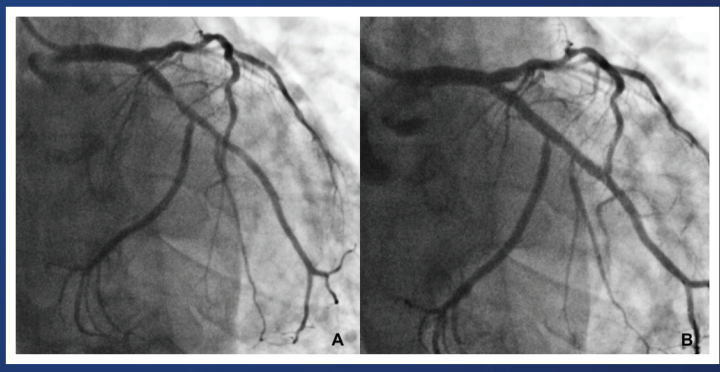

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REVIEW / DERLEME

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Role of Macrophages in Organ Transplantation

Organ Naklinde Makrofajların Rolü

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Abstract

Organ transplantation is a life-saving treatment option for patients with end-stage organ failure. Graft rejection is a significant complication that can develop after an organ transplant, and its pathophysiology depends on many variables. Macrophages are one of the main cell types of the innate immune system. Clinical studies showed that macrophages recognize the antigens and play an important role in graft rejection. Infiltration of macrophages is associated with an increased incidence of graft rejection. Macrophage-targeted therapeutic studies are required to prevent long- and short-term graft rejection and increase graft survival. This review focused on the potential macrophage-targeted therapeutic strategies to improve graft survival. Also, we reviewed the literature regarding the role of macrophages in organ transplantation.

Keywords: Macrophages, transplantation, graft survival, rejection, ischemia-reperfusion injury

Öz

Organ nakli, son dönem organ yetmezliği olan hastalar için hayat kurtaran bir tedavi seçeneğidir. Greft reddi, organ naklinden sonra gelişebilecek ciddi bir komplikasyondur ve patofizyolojisi birçok değişkene bağlıdır. Makrofajlar, doğuştan gelen bağışıklık sisteminin temel hücre gruplarındandır. Klinik çalışmalar, makrofajların antijenleri tanıdığını ve greft reddinde önemli rol oynadığını göstermiştir. Makrofaj infiltrasyonu, artan greft reddi insidansı ile ilişkilidir. Uzun ve kısa süreli greft reddini engellemek ve greft sağkalımını artırmak için makrofaj hedefli terapötik çalışmalara ihtiyaç vardır. Bu derleme, greft sağkalımını artırmak için potansiyel makrofaj hedefli terapötik stratejilere odaklandı. Ayrıca, organ naklinde makrofajların rolü ile ilgili literatürü gözden geçirdik.

Anahtar Kelimeler: Makrofaj, transplantasyon, greft sağkalımı, rejeksiyon, iskemi reperfüzyon hasarı

Introduction

Organ transplantation is an ideal treatment option for patients with end-stage organ dysfunction. The success of organ transplants depends on suppressing the host immune response and the immune cells participating in the rejection process[1]. Graft survival has risen to nearly 90%, especially with developments in surgical procedures and immunosuppressive drugs[2]. Conversely, chronic graft rejection can reduce long-term graft survival. Chronic graft rejection is particularly relevant to macrophages, which play a vital role in the innate immune system. It has been recognized since the 1970s that macrophages play a role in graft rejection[3].

Macrophages play an essential role in host defense, inflammatory processes, ischemia-reperfusion injury, and tissue homeostasis[4]. In addition, they are involved in

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the phagocytosis of pathogens and can present antigens and initiate adaptive immune responses[5]. Therefore, the identification and characterization of macrophages with different phenotypes may provide new therapeutic targets to improve graft survival following transplantation.

This review focused on potential macrophage-targeted therapeutic strategies to improve graft survival. In addition, we reviewed the literature regarding the role of macrophages in organ transplantation. We used the PubMed interface (pubmed.gov) to generate a query using the combination of the following two keyword groups: The first group included the keywords "organ transplantation", "graft rejection", "graft survival", while the second group included "macrophages" and "macrophage polarization". Each keyword in the same group was combined using the Boolean operator "OR", while the two groups were combined using the Boolean operator "AND".

Macrophages

Macrophages are important innate immune system cells that function as the initial line of defense against pathogens[6]. They contain various receptors involved in cell activation, antigen presentation, phagocytosis, and microorganism recognition (Figure 1). These receptors enable macrophages to respond to various immunological and inflammatory agents. In addition, macrophages express major histocompatibility complex (MHC) class II molecules under homeostatic conditions[7]. The expression of such receptors and surface markers divides macrophages into subsets, particularly in terms of their activation state and functional activity (Figures 1 and 2)[8,9].

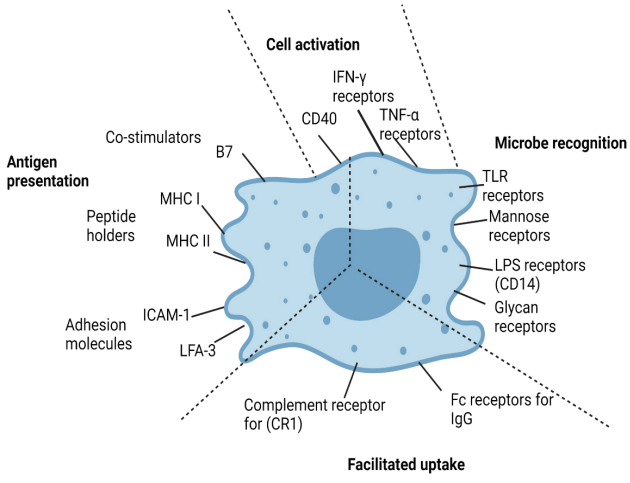

Figure 1. The function of macrophages is mediated by their surface features[8]. Figure were created with BioRender.com

ICAM-1: Intercellular adhesion molecule-1, IFN-γ: Interferon-γ, Ig: Immunoglobulin, LFA-3: Leukocyte function-associated antigen-3, LPS: Lipopolysaccharide, MHC: Major histocompatibility antigen I or II, TNF-α: Tumor necrosis factor-α

Macrophages originate from myeloid precursors in the bone marrow, differentiate from monocytes, and take on distinct features depending on the tissues in which they are found[7,10]. For example, macrophages are osteoclasts in bone, Kupffer cells in the liver, and microglia in the brain (Figure 3). These tissue-specific macrophage subpopulations can modify their phenotype and function in response to environmental signals[6].

Macrophages have two well-defined phenotypes: Classically activated macrophages (M1) induced by lipopolysaccharide (LPS) or interferon-gamma (IFN-γ), and alternatively

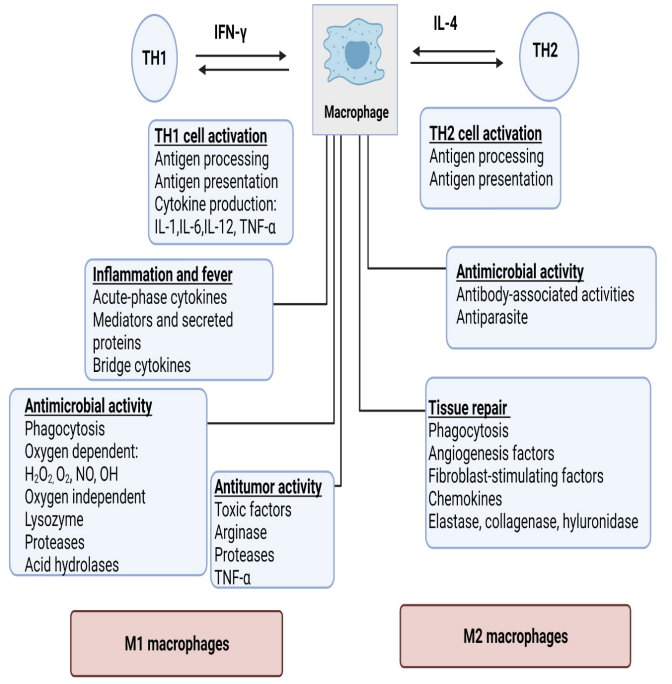

Figure 2. The many functions of the macrophage family[9]. M2 macrophages facilitate wound healing and promote angiogenesis and tissue repair. M1 macrophages promote antimicrobial activity and inflammation. Figure were created with BioRender.com

H_2O_2: Hydrogen peroxide, NO: Nitric oxide, O_2: Oxygen radical, OH: Hydroxyl radical, TH: T helper (cell), TNF-α: Tumor necrosis factor-α, IFN-γ: Interferon-γ; IL: Interleukin

activated macrophages (M2) induced by interleukin (IL)-4 or IL-10 (Figure 2)[10]. M1 macrophages are potent pro-inflammatory cells that secrete cytokines such as nitric oxide (NO) and reactive oxygen species (ROS). They express high levels of MHC class II, CD80, CD86, CD215, CCR7, CCL8/15/20, and CXCL9/10/11/13 on the cell surface[7]. In contrast, M2 macrophages have anti-inflammatory features and are associated with wound healing and fibrosis[10]. They are induced in the presence of IL-4 and IL-13; they differ in terms of the expression of CD163, CD169, CD206 (mannose receptor), and CD209 (DC-SIGN). M2 macrophages are classified into M2a-b-c-d subgroups based on the differences in the cytokine environment in which they are activated[11].

In addition, regulatory macrophages (Mreg) have anti-inflammatory features and play a protective role in graft recipients[6].

Macrophages in Ischemia– Reperfusion Injury (IRI)

IRI involves both innate and adaptive immune cells. Clinical studies have shown that macrophages play a role in short- and long-term IRI. Furuichi et al.[12] reported that monocyte chemoattractant protein-1 (MCP-1) plays a crucial role in the pathogenesis of renal IRI by activating macrophages and stimulating macrophage infiltration. Zhang et al.[13] showed that targeting T-cell immunoglobulin mucin-1 (TIM-1) on $CD4^+$ T-cells in a liver graft reduced T-cell-mediated activation of macrophages and the severity of IRI.

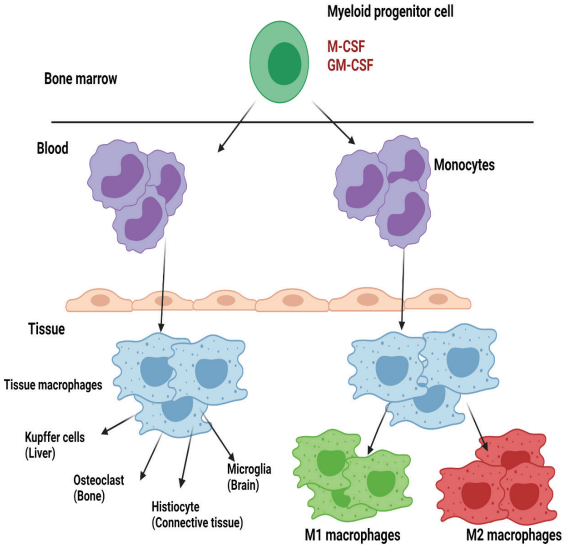

Figure 3. Origin and types of macrophages. Figure were created with BioRender.com

According to Busuttil et al.[14], selectin antagonists (rPSGL-1) reduce hepatic IRI and the severity of macrophage infiltration.

M1 macrophages cause damage during IRI, whereas M2 macrophages promote damage repair. In addition, it was stated that M1 macrophages may mediate the inflammatory process during the initiation of IRI, whereas M2 macrophages play a role in the pathophysiology of IRI.

Macrophages in Acute Rejection

In acute rejection, macrophages constitute 38-60% of graft-infiltrating cells in human graft biopsies and contribute to graft injury through various mechanisms[7]. Macrophage depletion has been proven to alleviate graft injury and reduce inflammation in multiple experimental animal models[15]. When macrophages infiltrate the graft, they exhibit a pro-inflammatory phenotype by secreting inflammatory cytokines and directly causing tissue damage. Pro-inflammatory macrophages are the primary source of reactive oxygen and nitrogen species that can directly damage the graft and increase the risk of acute rejection[7]. Pro-inflammatory cytokines secreted by macrophages, such as IL-1, IL-6, IL-12, IL-18, tumor necrosis factor-alpha (TNF-α), and IFN-γ, play a role in various processes, including the activation of endothelial cells and cytotoxic T-cells[16]. Oliveira et al.[17] reported that IL-18 expression increased during acute graft rejection.

The presence of $CD68^+$ macrophages was also associated with acute rejection[3]. van den Bosch et al.[18] reported that high $CD68^+$ and $CD163^+$ M2 macrophage counts were related to severe fibrosis in post-transplant 1-year graft biopsies. Toki et al.[19] showed that infiltrating macrophages in renal grafts had the $CD68^+CD206^+$M2 phenotype one year after transplantation.

It was also reported that the levels of monocyte colony-stimulating factor (M-CSF) were high in the grafts after acute rejection, and this finding was consistent with the increased macrophage/monocyte infiltration[20]. Monocytes can be detected in the circulation before the clinical symptoms of acute rejection occur. Ordikhani et al.[2] denoted that $CD16^+$ monocytes could inhibit T regulatory (Treg) cells, and this inhibition might be responsible for acute graft rejection.

Macrophages in Chronic Rejection

Chronic rejection is the leading cause of long-term graft loss that occurs months or years after organ transplantation. It is characterized by progressive neointima formation,

tissue fibrosis that leads to vascular blockage, and graft vasculopathy[21]. There is strong evidence that macrophages contribute to chronic rejection. Macrophages accumulate in significant amounts around graft vessels in chronically rejected grafts. In biopsies of human cardiac grafts, the number of macrophages is greater than that of T-cells in grafts[22].

The endothelial cells of the graft blood vessels produce considerable amounts of the chemokine fractalkine (CX3CL1). Monocytes/macrophages expressing the fractalkine receptor (CX3CR1) are recruited from the circulation to the vicinity of blood vessels by CX3CL1. The macrophages cause the vascular smooth muscle cells to overproliferate, producing large numbers of fibrogenic factors such as fibroblasts and collagen. These factors cause graft tissue fibrosis and vascular lumen occlusion, resulting in chronic transplant rejection. Actin is required for macrophage receptor expression and recycling, and the RhoA pathway regulates it. Interfering with the RhoA pathway causes dysfunction of actin filaments and actin-dependent activities, including receptor production and recycling. Decreased CX3CR1 receptor expression makes macrophages less responsive or non-responsive to fractalkine, preventing their infiltration into the graft and chronic rejection (Figure 4) [1].

M2 macrophages constitute the most common type of macrophages in chronic renal graft injury, and it has been suggested that they are associated with the severity of fibrosis and graft rejection[23]. Kaul et al.[24] reported that mRNA levels of M2 macrophage markers (Ym1, Fizz1, VEGF, TGF-β, and CD206) increased after heart transplantation. Despite the critical role of M2 macrophages in chronic rejection, M1 macrophages contribute to the production of proteases, ROS, and NO and play a significant role in graft damage[25].

Liu et al.[26] investigated the role of macrophage depletion in preventing chronic rejection after heart transplantation. This study showed that macrophage depletion after heart transplantation could reduce chronic rejection by altering M2 polarization and expression levels of IFN-γ, TNF-α, MCP-1, and IL-10. Manipulation of M1/M2 macrophage polarization was also used to prevent graft rejection. Zhao et al.[27] showed that M1/M2 macrophage polarization depended on tumor necrosis factor receptor-associated factor 6 (TRAF6) and the mammalian target of rapamycin (mTOR).

Wu et al.[28] investigated the differences between M1 and M2 macrophages and identified the adenosine triphosphate (ATP) gated ion channel (P2x7r) as a hallmark of M2 cells. Interestingly, blocking P2x7r using oxidized ATP (oATP) prevented M2 polarization *in vitro* and graft infiltration *in vivo*, leading to long-term graft survival (Figure 5). This study showed that targeting graft-infiltrating M2 macrophages could reduce the risk of chronic rejection and increase graft survival[28].

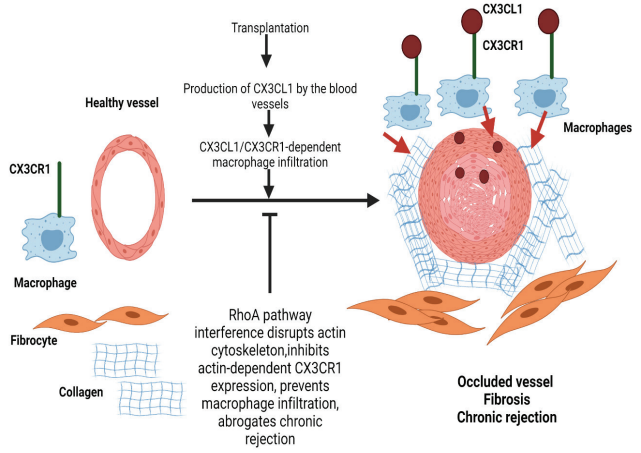

Figure 4. Role of macrophages in chronic rejection(1). Figure were created with BioRender.com

CX3CL1: Chemokine fractalkine, CX3CR1: Chemokine fractalkine receptor

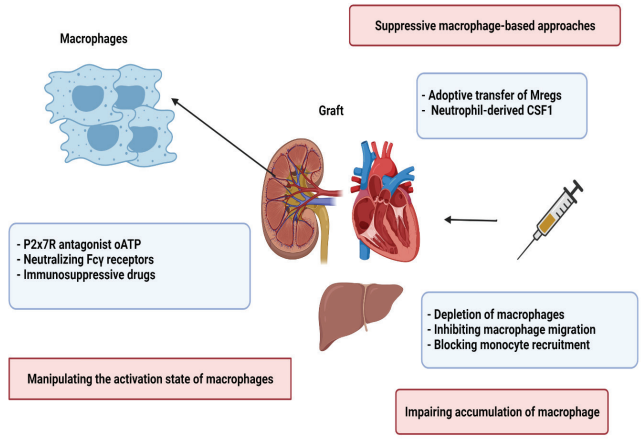

Figure 5. Macrophage-targeted treatment for graft tolerance[30]. Macrophage-targeted therapy strategies include immunosuppressive drug, macrophage proliferation inhibitors, chemokine antagonists, macrophage activation inhibitors, and macrophage depletion strategies. Figure were created with BioRender.com

CSF1: Colony stimulating factor 1, oATP: Oxidized adenosine triphosphate

Macrophage-targeted Therapies

Data regarding the critical role of macrophages in rejection processes form the basis for the development of macrophage-targeted therapies to improve graft survival. The main goals of these therapies are to induce graft tolerance and save patients from chronic rejection[21]. Macrophage-targeted therapy strategies include toll-like receptor (TLR) antagonists, macrophage proliferation inhibitors, chemokine antagonists, macrophage activation inhibitors, and macrophage depletion strategies[29].

Neutralizing the Fc receptor or treating patients with immunosuppressive drugs such as glucocorticoids and rapamycin inhibitors suppress pro-inflammatory macrophages and promote graft survival (Figure 5)[30]. Glucocorticoids, which are commonly used immunosuppressive drugs, promote the survival of anti-inflammatory monocytes[31]. Rapamycin, a prototypical inhibitor of mTOR, is considered an immunosuppressive agent and is currently used to prevent kidney transplant rejection[32]. Rapamycin has a selective effect on M1/M2 survival and leads to changes in cytokine release depending on the type of polarization. Rapamycin therapy breaks the balance in favor of an M1-like inflammatory response *in vivo*. M1 is resistant to rapamycin-induced apoptosis; it inhibits M2 polarization and promotes suppressor macrophage generation[33]. The differences in the sensitivities of M1 and M2 to rapamycin suggest that different intracellular pathways regulate survival[32]. In addition, macrophages treated with rapamycin have impaired antigen-presenting abilities and reduced CD80 expression[3]. Rapamycin also inhibits the production of the inflammatory mediator iNOS in macrophage cell lines[34].

Bortezomib is a proteasome inhibitor. This agent downregulates the immunological response of T-cells and is increasingly being used for the treatment of antibody-mediated rejection. It was shown to reduce inflammatory cytokine production in LPS-stimulated macrophages *in vitro*[3]. In addition, bortezomib has potent suppressive effects on humoral immunity. It leads to an increase in the $CD4^+$ T-regulatory cell population and decreases the serum levels of several pro-inflammatory and angiogenesis-inducing cytokines and chemokines. Gastrointestinal events, hematological toxicity, and peripheral neuropathy are the most common side effects of bortezomib[35].

Calcineurin has multiple effects on macrophage functions. The calcineurin inhibitors cyclosporin A (CsA) and tacrolimus (FK506) regulate TLR-mediated pathways in myeloid cells and cause macrophage activation by inhibiting the calcineurin/NFAT pathway[3]. High non-therapeutic concentrations of FK506 affect the maturation and polarization of macrophages. Thus, macrophage polarization shifts to an M2-like phenotype in the presence of FK506[36]. Clinical studies showed that FK506 was more effective than CsA in inhibiting macrophages during chronic rejection. Compared with FK506, CsA is more likely to promote fibrosis in kidney allografts[37]. CsA enhances the allograft infiltration of macrophages. Kakuta et al.[38] reported that CsA promoted the infiltration of $CCR5^+$ and $CXCR3^+$ macrophage grafts in rat kidney allograft transplantation. Significant macrophage infiltration was also found in the kidneys of rats afflicted by CsA nephrotoxicity. CsA may enhance the production of macrophage-derived molecules involved in chronic allograft injury[33].

Butyric acid is used to treat autoimmune disorders; it inhibits IL-12 and induces IL-10 production in human monocytes. Thus, butyric acid is associated with the formation of anti-inflammatory macrophages[39].

Mycophenolic acid is a widely used immunosuppressive and antimetabolite drug. Several studies have reported the effects of mycophenolic acid on macrophage functions. Weimer et al.[40] showed that mycophenolic acid could suppress the production of IL-1β and IL-6 by activated monocytes, but the effects of mycophenolic acid on monocyte differentiation are unknown. Overexposure to mycophenolic acid has frequent mild-to-moderate adverse effects, which lead to increased patient non-adherence and affect patients' quality of life. Bunnapradist et al.[41] confirmed that gastrointestinal side effects are dose-dependent in patients treated with mycophenolic acid. Otherwise, underexposure to mycophenolic acid may be linked to the risk of graft rejection and long-term allograft survival after transplantation[42]. In summary, manipulating the activation of macrophages may help to weaken both acute and chronic rejection.

Conclusion

The use of macrophage-targeted therapies is becoming popular in transplantation immunology. Significant accumulation of macrophages in the grafts and the close association of this process with poor transplant outcomes have increased researchers' interest in studies regarding macrophage function and macrophage-targeted treatment regimes. Subsequently, the identification of *in vivo* signaling pathways that affect macrophage polarization and function

expanded the number of potential new macrophage-targeted treatments that enable graft survival. However, further research is needed to better understand macrophages' roles in graft survival. In addition, comprehensive research concerning different macrophage phenotypes is vital for developing new macrophage-targeted therapy strategies that support short- and long-term graft survival.

Ethics

Authorship Contributions

Concept: T.Ö., M.P., İ.P., Design: T.Ö., M.P., Data Collection or Processing: T.Ö., Literature Search: T.Ö., Writing: T.Ö., M.P.

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

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Predictive Value of the Neutrophil/Lymphocyte Ratio in Testicular Torsion

Testis Torsiyonunda Nötrofil/Lenfosit Oranının Öngörü Değeri

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Abstract

Objective: The association between blood markers and testicular viability after testicular torsion (TT) is not well known. Here, the role of the neutrophil-to-lymphocyte ratio (NLR) in predicting testicular viability in children with TT was evaluated.

Methods: Clinical data of eighty children younger than 18 years of age who underwent TT between 2018 and 2023 were analyzed. Age, symptom duration, degree of spermatic cord torsion, surgical approach adopted, and hematological parameters including neutrophil, lymphocyte, and C-reactive protein (CRP) levels were obtained. The NLR was calculated.

Results: The median age was 14 (1-17) and the median duration of symptoms was 24 h (1-168 h). Testicular blood flow in color Doppler ultrasonography was absent in 64 patients (81%). During scrotal exploration, 39 patients (49%) underwent orchiopexy and 41 (51%) underwent orchiectomy. Median NLR (2.8 vs 5 p<0.001), and CRP (2.6 vs 27 p<0.001) were higher among patients who underwent orchiectomy. Patients with higher than 3.5 NLR were significantly more likely to undergo orchiectomy (37% vs 63%).

Conclusion: NLR and CRP were significantly associated with testicular viability, and both parameters can be used to predict the outcome of testis in TT.

Keywords: Testicular torsion, pediatric testicular torsion, orchiectomy, orchiopexy, neutrophil/lymphocyte ratio

Öz

Amaç: Bu çalışmanın amacı testis torsiyonu (TT) görülen çocuklarda testiküler canlılığı tahmin etmede nötrofil lenfosit oranının (NLR) rolünün değerlendirilmesidir.

Yöntem: 2018-2023 yılları arasında TT nedeniyle ameliyat edilen 18 yaş altındaki 80 çocuk çalışmaya dahil edildi. Yaş, semptom süresi, spermatik kord torsiyonunun derecesi, uygulanan cerrahi yaklaşım ve başvuru anında görülen C-reaktif protein (CRP), mutlak nötrofil ve lenfosit değerleri incelendi, NLR hesaplandı.

Bulgular: Ortalama yaş 14 (1-17) ve semptom süresi 24 saat (1-168 saat) idi. Renkli Doppler ultrasonografide 64 hastanın (%81) testiküler kan akımı yoktu. Skrotal eksplorasyon sırasında, 39 hastaya (%49) orşiopeksi, 41 hastaya (%51) orşiektomi yapıldı. Orşiektomi yapılan hastalarda median NLR (2,8 vs 5, p<0,001) ve CRP (2,6 vs 27, p<0,001) daha yüksekti. NLR'si 3,5'in üzerinde olan hastalara orşiektomi yapılma sıklığı anlamlı oranda daha yüksekti (%37 vs %63).

Sonuç: NLR ve CRP, testiküler canlılık ile anlamlı şekilde ilişkilendi ve her iki parametre de TT'de testiküler dokunun canlılığını değerlendirmede kullanılabilir.

Anahtar Kelimeler: Testis torsiyonu, çocuklarda testis torsiyonu, orşiektomi, orşiopeksi, nötrofil lenfosit oranı

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Introduction

Testicular torsion (TT) is a common cause of acute scrotum in children that requires urgent care with prompt diagnosis with 3.8 per 10,000 incidence rates in males younger than 18[1]. TT occurs when the spermatic cord twists around its own axis, resulting in the initial obstruction of venous blood flow. Subsequently, arterial obstruction may develop, potentially leading to the loss of the affected testis[2].

Surgical intervention due to acute TT may lead to either the preservation of the testis through detorsion and orchiopexy or testicular loss via orchiectomy due to irreversible damage. A high index of suspicion and rapid and accurate diagnosis with timely exploration are essential to reduce testicular loss. In general, detorsion performed within the first 8 h of symptom onset can significantly result in higher chances of testicular salvage, whereas duration of symptoms more than 12 hours mostly results with orchiectomy[3].

Numerous publications suggest that hematologic parameters such as absolute neutrophil and lymphocyte counts, platelets, and certain inflammatory markers may serve as valuable tools in diagnosis of TT[4]. Recent research has highlighted the utility of mean platelet volume, platelet-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio (NLR) as indicators of inflammation, with specific studies investigating their potential for aiding in the diagnosis of TT[5]. Herein, we aimed to demonstrate the practical utility of NLR in assessing the outcomes of TT. Our objective was to determine whether the NLR can serve as a predictive marker for gaging the severity of the testicular condition in cases of torsion.

Materials and Methods

In this study, we reviewed the electronic medical records of a cohort comprising 80 boys under the age of 18 who underwent scrotal exploration for TT at our medical center between 2018 and 2023. The inclusion criteria were TT confirmed by surgery. Newborns with TT and children with organ dysfunction or hematologic disorders were excluded from this study. The information collected included patient age in years, duration of symptoms (time between the onset of symptoms and the medical care), side of torsion, degree of spermatic cord twisting, type of surgery, and hematological parameters. All patients had a complete blood count (CBC) before scrotal exploration. The white blood count, absolute neutrophil count, and absolute lymphocyte count were obtained. These values were subsequently used to calculate the NLR. In addition, if available, we collected C-reactive protein (CRP) values as part of our data collection process. These values were then used to calculate the NLR. CRP values were also collected if available.

During surgery, the affected testis was carefully detorted and its viability was assessed. In cases where there was concern about testicular viability, fasciotomy of the tunica albuginea was performed for fresh bleeding, and the testis was enveloped in warm, saline-soaked gauze for 20 min and then reevaluated. In the cases where the testis was determined to be non-viable, orchiectomy was performed. For all patients, orchiopexy was performed on the contralateral testis. The patients were divided into two groups depending on the outcome of surgery.

The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital's Non-Interventional Research Ethics Committee (approval no.: 2023/11-01, date: 21.12.2023).

Statistical Analysis

Data were analyzed using IBM SPSS (Chicago, IL, USA). Kolmogorov-Smirnov tests were used to determine whether the data had normal distributions. For data with a non-normal distribution, comparison between the groups was performed using the non-parametric Mann-Whitney U test. All data were non-normally distributed; and are presented as a median (minimum-maximum). Spearman's correlation test was used to examine the relationship between the duration of symptoms and NLR. Receiver operating characteristic (ROC) curve analysis was used to assess the area under the curve (AUC) and identify optimal cut-off values. The level of significance was taken as $p<0.05$.

Results

In total, data from 80 children were analyzed for this study. The median age was 14 (1-17) and the median duration of symptoms was 24 h (1-168 h). Testicular blood flow in color Doppler ultrasonography (CDUS) was absent in 64 patients (81%). Children were classified into two groups. The orchiopexy group included 39 children treated with detorsion and orchiopexy, and the orchiectomy group included 41 children treated with orchiectomy due to TT. There was no statistically significant difference between the groups in terms of age and side and blood flow in CDUS. The duration of symptoms, NLR, and CRP levels were significantly different between the orchiopexy and orchiectomy groups (Table 1).

When the correlation between the duration of symptoms and NLR values was further evaluated, no statistically significant association was found within each group (orchiectomy; p=0.047 vs. orchiopexy; p=0.206).

The ability of NLR to predict testicular viability in TT was further evaluated using a ROC curve. The AUC was 0.748. The AUC-ROC was significantly higher than 0.5 (p=0.008; p<0.05) (Figure 1). Patients with NLR higher than 3.5 were significantly more likely to undergo orchiectomy (37% vs. 63%). The sensitivity, specificity, positive predictive value, and negative predictive value of NLR in identifying patients with non-viable testes who underwent orchiectomy were 63%, 72%, 63.4%, and 66.7%, respectively.

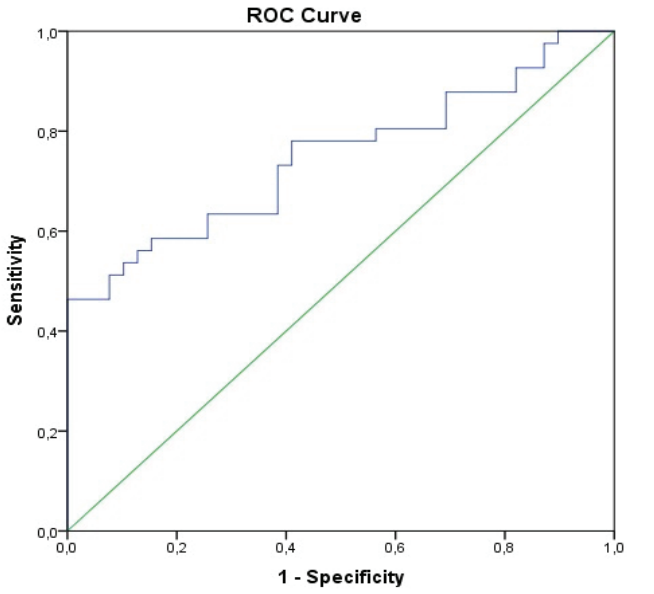

Figure 1. The area under the ROC curve for NLR to predict testicular viability was significantly higher than 0.5

ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio

Discussion

TT is a urological emergency that may lead to testicular ischemia and even testicular necrosis if not diagnosed and promptly treated. The survival rate of the testis after TT mainly depends on the degree of torsion and duration of symptoms[6]. The European Association of Urology's Pediatric Urology guidelines state that the duration of symptoms and the degree of cord twisting are the most significant predictors of the early salvage rate of the testis[7]. performing detorsion within the first 8 h of symptom onset has a substantial impact on salvaging the affected testis[8].

Although the role of CDUS in the diagnosis of TT is undisputable, its ability to differentiate testicular viability ahead of surgical exploration is limited[9]. Despite its high sensitivity and specificity (up to 97%), both false-negative and false-positive results still occur[10]. In our study, we found no substantial difference in CDUS findings between the orchiectomy and orchiopexy groups. The only differentiator between the two groups was preoperative inflammatory markers.

In recent years, various studies have focused on a range of hematological parameters, examining their relevance in predicting the risk of TT. In addition, acute phase reactants such as CRP and erythrocyte sedimentation rate were reported to increase in TT[11]. A promising link between hematological

Table 1. Baseline characteristics of children who underwent scrotal exploration for testicular torsion

Variables	Orchiopexy (n=39)	Orchiectomy (n=41)	p-value
Age (years)	14 (5-17)	14 (1-17)	0.730
Side			
Left	20 (51.3%)	27 (65.9%)	0.256
Right	19 (48.4%)	14 (34.1%)	
Duration of torsion (h)	24 (1-72)	72 (8-168)	<0.001
Blood flow in color Doppler US			
Present	8 (20.5%)	7 (17.1%)	0.781
Absent	31 (79.5%)	33 (82.9%)	
N/L ratio	2.8 (0.5-5.7)	5 (1.1-20)	<0.001
CRP	2.6 (0.2-44)	27 (0.9-375)	<0.001

Continuous data were presented as median (minimum-maximum), categorical data were presented as number (percent).
US: Ultrasonography, N/L: Neutrophil-to-lymphocyte, CRP: C-reactive protein

parameters and the prediction of testicular viability in TT has been investigated by various researchers[12,13]. These parameters can be readily established through routine CBC analysis conducted before surgery. Furthermore, they are cost-effective, easily calculable, pragmatic, and widely employed in clinical practice. In a clinical cohort of male adult patients investigating various hematological biomarkers as potential indicators of testicular viability in TT, Güneş et al.[14] reported a significant relationship between scrotal tenderness, NLR, and platelet counts. Bitkin et al.[15] reported that NLR can be used in the differential diagnosis of TT and epididymitis with 70.1% sensitivity and 76.9% specificity. In a similar study conducted on 60 TT patients, 38 underwent orchiectomy and 22 underwent orchiopexy Jang et al.[16] revealed that the duration of symptoms determines the viability of testis notably, NLR emerged as an independent predictor of testis survival, particularly in cases where surgical correction occurred with only a marginal delay in diagnosis. This identifies NLR as a potential indicator for assessing testicular viability in TT[16].

The results of this study have significant clinical relevance. Both NLR and CRP were significantly higher in TT resulting in testicular loss. Here, NLR demonstrated 63% sensitivity and 72% specificity in predicting the viability of testis in TT. These findings suggest the possible use of NLR in children with TT to determine the viability of torted testis before surgery.

Study Limitations

There are several limitations in this study, mainly due to the single-centered retrospective design. The sample size also was not large. Further multicenter randomized prospective studies with large sample sizes should be conducted to better assess the value of NLR in determining testicular viability in TT.

Conclusion

Identifying a reliable marker for predicting the risk of orchiectomy following acute TT is crucial for improving patient and parental counseling during surgical intervention. NLR has emerged as a promising and reliable predictor of testicular viability in children with TT. Incorporating NLR into the assessment protocol may enhance the precision of prognostic information provided to patients and their parents, thus facilitating more informed decision-making during the critical period of surgical intervention.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital's Non-Interventional Research Ethics Committee (approval no.: 2023/11-01, date: 21.12.2023).

Informed Consent: Retrospective study.

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Role of Combined Nutritional Deficiency in Microcytic Anemia: A Retrospective Study

Mikrositik Anemide Kombine Beslenme Eksikliğinin Rolü: Retrospektif Bir Çalışma

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Abstract

Objective: The mean erythrocyte volume (MCV) plays an important role in the differential diagnosis of nutritional anemia. Generally, the causes of microcytic anemia in low MCV and macrocytic anemia causes in high MCV are considered. In this study, it was aimed to examine the relationship between nutritional anemias and erythrocyte indices.

Methods: The files of patients with nutritional anemia in the pediatric hematology outpatient clinic were analyzed retrospectively. Patients whose hemogram parameters, iron, total iron binding capacity, ferritin, B12 and folic acid levels were studied were included in the study. Combined nutritional anemia was defined as the coexistence of both types of anemia (iron deficiency and B12 deficiency).

Results: A total of 407 patients, 252 (61.9%) female and 155 (38.1%) male, were included in the study. The mean age of the patients was 8.82±6.15 years. Iron deficiency anemia was found in 192 (47.2%) patients, combined nutritional anemia in 185 (45.4%) patients, and B12 deficiency anemia in 23 (5.7%) patients. MCV, iron and transferrin saturation were found to be lower in the iron deficiency anemia group compared to the group with combined nutritional anemia ($p<0.05$). However, both the iron deficiency group and the combined nutritional anemia group had microcytic anemia (respectively, MCV: 70.39 fL, MCV: 78.18 fL).

Conclusion: Combined nutritional anemia is as common as iron deficiency anemia and may present as microcytic anemia. MCV is not a guide in these patients. Therefore, B12 levels should be checked in addition to iron parameters in patients who present with microcytic anemia and are thought to have nutritional anemia.

Keywords: Mean erythrocyte volume, iron deficiency, B12 deficiency, combine nutritional anemia

Öz

Amaç: Ortalama eritrosit hacmi (MCV), beslenme anemisinin ayırıcı tanısında önemli bir rol oynar. Genellikle düşük MCV'de mikrositik anemi nedenleri, yüksek MCV'de ise makrositik anemi nedenleri ele alınır. Bu çalışmada beslenme anemileri ile eritrosit indeksleri arasındaki ilişkinin incelenmesi amaçlandı.

Yöntem: Çocuk hematoloji polikliniğinde beslenme anemisi tanısı alan hastaların dosyaları retrospektif olarak incelendi. Hemogram parametreleri, demir, total demir bağlama kapasitesi, ferritin, B12 ve folik asit düzeyleri çalışılan hastalar çalışmaya dahil edildi. Kombine beslenme anemisi, her iki anemi tipinin (demir eksikliği ve B12 eksikliği) bir arada bulunması olarak tanımlandı.

Bulgular: Çalışmaya 252'si (%61,9) kadın, 155'i (%38,1) erkek olmak üzere toplam 407 hasta dahil edildi. Hastaların yaş ortalaması 8,82±6,15 yıldı. Hastaların 192'sinde (%47,2) demir eksikliği anemisi, 185'inde (%45,4) kombine beslenme anemisi, 23'ünde (%5,7) B12 eksikliği anemisi saptandı. Demir eksikliği anemisi

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Öz

grubunda MCV, demir ve transferrin satürasyonu kombine beslenme anemisi olan gruba göre daha düşük bulundu (p<0,05). Ancak hem demir eksikliği grubunda hem de kombine beslenme anemisi grubunda mikrositik anemi mevcuttu (sırasıyla MCV: 70,39 fL, MCV: 78,18 fL).

Sonuç: Kombine beslenme anemisi, demir eksikliği anemisi kadar yaygındır ve mikrositik anemi ile ortaya çıkabilir. MCV bu hastalarda yol gösterici değildir. Bu nedenle mikrositer anemi ile başvuran ve beslenme anemisi olduğu düşünülen hastalarda demir parametrelerinin yanı sıra B12 düzeylerine de bakılmalıdır.

Anahtar Kelimeler: Ortalama eritrosit hacmi, demir eksikliği, B12 eksikliği, kombine beslenme anemisi

Introduction

Pediatric patients with anemia are frequently encountered in pediatric outpatient clinics. Because anemia is a symptom, not a disease, the underlying cause must be investigated and treated. The most common causes of anemia in children are nutritional anemia, thalassemia, and chronic disease. Nutritional anemia is the most common type of anemia worldwide. It develops due to a deficiency of micronutrients such as iron, vitamin B12, folic acid, and zinc, which play a vital role in the synthesis of hemoglobin[1,2]. In various studies conducted in Turkey, the frequency of iron deficiency anemia was reported to be in a wide range between 3.29% and 29.9%[3,4]. Vitamin B12 and folic deficiency anemia are less common than iron deficiency anemia. Specifically, in children younger than two years of age, B12 deficiency is known to cause anemia and neurological development retardation. Delay in treatment can lead to serious complications such as severe anemia and irreversible neurological damage[5]. Hence, early diagnosis and treatment of B12 deficiency anemia are important. In classifying anemia, the mean erythrocyte volume (MCV) is utilized, according to which iron deficiency causes microcytic anemia, B12, and folic acid deficiencies give rise to macrocytic anemia. In iron deficiency anemia associated with vitamin B12 deficiency, normal or low MCV levels may be observed, which may lead to a misdiagnosis of B12 deficiency[6]. This study explores the potential relationship between nutritional anemia, notably combined nutritional anemia, and MCV levels in children.

Materials and Methods

Our study was designed as a single-center retrospective study. The patients' data followed in the Pediatric Hematology Polyclinic of Manisa Celal Bayar University Faculty of Medicine between January 2015 and December 2020 were extracted from the electronic data system. It comprises patients diagnosed with anemia, whose ages vary between one month and 18 years, and whose hemogram, iron parameters, B12, and folic acid values were measured simultaneously at the time of diagnosis. Those without nutritional anemia (thalassemia trait, anemia of chronic disease, aplastic anemia, etc.) were excluded from the study. Because the study was retrospective, all patients with suspected thalassemia trait did not undergo hemoglobin electrophoresis. All patients with an MCV/red blood cell (RBC) ratio 13 were excluded from the study because of a suspicion of thalassemia. Accordingly, the lower limits for hemoglobin levels for the age groups were as follows: 11 g/dL from 6 months to 5 years, 11.5 g/dL from 5 to 12 years, and 12 g/dL from 12 to 15 years, regardless of gender. For those older than 15 years, 12 g/dL in girls and 13 g/dL in men[7]. The formulas used to obtain the MCV's lower and upper limits were as follows: For the former, 70+ age for those younger than 10 years and 80 fL for the older ones, and 84+ (0.6x age) for the latter. In patients younger than one year of age, the lower limit for MCV was accepted as 73 fL and the upper limit as 85 fL[2,4,8]. The lower limits for ferritin were taken as 12 mcg/L, and those for folic acid and vitamin B12 were assumed to be 3 ng/mL and 200 pg/mL, where B12 values below 120 pg/mL referred to B12 deficiency[4,9]. The patients were divided into four groups by age: Infants (0-2 years), toddlers (2-6 years), schoolchildren (6-12 years), and adolescents (12-18 years). The term "combined nutritional anemia" was defined as the coexistence of both types of anemia (iron deficiency and B12 deficiency).

Statistical Analysis

Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS) 23 package program. All statistical tests (Mann-Whitney U and Students' t-tests for the comparison of non-normally and normally distributed continuous measurements, respectively) were performed at the p<0.05 significance level. Categorical data were evaluated using the chi-square test. Ethical approval for the current study was obtained from the Scientific Research Ethics Committee of Manisa Celal Bayar University the approval number: 20.478.486/692, dated: 30/12/2020.

Results

Of 407 patients, 252 (61.9%) were female and 155 (38.1%) were male, with a mean age of 8.82±6.15 years. In particular, 21.9% (n=89) were infants, 20.4% (n=83) toddlers, 14.5% (n=59) schoolchildren, and 43.2% (n=176) adolescents. Isolated iron deficiency anemia was the most common type of nutritional anemia in 192 (47.2%) patients, followed by combined nutritional anemia in 185 patients (45.4%). Only 23 patients had isolated B12 deficiency anemia (Table 1). Most patients in our study consisted of patients who were followed up in other outpatient clinics for complaints unrelated to anemia or who were diagnosed with anemia incidentally. Overall, 181 (44.4%) patients had no anemia-related problems, but the remaining 226 patients (55.6%) had such complaints. The most frequent issues were fatigue (50.8%), pallor (29.2%), and anorexia (27.8%) (Table 2). Analysis of the distribution of subgroups of nutritional anemia by age groups revealed that combined nutritional anemia was most common in infants and adolescents (57.3% and 48.6%, respectively), and iron deficiency anemia was most frequent in toddlers and schoolchildren (61.5% and 61%, respectively) (Table 3). The comparison of hemogram parameters of patients with iron deficiency anemia and those with combined nutritional anemia revealed that while the B12 value was lower in the group with combined nutritional anemia, MCV, iron, and transferrin saturation were higher ($p<0.05$). No significant difference was found in terms of other parameters. The mean MCV value was 70.39 fL in the iron-deficient group and 72.18 fL in the combined nutritional anemia group. Both groups had microcytic anemia (Table 4). The comparison of the B12 deficiency anemia and combined nutritional anemia groups revealed that the latter was associated with lower MCV, MCH, MCHC, iron, ferritin, and TS but higher RBC, red cell distribution width, TDBK, B12, and platelet count (PLT)/MCH levels ($p<0.05$) (Table 5). There were 213 patients with B12 levels <200 pg/mL. When the MCV levels of patients with B12 <120 pg/mL (n=82) and those with 120-200 pg/mL (n=131) were compared, 75.1±9.8 fL and 71.8±8.2 fL were found, respectively ($p=0.1$). Macrocytosis was detected in only one (4.3%) of 23 patients with isolated B12 deficiency. Eight (34.7%) patients had microcytosis and 14 (60.9%) patients had normocytosis. Five (21.7%) patients in the isolated B12 deficiency anemia group were under one year old.

Table 1. Nutritional anemias detected in patients

Type of nutritional anemia	n=407	%
Iron deficiency anemia	192	47.2
Iron deficiency + B12 deficiency anemia*	185	45.4
B12 deficiency anemia	23	5.7
Iron deficiency and folic acid deficiency anemia	4	1
Iron deficiency-B12 deficiency-folic acid deficiency anemia	2	0.5
B12 deficiency and folic acid deficiency anemia	1	0.2

*: Iron deficiency + B12 deficiency anemia; combined nutritional anemia

Table 2. The complaints of the patients

Complaints	n=226	%
Fatigue	115	50.8
Pallor	66	29.2
Anorexia	63	27.8
Anorexia and fatigue	34	15
Fatigue and pallor	20	8.8
Dizziness	13	5.7
Palpitation	7	3
Motor retardation	5	2.2
Hair loss	5	2.2
Failure to thrive	4	1.7
Pica	4	1.7
Fatigue and hair loss	3	1.3
Bloody stool	3	1.3
Breath holding spell	3	1.3
Nose bleeding	1	0.4

Discussion

Nutritional anemia develops because of the deficiency of micronutrients such as iron, vitamin B12, folic acid, and zinc, which play crucial roles in hemoglobin synthesis. While it is the primary type of nutritional anemia, iron deficiency anemia is also the most prevalent type of anemia in childhood[1,4]. The prevalence of iron deficiency anemia among children in low- and middle-income countries varies between approximately 35% and 90%[10,11]. Nutritional vitamin B12 deficiency anemia, similar to iron deficiency anemia, is a significant health problem, particularly in developing countries. Some studies have reported that the incidence of vitamin B12 deficiency anemia changes between 22% and 65% in regions with low socioeconomic status[12,13]. In our study, iron deficiency anemia was the predominant form (47.2%), followed by combined nutritional anemia (185 patients-45.4%), and isolated B12 deficiency anemia (23 patients-5.7%). Among 185 patients with combined nutritional anemia, 61 had B12 levels below 120 pg/mL. Even though nutritional anemia patients often present with different complaints, such as weakness, loss

Table 3. Distribution of nutritional anemias by age groups

Age groups	n	%	Type of nutritional anemia	n	%
0-2 years	89	21.9	Iron deficiency	32	36
			B12 deficiency	6	6.7
			Iron deficiency + B12 deficiency	51	57.3
2-6 years	83	20.4	Iron deficiency	51	61.5
			B12 deficiency	5	6
			Iron deficiency + B12 deficiency	27	32.5
6-12 years	59	14.5	Iron deficiency	36	61
			B12 deficiency	4	6.8
			Iron deficiency + B12 deficiency	17	28.8
			Iron deficiency + B12 deficiency + folic acid deficiency	1	1.7
			B12 deficiency + folic acid deficiency	1	1.7
12-18 years	176	43.2	Iron deficiency	73	41.7
			B12 deficiency	8	4.5
			Iron deficiency + B12 deficiency	90	48.6
			Iron deficiency+ folic acid deficiency	2	1.1
			Iron deficiency + B12 deficiency + folic acid deficiency	3	1.7
0-18 years	407	100		407	

Table 4. Laboratory parameters of iron deficiency anemia and combined nutritional anemia

	Iron deficiency anemia (n=192)	Combined nutritional anemia (n=185)	p-value *
WBC (/mm³)	7897.70±2334.46	7792.37±2475.12	0.671
RBC	4.37±0.43	4.28±0.57	0.098
HB (g/dL)	9.42±1.46	9.43±1.68	0.983
HTC (%)	30.60±3.76	30.50±4.63	0.818
MCV (fL)	70.39±7.44	72.18±8.69	**0.032**
MCH (pg)	21.78±3.31	22.46±3.80	0,066
MCHC (g/dL)	30.67±1.92	30.95±1.99	0.166
RDW (%)	17.53±3.27	17.6±3.15	0.159
PLT (/mm³)	357208.33±124947.06	351054.05±111148.63	0.614
PLT/MCV (mm³/fL)	5175.74±2091.34	4958.55±1834.47	0.285
PLT/MCH (mm³/pg)	16981.18±7755.34	16228.52±6505.28	0.309
FE (ug/dL)	21.37±10.16	24.88±10.16	**0.006**
TDBK (ug/dL)	431.21±69.31	426.34±77.48	0.520
TS (%)	5.03±2.53	5.95±3.78	**0.005**
Ferritin (ng/mL)	6.25±3.55	6.33±3.59	0.830
B12 (pg/mL)	325.58±113.38	133.50±37.36	**0.000**
Folic acid (ng/mL)	10.86±5.05	11.23±6.08	0.525

*: p<0.05, FE: Iron, TDBK: Total iron-binding capacity, TS: Transferrin saturation, WBC: White blood cell, RBC: Red blood cell, MCV: Mean erythrocyte volume, HTC: Hydrochlorothiazide, MCH: Mean corpuscular hemoglobin concentration, PLT: Platelet count

Table 5. Laboratory parameters of B12 deficiency anemia and combined nutritional anemia			
	B12 deficiency anemia (n=23)	**Combined nutritional anemia (n=185)**	**p-value ***
WBC (/mm³)	7940.86±2081.47	7792.37±2475.12	0.458
RBC	3.95±0.72	4.44±0.62	**0.004**
HB (g/dL)	10.00±1.54	9.43±1.68	0.082
HTC %	31.38±5.00	30.50±4.63	0.190
MCV (fL)	80.22±7.12	72.18±8.69	**<0.001**
MCH (pg)	25.85±2.87	22.46±3.80	**<0.001**
MCHC (g/dL)	32.22±1.23	30.95±1.99	**0.001**
RDW (%)	15.04±2.37	17.06±3.15	**<0.001**
PLT (/mm³)	347521.73±153135.96	351054.05±111148.63	0.513
PLT/MCV (mm³/fL)	4386.02±2002.31	4958.55±1834.47	0.078
PLT/MCH (mm³/pg)	13654.21±6264.97	16228.52±6505.28	**0.036**
FE (ug/dL)	82.11±69.19	24.88±10.16	**<0.001**
TDBK (ug/dL)	353.46±72.04	426.34±77.48	**<0.001**
TS (%)	22.61±14.91	5.95±5.78	**<0.001**
Ferritin (ng/mL)	16.52±13.63	6.33±3.59	**<0.001**
B12 (pg/mL)	107.04±41.78	133.50±37.36	**0.004**
Folic acid (ng/mL)	10.90±5.67	11.23±6.08	0.984

*: p<0.05, FE: Iron, TDBK: Total iron-binding capacity, TS: Transferrin saturation, WBC: White blood cell, RBC: Red blood cell, MCV: Mean erythrocyte volume, HTC: Hydrochlorothiazide, MCH: Mean corpuscular hemoglobin concentration, PLT: Platelet count

of appetite, pallor, and pica, those with mild anemia may have no complaints, which in turn renders the diagnosis incidental. In fact, in our study, most patients (44.4%) had no complaints, and these patients applied to other clinics for various unrelated reasons. In a prospective study that focused on nutritional anemia, the most common symptoms were cited as anorexia (71%), fatigue (45%), and pica (36.3%), respectively[14]. In our study, the most common complaints were fatigue (50.8%), pallor (29.2%), and anorexia (27.8%).

Nutritional anemia is more frequent in infancy and adolescence, during periods of rapid growth and increased nutritional needs. We found that anemia was most prevalent among the 12-18-year-old group (43.2%). Our finding is in harmony with the results of an earlier study, which also revealed that this age group had higher deficiencies of iron, folate, and vitamin B12 than the others[15]. In a similar study that explored 1120 randomly selected children aged between 12 and 16 years, anemia was identified in 5.6% of them, of whom the majority had iron deficiency anemia (59%), and the remaining had (41%) combined nutritional anemia[16]. In contrast, in our study, the preponderance had combined nutritional anemia (48.6%), followed by iron deficiency anemia (41.7%). More importantly, combined nutritional anemia was detected at a high rate in the 0-2 age group (57.3%). Because neurological development is rapid in this age group, it is vital to detect and treat B12 and iron deficiency.

Mean erythrocyte volume, one of the erythrocyte indices, is one of the most important parameters used in the classification of anemia. In anemic patients, high MCV indicates macrocytosis and low MCV indicates microcytosis. Often, isolated B12 deficiency anemia manifests itself as macrocytic anemia, but some studies have presented evidence against it. A retrospective study on children and adolescents with anemia indicated that only 3.5% of patients with isolated B12 deficiency had macrocytosis[15]. We reached a similar result: Macrocytosis was present in only one of 23 isolated cases of B12 deficiency anemia (4.3%). Remarkably, macrocytosis was rare in isolated B12-deficient anemia. A study investigating the relationship between the level of B12 deficiency and MCV could not find a significant difference between the two groups of patients: Those having B12 levels of 200-300 pg/mL and the others below 200 pg/mL (The respective MCVs were 80.12±7.25 and 80.57±5.33)[17]. In our study, we did not find a significant difference between the MCV levels of patients with B12 levels <120 pg/mL and those with 120-200 pg/mL (75.1 fL and 71.8 fL, respectively). Overall, these findings demonstrate that MCV levels may be misleading in estimating isolated B12 deficiency anemia. In addition,

macrocytosis may be masked when B12 deficiency anemia is accompanied by thalassemia, iron deficiency anemia, or anemia of chronic disease, resulting in underdiagnosis of B12 deficiency anemia[6,18]. In fact, a study that investigated MCV levels in combined nutritional anemia found the mean MCV levels were low (59.8±6.6 fL)[14]. Likewise, in our study, microcytosis was observed not only in iron deficiency anemia but also in combined nutritional anemia (MCV 70.39±7.44 and 72.18±8.69, respectively). Overall, a patient presenting with microcytic anemia need not have solely isolated iron deficiency anemia, as iron deficiency anemia can coexist with B12 deficiency anemia. Because MCV alone is not a complete guide in combined nutritional anemia, some studies have examined specific parameters such as MCV/PLT or MCH/PLT. A study performed on adults discovered that combined nutritional anemia patients had higher platelet levels and lower MCV levels than those with pure iron deficiency anemia. Consequently, the authors found that the PLT/MCV ratio was significantly higher when iron deficiency was copresent with vitamin B12 deficiency, recommending the measurement of vitamin B12 levels in patients with iron deficiency anemia with a high PLT/MCV ratio[19]. However, our results indicated no difference between the two groups regarding the above-mentioned parameters. On the other hand, when we compared patients with combined nutritional anemia with those with B12 deficiency anemia, the former was associated with an elevated PLT/MCH ratio. This increase may be due to the higher incidence of thrombocytosis and lower MCH levels in patients with iron deficiency.

B12 deficiency can cause not only megaloblastic anemia and severe neurological deficits. A study on 15 B12 deficiency anemia patients (with a mean age of 11.7 months), of whom 46.6% presented with epileptic seizures, observed neurodevelopmental retardation, pallor, hypotonia, and anorexia[20]. In the same vein, another study reported motor and developmental retardation in infants whose mothers were vegan, vegetarian, or had a B12-restricted diet[21]. In congruence with the research above, our outpatient clinic examination identified motor retardation in five patients with B12 deficiency anemia. Two of the patients presenting with motor retardation had isolated B12 deficiency anemia, whereas the other three were from the combined nutritional anemia group.

Study Limitations

The fact that the research was conducted in a single center can be considered as one of the limitations of the study. It is also a retrospective study, but we used a standard study form to collect data, and the same clinician performed the data collection.

Conclusion

Especially in microcytic anemia due to nutritional reasons, iron deficiency is likely to be accompanied by B12 deficiency. Early diagnosis and appropriate treatment of vitamin B12 deficiency are necessary because they can lead to severe neurological and hematological problems if left untreated. Therefore, it is essential to measure serum vitamin B12 levels and iron parameters in patients presenting with microcytic anemia.

Ethics

Ethics Committee Approval: Ethical approval for the current study was obtained from the Scientific Research Ethics Committee of Manisa Celal Bayar University the approval number: 20.478.486/692, dated: 30/12/2020.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: A.T.Y., Design: A.T.Y., Data Collection or Processing: Ş.A.A., Analysis or Interpretation: Ş.A.A., A.T.Y., Literature Search: Ş.A.A., A.T.Y., Writing: Ş.A.A., A.T.Y.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Evaluation of the Factors Causing Type 2 Diabetes Mellitus on Age of Onset in the İstanbul Kartal Region

İstanbul Kartal Bölgesi'nde Tip 2 Diabetes Mellitusun Başlangıç Yaşını Belirleyen Faktörlerin Değerlendirilmesi

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Abstract

Objective: We planned to investigate the age of onset of type 2 diabetes mellitus (T2DM) in our region and the factors affecting it in the İstanbul Kartal Region.

Methods: Age at diagnosis, body mass index, exercise, alcohol consumption, smoking, and co-morbidity anamnesis were taken from 566 T2DM patients who applied to our hospital. Factors related to diabetes were questioned in these cases.

Results: The mean age of onset for all cases was 50.01±10.50 years, whereas the age at diagnosis was 49.20 years in females and 51.40 years in males. The mean age at diagnosis is 47.11±9.56 (p=0.001) years in women with maternal T2DM, and it decreased to 45.89±9.57 years in women with paternal T2DM (p=0.001). In males, the mean age at diagnosis was 54.16±11.10 years in the absence of maternal T2DM, whereas it decreased to 47.93±9.58 years in the maternal T2DM (p=0.001). The presence of T2DM on the paternal side in men did not affect the age at diagnosis. In addition, a positive correlation was found between the number of pregnancies and age at diagnosis (p=0.001). Obesity, educational status, exercise, nutritional status, smoking, and marital status did not affect the age of onset.

Conclusion: Our study showed that female gender and family history decreased the age of onset of T2DM, whereas the total number of pregnancies increased the age at diagnosis. Our study results suggest that T2DM screening should be performed earlier in women and/or those with a family history of T2DM.

Keywords: Type 2 diabetes mellitus, diagnostic age, body mass index, family history

Öz

Amaç: Bölgemizde tip 2 diabetes mellitusun (T2DM) başlangıç yaşını ve bunu etkileyen faktörleri araştırmayı planladık.

Yöntem: Hastanemize başvuran 566 T2DM olgusunun tanı yaşı, yaş ve cinsiyetleri, beden kitle indeksleri, egzersiz, alkol, sigara, eşlik eden hastalık anamnezi, eğitim durumu, medeni hali, hepatosteatoz öyküsü, prediyabet, bozulmuş açlık glukozu öyküsü, beslenme öyküsü kaydedilmiştir. Kadın hastalara ek olarak toplam gebelik sayısı, iri bebek doğurma öyküsü (4000 gr ve üzeri), gestasyonel DM öyküsü ve polikistik over sendromu öyküsü sorgulanmıştır.

Bulgular: Tüm olguların ortalama başlangıç yaşı 50,01±10,50 iken, kadınlarda tanı yaşı 49,20 erkeklerde ise 51,40 bulundu. Anne tarafı akrabalarında T2DM olan kadınlarda ortalama tanı yaşı 47,11±9,56 (p=0,001), baba tarafı akrabalarında T2DM olan kadınlarda tanı yaşı 45,89±9,57'ye inmektedir (p=0.001). Erkeklerde ise anne tarafında T2DM olmadığında ortalama tanı yaşı 54,16±11,10 iken, anne tarafında T2DM tanısı olması halinde DM yaşı 47,93±9,58'e inmektedir (p=0,001). Erkeklerde baba tarafında T2DM varlığı tanı yaşını etkilememektedir. Ayrıca gebelik sayısı ile DM yaşı arasında pozitif ilişki de tespit edilmiştir (p=0,001). Türk toplumunda obezite, eğitim durumu, egzersiz, beslenme durumu, sigara kullanımı, medeni durum başlangıç yaşını etkilememektedir.

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Öz

Sonuç: Çalışmamız kadın cinsiyet ve aile öyküsünün T2DM başlangıç yaşını azalttığını, toplam gebelik sayısının ise tanı yaşını artırdığını göstermiştir. Kadınlarda ve/veya aile T2DM tanı öyküsü olanlarda T2DM taramalarının daha erken yapılması gerekliliğini çalışma sonuçlarımız düşündürtmektedir.

Anahtar Kelimeler: Tip 2 diabetes mellitus, tanı yaşı, vücut kitle indeksi, aile öyküsü

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) has increased rapidly in the 1990s and early 2000s[1], and it is estimated that more than 400 million people are affected worldwide[2]. T2DM has been diagnosed at younger ages over time[3]. Aging population, low physical activity, obesity, and increased urbanization rates increase the prevalence of T2DM. It is thought that obesity is the main reason for the increase in T2DM, and it increases the incidence of T2DM by 70-90%[4]. Family history, age, obesity, and immobility are observed in individuals at high risk for T2DM. Family history is related not only to genetic factors but also to the familial acquisition of diet and exercise habits. Women with a history of gestational diabetes mellitus and their children are at risk for T2DM in the future. Insulin resistance and impaired glucose tolerance increase the risk of T2DM. Current interventions to prevent and delay T2DM are those that aim to change the environmental risk factors such as reducing obesity and promoting physical activity. Knowing the risk factors for the development of T2DM encourages screening, early diagnosis, and treatment as well as treatment in high-risk populations to reduce both microvascular and macrovascular complications[5].

Study Objective

We planned to investigate the age of onset of diabetes in the Turkish society who live in the İstanbul Kartal Region and which factors most affect the age of onset of the disease.

Materials and Methods

Five hundred sixty-six T2DM cases consecutively admitted to the internal medicine outpatient clinic were included in the study. T2DM cases that we were following with the diagnosis of T2DM or newly diagnosed T2DM were included in the study if consent was obtained. Cases followed for T1DM history, DM developed because of steroid use, and gestational DM were not included in our prospective and randomized study. Patients who were mentally competent to answer the questions were included in the study, and patients with dementia were excluded. Age at diagnosis, age and gender of the patients, body mass index, exercise (30 minutes of walking 5 days a week and equivalent exercise), alcohol consumption, smoking, history of co-morbidity, educational status, marital status, history of hepatosteatosis, history of prediabetes, and nutritional status were recorded. In addition, the total number of pregnancies, history of giving birth to a large baby (4000 gr and above), history of gestational DM, and polycystic ovary syndrome were questioned in women. All patients were asked about their birth weight, and due to insufficient response, birth weight questioning, which may affect the development of T2DM, was excluded from the scope of the study and canceled.

Ethical committee approval was obtained for University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital (decision no: 2021/514/216/6).

Statistical Analysis

The Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used to evaluate the study data. The conformity of the quantitative data to the normal distribution was tested using the Shapiro-Wilk test and graphical examinations. The independent groups t-test was used for the comparison of the normally distributed quantitative variables between the two groups. One-Way Analysis of Variance and binary evaluations with Bonferroni correction were used for comparisons between groups of more than two normally distributed quantitative variables. Spearman correlation analysis was used to evaluate the relationships between the quantitative variables. Statistical significance was set as $p<0.05$.

Results

The study was conducted with a total of 566 cases, 63.3% (n=358) female, and 36.7% (n=208) male, in the internal medicine outpatient clinic between January and March 2022. The ages of the cases ranged from 27 to 88 years, and the mean age was 59.40±10.06 years (Table 1).

Table 1. Distribution of descriptive features		
		n (%)
Gender	Female	358 (63.3)
	Male	208 (36.7)
Age (year)	Mean ± SD	59.40±10.06
	Median (min-max)	59 (27-88)
Age of onset of DM (year)	Mean ± SD	50.01±10.50
	Median (min-maks)	50 (6-83)
Height (m)	Mean ± SD	1.63±0.08
	Median (min-max)	1.6 (1.4-1.9)
Weight (kg)	Mean ± SD	82.39±14.65
	Median (min-max)	80 (48-140)
BMI (kg/m^2)	Mean ± SD	30.97±5.57
	Median (min-max)	30.1 (17.7-49.5)
Educational status	Primary school	442 (78.2)
	Secondary school	39 (6.9)
	High school	54 (9.6)
	University	30 (5.3)
Marital status	Single	77 (13.6)
	Married	489 (86.4)
Exercise	No	380 (67.5)
	Yes	183 (32.5)
Alcohol	No	548 (96.8)
	Yes	18 (3.2)
Smoking	No	480 (84.8)
	Yes	86 (15.2)
Co-morbidity	No	124 (21.9)
	Yes	442 (78.1)
	Asthma	14 (3.2)
	HT	266 (60.2)
	HL	133 (30.1)
	Hypothyroidism	43 (9.7)
	CAD	70 (15.8)
	COPD	18 (4.1)
	CRF	9 (2.0)
	CVA	5 (1.1)
	Malignancy	9 (2.0)
	RA	6 (1.4)
	Other	10 (2.3)
Maternal diabetes	No	274 (48.4)
	Yes	292 (51.6)
Paternal diabetes	No	353 (62.4)
	Yes	213 (37.6)
No of pregnancy (n=358)	Mean ± SD	4.25±2.70
	Median (min-max)	4 (0-20)
LGA history (n=358)	No	206 (57.5)
	Yes	152 (42.5)
Gestational DM (n=358)	No	325 (90.8)
	Yes	33 (9.2)
PCOS (n=358)	No	290 (81.0)
	Yes	68 (19.0)
Hepatosteatosis	No	309 (54.6)
	Yes	257 (45.4)
Prediabetes	No	406 (71.7)
	Yes	160 (28.3)
Healthy diet	No	291 (51.4)
	Yes	275 (48.6)

SD: Standard deviation, DM: Diabetes mellitus, BMI: Body mass index, HT: Hypertension, CRF: Chronic renal failure, HL: Hyperlipidemia, SVO: Cerebrovascular accident, CAD: Coronary artery disease, RA: Rheumatoid arthritis, COPD: Chronic obstructive pulmonary disease, PCOS: Polycystic ovary syndrome, LGA: Large for a gestational age infant

The BMI measurements of the patients ranged from 17.7 kg/m^2 to 49.5 kg/m^2, and the mean BMI measurement was determined 30.97±5.57 kg/m^2.

When the educational status was examined, 78.2% (n=442) of the cases were primary school, 6.9% (n=39) secondary school, 9.6% (n=54) high school, and 5.3% (n=30) university graduates.

While 13.6% (n=77) of the participants in the study were single, 86.4% (n=489) were married. 32.5% (n=183) of the cases performed exercises.

Alcohol use was reported in 3.2% (n=18) (average consumption 30 gr/week) and smoking in 15.2% (n=86) (average use 1 pack/day).

There was at least one comorbidity in 78.1% (n=442) of patients. 60.2% (n=266) of the patients with additional disease had hypertension (HT), 30.1% (n=133) hyperlipidemia (HL), 15.8% (n=70) coronary artery disease (CAD), 9.7% (n=43) hypothyroidism, 4.1% (n=18) chronic obstructive pulmonary disease (COPD), 3.2% (n=14) asthma, 2% (n=9) chronic renal failure (CRF), 2% (n=9) malignancy, 1.1% (n=5) cerebrovascular accident (CVA), 1.4% (n=6) rheumatoid arthritis (RA), and 2.3% (n=10) other comorbidities.

The age at the diagnosis of DM in the cases ranged from 27 to 83 years, with a mean age of 50.01±10.50 years, and the average age for males was 51.48 years and 49.26 years for females.

T2DM was present in the mother in 51.6% (n=292), and in father in 37.6% (n=213) of cases. The number of pregnancies (live birth + still birth +abortion) of the cases ranged from 0 to 20, and the average number of pregnancies was 4.25±2.70. 42.5% (n=152) of the cases had a history of large for gestational age infant. 9.2% (n=33) of the women participating in the study had a history of gestational DM. 19% (n=68) of the women participating in the study had a history of PCOS. Fatty liver disease was present in 45.4% (n=257) of the cases. 28.3% (n=160) of the participants had prediabetes before being diagnosed with DM. 48.6% (n=275) of the participants in the study had a healthy and balanced diet (Table 2).

Table 2. Relationship between the age of onset of DM and BMI and number of pregnancies

		Age of onset of DM
BMI (kg/m²)	r	-0.079
	p	**0.062**
No of pregnancy	r	0.258
	p	**0.001****

r: Spearman correlation coefficient, **: p<0.01, DM: Diabetes mellitus, BMI: Body mass index

A statistically significant and weak correlation was found between the age of onset of DM and the number of pregnancies (the age of onset of DM increased with an increase in the number of pregnancies) (r=0.258; p=0.001; p<0.01).

No statistically significant correlation was found between the age of onset of DM in the cases and their BMI measurements (p>0.05) (Table 3).

The age of onset of DM in women was found to be significantly lower than men (p=0.021; p<0.05).

There was no statistically significant difference between the age of onset of DM in men and women according to their marital status, education, exercise, and healthy diet (p>0.05) (Table 4).

While the mean age of onset was 51.86±9.93 years in women without a history of maternal diabetes, the mean age of onset decreased to 47.11±9.56 years in the presence of maternal diabetes. The age of onset of DM in women with maternal diabetes was found to be significantly lower than that in those without (p=0.001; p<0.01).

While the mean age of onset was 51.53±10.02 years in women without a history of paternal diabetes, it decreased to 45.89±9.57 years with a history of paternal diabetes. The age of onset of DM in women with paternal diabetes was found to be significantly lower than that in those without (p=0.001; p<0.01).

Table 3. Evaluation of age of onset of DM according to descriptive features

		Age of onset of DM		p
		Mean ± SD	**Median (min-max)**	
Gender	Female	49.23±10.21	49 (23-79)	[a]**0.021***
	Male	51.34±10.87	50 (6-83)	
Marital status	Single	51.36±11.74	52 (27-75)	[a]**0.223**
	Married	49.79±10.29	50 (6-83)	
Educational school	Primary school	50.46±10.67	50 (6-83)	[b]**0.192**
	Secondary school	48.72±8.67	48 (33-69)	
	High school	48.56±9.21	48 (29-71)	
	University	47.1±11.58	47 (27-71)	
Exercise	No	50.07±10.63	50 (6-83)	[a]**0.917**
	Yes	49.97±10.26	50 (27-78)	
Healthy diet	No	49.85±10.46	50 (23-79)	[a]**0.718**
	Yes	50.17±10.55	50 (6-83)	

[a]: Student's t-test, [b]: One-Way ANOVA test, *: p<0.05, SD: Standard deviation, DM: Diabetes mellitus

Table 4. Evaluation of the age of onset of DM according to the existence of maternal and paternal DM in women

		Age of onset of DM		p
		Mean ± SD	Median (min-max)	
Maternal diabetes (in women)	No	51.86±9.93	50 (27-78)	[a]0.001**
	Yes	47.11±9.56	47 (23-79)	
Paternal diabetes (in women)	No	51.53±10.02	50 (27-79)	[a]0.001**
	Yes	45.89±9.57	46 (23-75)	
Maternal diabetes (in men)	No	54.16±11.10	54 (6-83)	[a]0.001**
	Yes	47.93±9.58	48 (27-71)	
Paternal diabetes (in men)	No	51.84±10.82	51 (6-77)	[a]0.341
	Yes	50.30±11.00	50 (27-83)	

[a]: Student's t-test, **: p<0.01, DM: Diabetes mellitus, SD: Standard deviation

While the mean age of onset was 54.16±11.10 years in men without a history of maternal diabetes, it decreased to 47.93±9.58 years with the history of maternal diabetes. The age of onset of DM in women with maternal diabetes was found to be significantly lower than that in those without (p=0.001; p<0.01).

While the mean age of onset was 51.84±10.82 years in men without a history of paternal diabetes, it decreased to 50.30±11.00 years with the history of paternal diabetes. There was no statistically significant difference in the age of onset of DM in men according to the presence of paternal diabetes (p>0.05).

Discussion

Individuals diagnosed with T2DM have drastic reductions in life expectancy. If an individual is diagnosed at the age of 40, it is predicted that 11.6 life-years will be lost in men and 14.3 life-years in women[6]. Individuals diagnosed with T2DM at a young age have a higher incidence of obesity and higher HbA1c levels than those diagnosed at an older age. Their glycemic regulation also worsens faster. This supports the idea that early-onset T2DM may be a more pathogenic condition than late-onset disease[7]. All these findings show how important early onset age is in T2DM. In our study, there was no relationship between early onset age and BMI, and the mean BMI of the patients in our study was 30.1 kg/m^2. Since Turks in general and thus diabetic patients in our study are obese, and Turkey is the first in Europe for obesity in the World Health Organization 2022 report[8], our results cannot be generalized to the universe due to the small number of cases.

63.3% (n=358) of our cases were female and 36.7% (n=208) were male. At the same time, T2DM in women were diagnosed with DM on average 2.22 years earlier. Lifestyle, environment, socio-economic status, and biological and cultural differences affect the susceptibility and development of diabetes. There are serious differences in gender ratios between countries. The high tendency of obesity in women is also a factor in this. It is an essential biological factor that plays a key role in the regulation of metabolic homeostasis and causes vulnerability to the emergence, clinical presentation, and management of T2DM[9]. We believe that factors such as obesity, immobility, sex hormones and their postmenopausal changes, differences in body fat ratio and distribution between sexes, differences in muscle mass, and immobilization are effective in the gender distribution, which is almost F/M 2/1, and women being diagnosed earlier with DM. In addition, according to our observations in our country, the rate of admission to a health institution is higher for women than for men. This may lead to a later diagnosis in men.

Although the prevalence of T2DM is higher in men, there are more elderly women than elderly men all over the world. In a large cohort study, the prevalence of T2DM was 10.5%; 9.6% in men and 11.2% in women. It was reported in this study that the cases were mostly in the age range of 46-60 years[10]. Koopman et al.[11] showed that in the USA in 2000, the average age at diagnosis decreased from 52 to 46years. In the TURDEP-II data, the prevalence of T2DM in our population was 13.7%, which was slightly lower in men than in women. In the TURDEP-I study published in 1998, the diagnosis of T2DM was frequently made between the ages of 45 and 49 years, while the age of onset was reduced to 40 and 44 years in TURDEP-II in 2010[12]. In the years from TURDEP-I to TURDEP-II, the age at diagnosis of T2DM decreased by 5 years in our country. However, a more up-to-date age at diagnosis is not available for the Turkish population. The mean age at diagnosis for DM was 50 years.

In their study involving 2825 patients with T2DM, Svensson et al.[13] detected a parental history of T2DM in 34% of the cases and showed that the prevalence of diagnosis under 40 years of age was higher in those with a parental history. Parental history suggests that there may be more severe pancreatic beta-cell dysfunction at the time of diagnosis[13]. In our study, the DM family history of all cases was analyzed separately as maternal and paternal. It was observed that 51.6% (n=292) of the cases had maternal diabetes and 37.6% (n=213) had paternal diabetes. We showed that the presence of maternal and paternal DM in women showed a statistically significantly lower age at diagnosis, whereas in men, maternal DM decreased the age at diagnosis, whereas paternal DM did not affect the age at diagnosis. These results may be related to genetic transmission. Moreover, considering that the history of consanguineous T2DM does not affect the age of onset in males, the results of our study suggest that T2DM lineage transmission may be related to the X chromosome, a sex chromosome. Simultaneously, it also makes us think that the effect of parents, especially the mother, on the development of diet habits may affect DM susceptibility and age of onset. Our study is the only one examining the effect of maternal and paternal family history on age at diagnosis in men and women.

In a cross-sectional study of 5115 people in the Danish T2DM cohort, it was shown that daily smoking frequency was more common in those diagnosed with T2DM under the age of 45 years and that these cases did not have any exercise habits[14]. In our study, however, no relationship was found between exercise habits and the age of DM. No evaluation was made on the effects of age on T2DM diagnosis because only 15.2% of our patients were smoking and 3.2% were using alcohol.

Geiss et al.[15] showed that the incidence of DM is higher among those with a high school education and below than among those with a university education. In our study, no significant relationship was shown between education level and age of DM. The cases in our study do not have a balanced distribution in terms of educational status, and only 5.3% of all cases received a university education. Although our study, in which the individuals of Turkish society with T2DM are evaluated cross-sectionally, reflects the education level of that age group perfectly for our society, we think that different results can be obtained in terms of education level distribution in different societies. The result is generalizable to Turkish society and not to the universe.

A study on male diabetic cases showed a 16% higher risk of developing DM in single men than in married ones[16], and there is no other study investigating the status of women or the effect of marital status on diabetes age. However, in our study, we did not find a relationship between marital status and age at diagnosis of DM in female and male diabetics. Our study is the only one examining this situation.

In addition, contrary to our expectations, a weak positive correlation was observed between the total number of pregnancies and the age of onset of diabetes in female diabetics in our study. In a Danish birth cohort, the risk of diabetes diagnosis increased with parity[17]. This study was a risk assessment study, while our study examined the effect of the total number of pregnancies on the age at diagnosis and was the only study in which the effect of the current situation on the age at diagnosis of T2DM was examined. Insulin sensitivity decreases during pregnancy due to the activation of some hormones such as placental lactogen, estrogen, leptin, progesterone, prolactin, cortisol, and adiponectin. It has been reported that the decrease in insulin sensitivity due to all these hormones plays a central role in the pathophysiology of gestational diabetes[18]. While the total fertility rate was 1.7 in our country as of 2021[19], the mean number of pregnancies in pre/postmenopausal women was 4.25 in our study. Since our society is fertile in that age group, this may have resulted in this way. We believe that the effect of parity and the total number of pregnancies on the age at diagnosis of T2DM will be less, and a comparative evaluation may yield more accurate results with a group of multiparous women. When we make predictions about the socio-cultural levels of our cases based on their education levels, it is seen that all segments of society are not represented homogeneously and at a similar level. In addition, we believe that the susceptibility to diabetes will be affected by the change in the socio-cultural level, the change in nutrition-exercise-diet habits, the differentiation of healthy food access opportunities, and the change in birth-pregnancy rates. Although our study, which included randomized cases, reflects the perfect educational and cultural distribution of diabetic cases in our society, we do not think that our current data can be generalized due to the number of births and cultural reasons, due to the socio-cultural misrepresentation of all segments in our society at equal levels. We believe that better results can be obtained in countries with a more balanced class distribution, such as Central and Western Europe, and with social data where there is no significant difference between income level, education level, and socio-cultural classes.

Because of all our evaluations, we have concluded that factors that may affect the age of DM include female gender and maternal diabetes. Our study is the only study in the literature that comprehensively examines the effect of factors on the age of DM onset.

Study Limitations

With a study to be conducted in a population balanced in terms of educational status, more results could be obtained regarding the effect of education status on the age of DM. Likewise, due to the fact that our society is obese, a study to be conducted in a society that is more balanced in terms of weight and BMI will more accurately reflect the relationship between BMI and age of onset of D at diagnosis. Because alcohol consumption for religious reasons is very low in our country, the effect of alcohol consumption could not be evaluated in our study. The limitations of our study are the fact that elderly patients do not know whether they have a history of gestational diabetes and/or did not have the necessary medical follow-up or treatment because they do not have any clinical follow-up, their prediabetes history is not sufficiently known, and the subjective responses we received about exercises.

Conclusion

The mean age of onset of DM in our study was 50 years, and women were diagnosed with T2DM 2.2 years earlier at the age of 49.2 years, which is statistically significant. A history of both maternal and paternal T2DM significantly reduces the age at diagnosis in women. In males, although a history of maternal T2DM significantly reduces the age at diagnosis, the effect of a history of paternal T2DM on the age of onset was not demonstrated in our study. This situation made us think that there is a possibility that there may be a connection between sex chromosome X and age at diagnosis. Contrary to our expectations, the age at diagnosis increased as the number of pregnancies increased. This may have resulted in this way because of the high fertility rate in women in the age group diagnosed with DM in our society. No relationship could be established between BMI, smoking, nutritional status, exercise status, educational status, marital status, and age at diagnosis of DM. In conclusion, female gender and especially maternal family history are the most important factors in lowering the age of T2 onset.

As of 2022, the age at onset has been determined to be 50 years in the Turkish population, and our study results suggest that T2DM screening should be increased a few years before this age, especially in women and those with a family history. In outpatient clinic conditions, not only fasting plasma glucose, HbA1c level, postprandial blood glucose, and even oral glucose tolerance tests can be useful in early diagnosis.

Ethics

Ethics Committee Approval: Ethical committee approval was obtained for University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital (decision no: 2021/514/216/6).

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: Z.K., S.A., Concept: Z.K., H.Ç.T., Design: Z.K., H.Ç.T., Data Collection or Processing: Z.K., S.A., Analysis or Interpretation: Z.K., S.A., Literature Search: Z.K., S.A., Writing: Z.K., H.Ç.T.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Association Between Sarcopenia, Insomnia, and Depression in Elderly Patients

Yaşlı Hastalarda Sarkopeni, Uyku Bozukluğu ve Depresyon İlişkisi

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Abstract

Objective: Sarcopenia is progressive and generalized loss of muscle mass, muscle strength, and function. In this study, we aimed to examine the relationship between the presence of depression and insomnia in elderly sarcopenic patients.

Methods: Volunteer patients to participate in the study who applied to the geriatric outpatient clinic with any complaints as of June 2022 were included. The inclusion criteria were being over 65 years of age and with a score of over 24 out of 30 in the mini-mental state examination. Neuropsychological tests were performed by specialist psychologists in an appropriate environment and at an appropriate time. Those diagnosed with depression according to the Geriatric Depression Scale were recorded. Patients with insomnias were questioned whether they had complaints about sleep onset latency, staying asleep, and duration of sleep.

Results: Two hundred-five patients were included in the study. The mean age of the patients was 75.54 (±6.5) years, with 117 females 57% and 88 males 43%. According to the European Sarcopenia Diagnostic Guide, 48 (23.4%) patients were found to be sarcopenic. There was no difference between men and women in terms of the frequency of sarcopenia. Depression was significantly more common in the sarcopenic group. We found out that patients with sarcopenia had a higher rate of insomnia. Sleep onset latency, staying asleep, and duration of sleep problems were more common in these patients.

Conclusion: When sarcopenic patients and non-sarcopenic patients were compared, depression and insomnia were more common in the sarcopenic group.

Keywords: Sarcopenia, elderly, insomnia, depression

Öz

Amaç: Sarkopeni; kas kütlesi, kas gücü ve fonksiyonlarında progresif ve jeneralize kayıptır. Biz bu çalışmamızda yaşlı sarkopenik hastalarda depresyon varlığı ve uyku bozukluğu ilişkisini araştırmayı amaçladık

Yöntem: Geriatri polikliniğine Haziran 2022 tarihinde itibaren herhangi bir şikayeti nedeni ile başvuran hastalar arasından çalışmaya katılmaya gönüllü olan hastalar alındı. Alınma kriterleri 65 yaş üstü, mini mental durum değerlendirme testi 30 puan üzerinden 24 puan üzerinde olanlar dahil edildi. Nöropsikiyatrik testler uygun bir ortamdan ve uygun bir sürede uzman psikologlar tarafından uygulandı. Geriatrik depresyon skorlamasına göre depresyon tanısı olanlar kayıt edildi. Uyku bozukluğu hastalara uykuya başlama, sürdürme ve süre ile ilgili şikayetlerinin olup olmadığı sorgulandı.

Bulgular: Çalışmaya 205 hasta dahil edildi. Hastaların yaş ortalaması 75,54±6,5 olup 117 (%57) kadın ve 88 (%43) erkekten oluşmaktaydı. Hastaların Avrupa Sarkopeni tanı Klavuzu'na göre 48 (%23,4) kişi sarkopenik olarak saptandı. Sarkopeni sıklığı açısından kadın ve erkekler arasında fark saptanmadı. Sarkopenik

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Öz

grupta depresyon anlamlı derecede daha fazla görülmekteydi. Sarkopenisi olan hastalarda uyku bozukluğu şikayeti daha fazla oranda olduğunu saptadık. Hastaların uykuya başlama, devam ettirme ve süre sorunları daha fazla görülmekteydi.

Sonuç: Sarkopenik hastalar ile sarkopenik olmayan hastalar karşılaştırıldığında sarkopenik grup hastalarda depresyon ve uyku bozukluğu daha fazla oranda görülmekteydi.

Anahtar Kelimeler: Sarkopeni, yaşlı, insomnia, depresyon

Introduction

Sarcopenia is a progressive and generalized loss of muscle mass, muscle strength, and function. The European study group on sarcopenia in the elderly, the European Working Group on Sarcopenia in Older People (EWGSOP), defined sarcopenia as low muscle mass and low muscle function[1]. While the prevalence of sarcopenia is between 13% and 27% at <70 years of age, it reaches 50% at >80 years of age[2]. It is a result of the aging process and is considered as a geriatric syndrome.

With the increase in the elderly population all over the world, the frequency of sarcopenia also increases, making it difficult to diagnose in clinical practice.

Sarcopenia is usually accompanied by a decline in physical inactivity and mobility, slow walking speed, falling, fractures, and decreased physical strength. In addition, it can cause health problems related to diabetes mellitus, metabolic syndrome, cardiovascular diseases, mortality, and physical inactivity[3]. The development of sarcopenia in elderly patients affects daily life and instrumental daily life activities[4]. The presence of sarcopenia causes poor quality of life in elderly patients, and there are studies showing that it can cause depression[5]. Due to the decrease in muscle strength and mobility, the socialization of the elderly is impaired and they become introverted. In some cases, the clinical pictures are intertwined. Insomnia is frequently observed in these patients[6].

Depression may develop in the elderly population for many reasons. Depression in the elderly presents with symptoms such as introversion, sadness, crying, sleep disorder, attention disorder, appetite, and weight loss[7]. These symptoms are often regarded as natural signs of aging. Causes such as chronic diseases, loss of family and friends, financial disorders, pain, social isolation, low socio-economic status, and physical deterioration may also cause depression in the elderly[8]. The frequency of depression and insomnia varies according to countries and societies. Reasons may vary in each society. Depression and insomnia are very common in some countries. Depression and insomnia may also differ between the young and old.

In this study, we aimed to investigate the relationship between the presence of depression and insomnia in elderly sarcopenic patients.

Materials and Methods

Volunteer patients to participate in the study who applied to the geriatric outpatient clinic with any complaints as of June 2022 were included. The study consent of all patients were obtained. The inclusion criteria were being over 65 years of age and having a score of over 24 out of 30 in the mini-mental status examination (MMSE). Patients with walking difficulties (due to pain, prosthesis, vision loss, etc.), vitamin D deficiency[9], or using ancillary tools (walker, cane, etc.), patients with sequelae and hip fractures after cerebrovascular disease, and those without postoperative 6 months were not included.

The Lawton-Brody instrumental activities of daily living (IADL) and the Barthel index for activities of daily living (ADL) tests were performed on the patients.

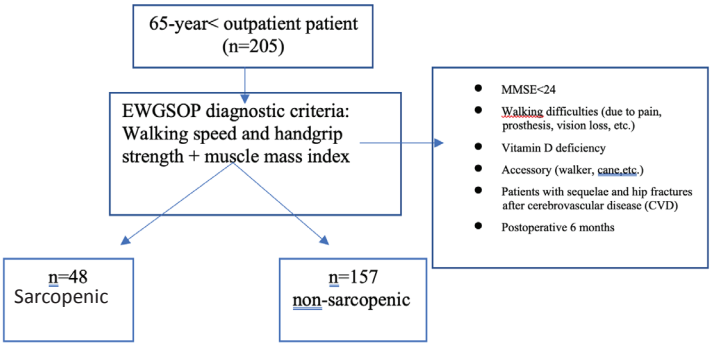
Neuropsychological tests were performed by specialist psychologists in an appropriate environment and at an appropriate time. Those with 4< according to the Yesavage Geriatric Depression Scale (YGDS) and those diagnosed with depression were recorded.

This study was approved by İzmir Katip Çelebi University (no: 0315, date: 16.06.2022).

Sarcopenia

EWGSOP diagnostic criteria were used for sarcopenia. Handgrip and walking speed of the patients who were admitted to the outpatient clinic were measured and bioelectrical impedance analysis for the diagnosis of sarcopenia[1]. First, patients were tested with a Jamar hand dynamometer twice on both arms at a 90-degree angle in each sitting position.

The highest measured value was set. A walking track of 4.5 m was created for the walking speed of the patients, and two trials were conducted. The patient's fastest walking speed was accepted. Sarcopenia was diagnosed by measuring the handgrip strength. A reference value of 32 kg in men and 22 kg in women was accepted for the diagnosis of sarcopenia[10]. A walking speed of 0.8 m/s> and a handgrip strength of 32 kg> for men and 22 kg> for women, a muscle mass index of 10.75 kg/m^2> for men, and a muscle mass index of 6.75 kg/m^2> for women are definitive for sarcopenia[11]. Those who were diagnosed as sarcopenic (48 patients, 23.4%). The muscle mass index of 5.37 kg/m^2 in the sarcopenic group, 14.7 kg/m^2 in the non-sarcopenic group, 5.20 kg/m^2 in the sarcopenic group of women, and 8.40 kg/m^2 in the non-sarcopenic group of women. The muscle mass index was calculated by dividing the square of the height in meters by the total muscle mass calculated by the "Tanita-300 Body Composition Analyzer" used in our study.



Triceps skin thickness and mid-arm circumference measurements are parameters that can be used for anthropometric evaluation, but they were not preferred in elderly patients because of changes in body fat distribution.

Depression and Insomnia

For the diagnosis of depression, the burnout status of the patients was questioned, and the Yesavage geriatric depression scale was implemented. The YGDS-15 test was preferred because of its validity and reliability in Turkish[12]. A 15-question test was performed for the diagnosis of depression. <4 score was considered depressive.

The patients were questioned regarding insomnia while taking anamnesis. Patients with sleep onset latency and total duration problems were classified as having insomnia. Patients with poor sleep hygiene (those who slept many times during the day) were not included.

Measurement of Other Variables

Height, weight measurements, smoking and/or alcohol use, educational status, marital status, and laboratory values of the patients were recorded during their admission. The examinations of the patients were performed during morning fasting. Comorbidities were questioned and checked through the health system.

The MMSE, the Barthel index for ADL, and the Lawton-Broody IADL were administered by expert psychologists in the appropriate environment and time. MMSE was applied separately for those who were educated and uneducated over 30 points, ADL-Barthel was evaluated over 100 points, and patients were scored in 10 different areas such as nutrition, bathing, self-care, dressing and undressing, incontinence of urine and feces, using the toilet alone, wheelchair use, mobility status, and climbing stairs. The IADL test consists of 8 sections and is evaluated over a score of 17. It tests the subjects of using the phone, shopping, preparing meals, cleaning the house, using laundry, using medicine, traveling, and financial affairs, and low scores are accepted as an indicator of addiction. Those who scored below 8 points were considered addicts.

Statistical Analysis

Demographic data are presented as frequency and percentage. Normal distribution was tested using the Kolmogorov-Smirnov test. Categorical values were compared using the chi-square test. Continuous data were compared using Student's t-test. A p-value <0.05 (two-tailed) was considered statistical significant. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Two hundred and five patients were included in the study. The mean age of the patients was 75.54 (±6.5) years, with 117 females 57% and 88 males (43%). According to the European Sarcopenia Diagnostic Guide, 48 (23.4%) patients were found to be sarcopenic. There was no difference between men and women in the frequency of sarcopenia.

Demographic data, marital status, educational status, height, weight, body mass index (BMI), smoking, and alcohol use of the patients and the most common comorbid conditions are presented in Table 1. There was no statistically significant difference between patients' age, BMI, educational status, use of alcohol, and smoking. Comorbidities other than hypertension were similar in terms of chronic diseases. The

cognitive functions of the patients were found to be low in the sarcopenic group, and the ADL and IADL tests were found to be significantly lower in the sarcopenic group. These patients needed help in their daily lives.

The mean MMSE score was 26.35 in the sarcopenic group and 28.15 in the non-sarcopenic group, and there was a significant difference between the two groups. MMSE scores in the sarcopenic group were lower. Patients with a score of 4< according to YGDS short form (15 questions) who were clinically compatible were diagnosed with depression. 63 (30.7%) patients had depression and 38 (18.5%) patients had insomnia.

Table 2 shows a comparison of the laboratory parameters of the patients. There was no significant difference between the sarcopenic and non-sarcopenic groups in terms of laboratory values.

Twenty-six elderly patients had been diagnosed with depression and are being treated. With our scans, this number increased to 63 patients. Thirty-seven patients were diagnosed with depression disorder. Depression was higher in women than in men. It was similar to other studies[13].

Depression was significantly higher in patients with sarcopenia. Table 3 relationship between depression and those with sarcopenia and non-sarcopenia is given. Depression was significantly more common in the sarcopenic group, with

Table 1. Patients characteristics (n=205)

	Sarcopenic	Non-sarcopenic	p
Age, yr	78.33	74.68	0.542
Sex (female/male)	33/15	84/73	0.62
Height (cm)	156.87	161.62	0.06
Weight (kg)	71.06	74.21	0.93
BMI, kg/m^2	28.89	28.44	0.46
Smoke N/Y %	23/33.3	77/66.7	0.47
Alcohol N/Y %	24/0	76/100	0.21
Educational status			
Un-educated %	25	75	0.72
Primary-secondary school	22.6	77.4	
High school	27.7	72.3	
University	16	84	
Hypertension %	35.7	64.3	0.03
Diabetes mellitus %	38.5	61.5	0.14
Ischemic heart disease %	26.7	73.3	0.57
Hyperlipidemia %	24.4	75.6	0.86
COPD %	21.1	78.9	0.79
Osteoporosis %	21.9	78.1	0.707
ADL	23.4	76.6	<0.001
LBIADL	23.4	76.6	<0.001
MMSE	26.35	28.15	<0.001
Walking speed (sn)	7.66	4.02	
Handgrip stregth M/F (kg)	18.2/13.45	24.14/14.5	
Muscle mass index M/F (kg)	4.96/5.14	14.72/8.34	

COPD: Chronic obstructive pulmonary disease, ADL: Activities of daily living, LBIADL: Lawton-Brody instrumental activities of daily living, MMSE: Mini-mental state examination, BMI: Body mass index

Table 2. Laboratory comparison between sarcopenia and non-sarcopenia

	Sarcopenic	Non-sarcopenia	p
Glucose (mg/dL)	113.08	111.68	0.22
Hemoglobin	13.40	13.90	0.47
BUN (mg/dL)	42.26	37.16	0.57
Creatinine (mg/dL)	1.00	1.00	0.10
Uric acid	6.54	6.52	0.35
Cholesterol	204.13	202.77	0.71
Triglyceride	129.67	141.26	0.68
HDL	57.11	52.90	0.35
LDL	123.40	121.79	0.43
AST (IU/L)	21.24	22.28	0.49
ALT (IU/L)	19.86	18.72	0.75
ALP	82.48	79.56	0.83
GGT	41.17	26.80	0.10
Protein (g/dL)	7.09	6.93	0.46
Albumin (mg/dL)	4.12	4.26	0.17
LD	200.94	200	0.46
Magnesium	2.01	2.00	0.07
Calcium (mg/dL)	9.39	10.38	0.10
Sodium	136.30	146.19	0.15
Potassium	4.55	4.44	0.44
Vitamin B12	535.65	501	0.43
Folate	9.74	18.25	0.31
Ferritin	81.85	71.39	0.52
Iron	79.73	75.70	0.34
TSH	2.74	2.02	0.39
Vitamin D	26.65	25.94	0.28

BUN: Blood urea nitrogen, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, LD: Lactate dehydrogenase, TSH: Thyroid-stimulating hormone

Table 3. Relationship between sarcopenia and depression

		Sarcopenia		
		Yes	**No**	**p**
Depression	Yes/no	25/23	38/119	<0.001
	%	39.7%/16.2%	60.3%/83.8%	100.0%
Total	Count	48	157	205

Table 4. Relationship between sarcopenia and insomnia

		Sarcopenia		p
		Yes	**no**	
Insomnia	No/yes	25/23	142/15	<0.001
		15.0%/60.5	85.0%/39.5	
Total		48	157	205

39.7% of sarcopenic patients having symptoms of depression.

We found that the rate of insomnia complaints was higher in patients with sarcopenia. Table 4 shows the relationship between insomnia and those with and without sarcopenia. The problems of sleep onset latency, staying asleep, and duration of sleep was more common in these patients. Insomnia was found in 38 (60.5%) of 48 patients with sarcopenia.

Discussion

There are many factors that can cause depression. Social isolation, being widowed, divorced or in a separate marital status, low socio-economic status, comorbid general medical conditions, uncontrolled pain, insomnia, functional disorder, and cognitive impairment can cause depression[8]. There are studies showing that sarcopenia has effects on mental health such as stress, anxiety, suicidal ideation, and depression[14-16]. There are studies showing that depression may also be the cause of sarcopenia. There are also studies stating that there is no relationship between them[17]. Decreased physical inactivity in depressed people may also cause sarcopenia[18]. Therefore, this issue needs to be clarified.

The negative effect of depression on sleep increases with age. Although the negative effects of depression on sleep have been described, untreated insomnia is also seen as a risk factor for the development and recurrence of depression[19]. Depression and insomnia are very common in patients who visit the outpatient clinic. In this study, we investigated the relationship between important morbidities affecting life in elderly sarcopenic patients.

In elderly people, circadian rhythm changes due to physiological changes[20]. In addition, insomnia is observed due to chronic diseases, drugs, pain, etc. Sleep onset problems were reported in 27-45% of the elderly, sleep disruption in 20-65%, early morning awakening in 15-54% and unrested awakening in 10%[19-21].

Sarcopenia's etiology is multifactorial[22]. Malnutrition, hormone levels, immobility, a sedentary lifestyle, increased inflammation and oxidative stress, co-morbidities, chronic diseases, and medications all have a role[23]. Vitamin D deficiency is known to cause the onset of sarcopenia in elderly patients[9]. Patients with vitamin D deficiency were excluded from the study.

Sarcopenia may develop as a natural consequence of age, or it may develop because of one or more underlying causes. Chronic conditions, such as endocrine disorders, malignancies, chronic inflammatory diseases, and severe organ failure, can increase sarcopenia through chronic inflammation and metabolic derangements[24]. Among the most major risk factors for sarcopenia in elderly patients is diabetes that is not well controlled[25].

There are studies indicating that inflammation may play a role in the development of sarcopenia, depression[26], and insomnia[27]; however, no proper study has determined an approved inflammatory marker and cut-off value.

We believe that it would be correct to detect sarcopenia or treat sarcopenia in these patients in addition to depression and insomnia treatment. The presence of sarcopenia may be the cause of depression and insomnia, or vise versa.

The MMSE scores of sarcopenic patients were found to be significantly lower than those of non-sarcopenic patients[16]. Sarcopenia indicates that it may also impact cognitive abilities[16].

Study Limitations

This was a cross-sectional study conducted on a group of elderly patients with chronic diseases; therefore, it is possible that multiple factors contribute to the development of depression and insomnia. In this study, we revealed that sarcopenia can also contribute to depression and insomnia.

Conclusion

When sarcopenic and non-sarcopenic patients were compared, depression and insomnia were more common in the sarcopenic group, and this was statistically significant. This relationship in elderly patients suggests that they may be

related to each other. In sarcopenic patients, social isolation and introversion can cause depression and insomnia. When the ADL and IADL scores of the patients were compared, it was found that the ADL of these patients were impaired in the sarcopenic group, and they were more dependent. There were also significant differences between the life activities of the patients.

Ethics

Ethics Committee Approval: This study was approved by İzmir Katip Çelebi University (no: 0315, date: 16.06.2022).

Informed Consent: The study consent of all patients was obtained.

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Effect of Radiologically Evaluated Sarcopenia on Survival in Advanced Pancreatic Cancer

Metastatik Pankreas Kanserinde Radyolojik Olarak Değerlendirilen Sarkopeninin Sağkalıma Etkisi

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Abstract

Objective: Pancreatic cancer is one of the deadliest cancers. The 5-year survival rate in advanced pancreatic cancer is 2%. The presence of sarcopenia in advanced pancreatic cancer is associated with negative outcomes. Although there are many measurements for the diagnosis of sarcopenia, there is still no standard method. In our study, the effect of radiological measurement of sarcopenia on the results of pancreatic cancer was investigated.

Methods: Seventy-four patients were retrospectively evaluated. Demographic data and laboratory and imaging parameters of the patients were recorded and analyzed using the SPSS 25 program.

Results: The mean age was 64.4 years, and the mean body mass index (BMI) was 25.5 kg/m^2. 58.1% of the patients were male. mOS was 9.3±2.4 months in patients with sarcopenia detected with Psoas muscle density (PMD) Hounsfield unit avarage calculation, and 16.1 16.1±1.5 months in those without (*p=0.002). mOS was 5.6±1.6 months in patients with sarcopenia detected with PMI and 16.1 16.1±1.5 months in those without (*p<0.0001). Age, gender, BMI, hemoglobin, CA19-9, and albumin levels did not affect overall survival.

Conclusion: Overall survival is significantly lower in patients with radiologically detected sarcopenia with PMD and PMI. The use of PMI and PMD is an effective method for radiological evaluation of sarcopenia.

Keywords: Sarcopenia, radiological measurements, pancreatic cancer

Öz

Amaç: Pankreas kanseri en ölümcül kanserlerden biridir. Metastatik pankreas kanserinde 5 yıllık sağkalım %2'dir. Metastatik pankreas kanserinde sarkopeninin varlığı olumsuz sonuçlarla ilişkilidir. Sarkopeni tanısına yönelik birçok ölçüm olmasına rağmen halen standart bir yöntem bulunmamaktadır. Çalışmamızda sarkopeninin radyolojik ölçümünün pankreas kanseri sonuçlarına etkisi araştırıldı.

Yöntem: Yetmiş dört hasta retrospektif olarak değerlendirildi. Hastaların demografik verileri, laboratuvar ve görüntüleme parametreleri kayıt altına alınarak SPSS 25 programına analiz edildi.

Bulgular: Ortalama yaş 64,4, ortalama vücut kitle indeksi (BMI) 25,5 kg/m^2 idi. Hastaların %58,1'i erkekti. Psoas kas dansitesi (PMD) Hounsfield ünitesi ortalama hesaplaması ile tespit edilen sarkopeni hastalarında mOS 9,3±2,4 ay, olmayanlarda ise 16,1±1,5 ay idi (*p=0,002). Psoas kas indeksi (PMI) ile sarkopenisi saptanan hastalarda mOS 5,6±1,6 ay, saptanmayanlarda ise 16,1±1,5 aydı (*p<0,0001). Yaş, cinsiyet, BMI, hemoglobin, CA19-9 ve albümin düzeyleri genel sağkalımı etkilemedi.

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Öz

Sonuç: PMD ve PMI ile radyolojik olarak sarkopenisi saptanan metastatik pankreas kanseri hastalarında genel sağkalım anlamlı olarak daha düşüktür. PMI ve PMD'nin kullanımı sarkopeninin radyolojik değerlendirmesinde etkili bir yöntemdir.

Anahtar Kelimeler: Sarkopeni, radyolojik ölçümler, pankreas kanseri

Introduction

Pancreatic cancer is one of the most common cancers, with a 5-year survival rate of less than 5%[1]. Most patients are unresectable, and the results are worse in this patient group. The stage of the disease, area of involvement, presence of additional diseases, and performance status determine the probability of resectability[2]. Sarcopenia is defined as a decrease in muscle mass and consequent decrease in measurable muscle strength. According to ESPEN, values below -2 standard deviations as measured by healthy young adults are defined as cachexia[3]. Decreased muscle density and muscle area are associated with decreased overall survival in many cancers. The relationship between sarcopenia and pancreatic cancer has been known for a long-time. In recent years, the number of studies on the negative effects of sarcopenia on survival outcomes in pancreatic cancer has been increasing[4]. In various studies, sarcopenia in pancreatic cancer has been shown to be between 20% and 65%[5-7]. This wide range may be due to the heterogeneity of the patient group and the differences in sarcopenia measurement techniques. Malnutrition and sarcopenia are common in pancreatic cancer due to localization of the disease, obstruction, inadequate oral intake, failure to meet the increased metabolic rate due to malignancy, and malabsorption due to exocrine hormonal failure[8]. Decreased performance due to sarcopenia adversely affects both post-surgical complications and chemotherapy-related outcomes[9]. Due to the differences in defining sarcopenia, there were also differences in measurement techniques[10,11]. Various measurements can be made with anthropometry, bioelectrical impedance, dual X-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI) in the evaluation of sarcopenia. To eliminate the subjectivity of measurement techniques, it is becoming increasingly common to evaluate using imaging methods[12]. There are many studies evaluating sarcopenia by measuring muscle with conventional imaging methods used in the diagnosis, staging, and follow-up of pancreatic cancer[13]. Sarcopenia assessments with CT and MRI are more sensitive than DEXA[14]. It has been shown that muscle measurement from L3 vertebrae correlates much better with whole body muscle mass, and measurements from L4-5 vertebrae can be an alternative to L3 measurement[15]. Besides which technique is used for measurement, it should also be considered whether it is evaluated according to height, weight, and body mass index.

In our study, the data of patients with advanced pancreatic cancer diagnosed in our clinic in the last five years were retrospectively analyzed. In addition to descriptive data such as age, gender, and performance status at the time of diagnosis, the effects of laboratory parameters and muscle measurements determined by CT imaging on progression-free survival (PFS) and overall survival (OS) were examined.

Materials and Methods

Measurements

Muscle measurements were calculated as follows: Psoas muscle index (PMI) and Psoas muscle density (PMD) hounsfield unit average calculation (HUAC) was used to evaluate cachexia. PMI: (Right psoas muscle area + left psoas muscle area)/height height. Right hounsfield unit (RHUC): (RHUC x right psoas muscle area)/total psoas muscle area. LHUC: (left hounsfield unit x left psoas muscle area)/ total psoas muscle area. PMD HUAC: RHUC +LHUC/2. Low skeletal muscle mass was defined as the lowest quartile in male and female patients separately in categorical analyses. The PMI cutoffs to define low skeletal muscle mass were 2,4 cm^2/m^2 in females and 3.3 cm^2/m^2 in males, and for Psoas Muscle Dansity, HUAC was 21.53 HU in females and 27,08 HU in males.

Manisa Celal Bayar University Ethics Committee date: 21.03.2022, decision no: 251 approval was received. The procedures followed were in accordance with the ethical standards of the Manisa Celal Bayar University Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2013.

Statistical Analysis

Overall survival (OS) and progression-free survival (PFS) analyzes were calculated using the Kaplan-Meier method,

and differences between curves were estimated using Log-Rank tests. The effect of low skeletal muscle mass on PFS and OS was evaluated using univariate and multivariate logistic regression analyses. Quantitative variables are expressed as medians. Variables are compared using the two-tailed Student's t-test or the Kruskal-Wallis test, whichever is appropriate. Categorical data were expressed as percentages (numbers) and compared using the χ^2 test or Fisher's Exact test, as appropriate. P-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 25 software.

Results

In our study, 87 patients diagnosed with advanced pancreatic cancer in our hospital between 2016 and 2021 were included in the study. Seventy-four patients whose data were fully accessible were included in the study. Thirteen patients were excluded from the study because of reasons such as change of institution for treatment, inability to access chemotherapy regimens, and undetectable PFS and OS data.

Mean age at diagnosis was 64.4 (31-82), mean weight was 70 kg (45-110), and mean BMI was 25.5 (15.6-40.4). 58.1% (n=43) of the patients were male. Pancreatic head tumor was the primary focus in 74.3% (55) of the patients, whereas 25.7% (19) had pancreatic body or tail tumor. Twenty-three percent (15) of the patients were ECOG-0, 62.2% (46) ECOG-1, 17.5% (13) ECOG-2. There were no ECOG-3 and ECOG-4 patients. 75.7% (56) of the patients were receiving oral nutritional support (ONS). While 36.5% (27) of the patients were using the first or even FOLFIRINOX regimen, 27% (20) had a single agent gemcitabine and 36.5% (27) had a second chemotherapy agent (cisplatin, carboplatin, nab-paclitaxel) together with gemcitabine. While all of the patients included in the study received first-line chemotherapy, 47.3% (35) of the patients who received the second-line chemotherapy were 25.7% (19) who could receive the third-line treatment. Descriptive statistics are presented in Table 1.

When all patients were evaluated, mPFS was 4.8±0.8 months and mOS was 14.3±1.2 months. PFS was not affected by gender (p=0.96) and being over or under 65 years old (p=0.14). OS was not affected by gender (p=0.50) and being over or under 65 years old (p=0.86).

While mPFS was 5.3 months in those who received ONS, mPFS was 2.4 months in those who did not (*p=0.004). There was no significant difference in mOS between those who received and those who did not receive ONS (p=0.66).

When laboratory data were examined, there was no significant difference in terms of PFS or OS between patients with hemoglobin (≤12 vs. >12) and CA19-9 (≤100 vs. >100). However, PFS and OS were significantly lower in those with albumin levels ≤3.5 g/dL.

While mPFS was 8±3.9 months in patients with BMI <18.5, mPFS was 4.8±0.8 months in patients with BMI ≥18.5 (p=0.54). OS was 13.6±6.4 months in patients with BMI <18.5, and 14.7±1.3 months in patients with BMI ≥18.5 (p=0.31). While mPFS was 2.6±0.4 months in those with PMD HUAC and sarcopenia, it was 5.8±0.5 months in those without (*p=0.009). While the mOS was 9.3±2.4 months in those

Table 1. Descriptives of advanced pancreatic cancer patients

	n	%		n	%
Sex			**ONS**		
Female	31	41.9	No	18	24.3
Male	43	58.1	Yes	56	75.7
Total	74	100.0	Total	74	100.0
Age			**Second line**		
<65	29	39.2	No	39	52.7
>65	45	60.8	Yes	35	47.3
Total	74	100.0	Total	74	100.0
ECOG			**BMI**		
0	15	20.3	<18	5	6.8
1	46	62.2	>18	69	93.2
2	13	17.5			
Total	74	100.0	Total	74	100.0
T			**PMI**		
2	40	54.1	Low	18	24.3
3	31	41.9	High	56	75.7
4	3	4.1	Total	74	100.0
Total	74	100.0			
n			**PMD HUAC**		
0	12	16.2	Low	19	25.7
1	27	36.5	High	55	74.3
2	35	47.3	Total	74	100.0
Total	74	100.0			
Localization			**1st-line regimen**		
Head	55	74.3	Gemcitabine	20	27.0
Tail	19	25.7	Gem-others	27	36.5
Total	74	100.0	Folfirinox	27	36.5
			Total	74	100.0

ONS: Oral nutritional support, BMI: Body mass index, PMI: Psoas muscle index

with sarcopenia with PMD HUAC, it was 16.1±1.5 months in those without (*p=0.002). While mPFS was 2.6±0.4 months in those with PMI and sarcopenia, it was 5.5±0.4 months in those without (*p=0.006). While mOS was 5.6±1.6 months in those with PMI and sarcopenia, it was 16.1±1.5 months in those without (*p<0.0001). While mPFS was 5.8±0.4 months in patients who received FOLFIRINOX as first-line therapy, mPFS was 4.0±0.8 months in patients who did not receive FOLFIRINOX (p=0.85), mOS in patients who received FOLFIRINOX as first-line therapy was 16.1±10 months, mOS was 13.9±3.5 months (p=0.61) in those who did not receive FOLFIRINOX. The PFS and OS data determined depending on the variables are presented in Table 2.

Affecting OS because of univariate analysis: ECOG status, second- line chemotherapy, PMD HUAC, PMI, NLR and albumin values were evaluated by multivariate analysis and the results are presented in Table 3.

Table 2. PFS and OS data depending on the variables

Variables	n/%	mPFS	p-value	mOS	p-value
ECOG					
0	15/20.3	5.9	0.004	26.5	0.009
1	46/62.2	5.5		13.6	
2	13/17.5	2.4		3.9	
Age					
<65	29/39.2	6.5	0.14	15.1	0.86
≥65	45/60.8	3.6		13.9	
Sex					
Female	31/41.9	5.1	0.96	13.9	0.50
Male	43/58.1	4.8		15.1	
Localisation					
Head	55/74.3	4.8	0.88	14.3	0.56
Tail	19/25.7	5.3		13.9	
ONS					
No	18/24.3	2.4	0.004	15.1	0.66
Yes	56/75.7	5.3		14.3	
2nd line					
No	39/51.4			7.2	0.007
Yes	35/48.6			16.1	
BMI					
<18	5/6.8	8	0.54	13.6	0.31
≥18	69/93.2	4.8		14.7	
PMI					
Low	18/24.3	2.6	0.006	5.6	<0.001
High	56/75.7	5.4		16.1	
PMD HUAC					
Low	19/25.7	2.6	0.009	9.3	0.002
High	55/74.3	5.8		16.1	
Folfirinox					
No	47/63.5	4.0	0.85	13.9	0.61
Yes	27/36.5	5.8		15.1	
HGB					
≤12	27/36.5	4.0	0.16	12.8	0.41
>12	47/63.5	5.5		15.4	
CA19-9					
≤100	32/43.2	5.8	0.76	15.4	0.22
>100	42/56.8	3.3		14	
Albumin					
≤3.5	9/12.2	2.3	0.027	9.0	0.026
>3.5	65/87.8	5.5		15.1	
NLR					
≤3	44/59.5	5.8	0.98	16.1	0.019
>3	30/40.5	2.9		9.0	

ONS: Oral nutritional support, BMI: Body mass index, OS: Overall survival, PMI: Psoas muscle index

Discussion

In our study, it was shown that the overall survival results were worse in patients with advanced stage pancreatic cancer who were found to have cachexia because of CT evaluation at the time of diagnosis. Other factors affecting mOS in the multivariate analysis were ECOG performance and the patient's ability to receive second-line therapy.

It should also be considered that the optimal treatment of sarcopenia is still unknown. Follow-up of patients with appropriate ONS before their condition worsens may affect survival outcomes. There is an increased catabolic process and fragility in sarcopenic patients[16]. In our study, it was seen that mPFS was detected better in ONS patients. It can be recommended to evaluate cachexia and sarcopenia in terms of diagnosis and to start ONS as early as possible in those who need it. While some studies have shown that the presence of sarcopenia is associated with worse overall survival, there are studies that do not support this data[7,17-20].

Many anti-inflammatory and proanabolic products have been tried to reverse sarcopenia, but many of them have not been shown to have a positive effect on the results. Although the results are contradictory, the use of polyunsaturated fatty acids has positive effects in patients receiving chemotherapy[21]. In addition, some studies have supported the role of megestrol acetate and medroxyprogesterone acetate in preventing the progression of sarcopenia[22,23]. However, because of the increased frequency of thromboembolic

Table 3. Univariate-multivariate analyses of overall survival

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**(95% CI)**	**p-value**	**HR**	**(95% CI)**	**p-value**
ECOG	1.95	(1.26-3.0)	0.009	2.69	(1.58-4.56)	<0.001
2nd line	0.47	(0.27-0.82)	0.008	0.32	(0.17-0.62)	0.001
PMI	0.33	(0.18-0.61)	0.026	0.48	(0.25-0.95)	0.034
PMD HUAC	0.40	(0.21-0.73)	0.003	0.40	(0.19-0.70)	0.008
Alb ≤3.5/>3.5	0.42	(0.20-0.90)	0.026	0.90	(0.38-2.12)	0.81
NLR ≤3/>3	1.95	(1.11-3.40)	0.019	1.46	(0.78-2.74)	0.24

CI: Confidence interval, PMI: Psoas muscle index, HR: Hazard ratio, Alb: Albumin

events in pancreatic cancer, these molecules can be used by considering the potential benefit-harm balance.

The presence of sarcopenia also affects the performance status of the patient. In patients with low performance scores, the preferred chemotherapy regimen may change. In addition, chemotherapy is more toxic in sarcopenic patients, which negatively affects survival outcomes[24].

There are studies showing that there are more serious complications with chemotherapy in patients with sarcopenia[24,25]. In our study, there was no difference in terms of mPFS or mOS between patients with BMI <18.5 and patients with >18.5 because of BMI evaluation. Cachexia can also be seen in patients who are in the obesity or normal group according to BMI. Therefore, BMI is considered insufficient in the evaluation of sarcopenia[26,27]. CT, PET-CT, and MRI can be used in the diagnosis and follow-up of cancer. While manual measurements may lead to subjective results in the evaluation of cachexia and sarcopenia, more objective results can be determined by CT. However, in CT measurements, the problem is that the standard values differ between nationalities. For this reason, it is recommended that countries determine their own sarcopenia values and studies are conduct studies in this direction[12,28,29]. It should be considered that both chemotherapy response and overall survival will be worse in patients with sarcopenia detected at the time of diagnosis. Disease management should be shaped according to this situation.

When the literature is evaluated, it is seen that there is more than one method in the evaluation of sarcopenia with imaging methods. PMD, HUAC, and PMI are two of these methods. Sarcopenia detected with PMD, HUAC, and PMI is an independent poor prognostic factor in pancreatic cancer. Other prognostic factors affecting mOS in our study were the patient's ECOG performance and ability to receive second-line chemotherapy. Having received second-line chemotherapy is also an indirect indicator of good performance status. There is no standard consensus regarding the assessment of sarcopenia. It is suggested that each nation determines an index according to their own data. The reason why we preferred PMD HUAC and PMI in our study is the effort to identify patients who are in the lowest quartile compared with our population, instead of using a standard value.

Study Limitations

The limitations of our study are the small number of patients and the retrospective nature of our study. The results may have been affected by individual differences in chemotherapy preference and difficulties in accessing nabpaclitaxel in our country. The fact that chemotherapy complications were not evaluated in our study is one of the limitations of our study. Complications were excluded from the evaluation because there were insufficient complication data in the file information.

Conclusion

The evaluation of sarcopenia in the imaging control performed during the staging of metastatic pancreatic cancer provides information both in terms of prognosis and gives an idea about the intensity of the treatment modality to be applied and the complications that may occur. In addition, in patients with sarcopenia at the time of diagnosis, ONS can be initiated at an early stage and contribute to the improvement of the results.

Ethics

Ethics Committee Approval: Manisa Celal Bayar University Ethics Committee date: 21.03.2022, decision no: 251 approval was received. The procedures followed were in accordance with the ethical standards of the Manisa Celal Bayar University Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2013.

Informed Consent: In our study, which was conducted as a retrospective patient file scan, a patient consent form was obtained.

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Effect of Symptom Severity on the Quality of Life in Women with Urinary Incontinence: A Comparative Study

Üriner İnkontinanslı Kadınlarda Semptom Şiddetinin Yaşam Kalitesine Etkisi: Karşılaştırmalı Bir Çalışma

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Abstract

Objective: This study was conducted to determine the effect of symptom severity on quality of life and urinary incontinence (UI) risk factors affecting quality of life in women with UI.

Methods: The study was conducted with a descriptive, cross-sectional, and comparative design. Data were collected using the "description form" and "King's health questionnaire (KHQ)" with 160 women applying to a university hospital's urogynecology polyclinic. The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for data analysis. The data were analyzed using numbers, percentages, Mann-Whitney U test, and linear regression analyses. P<0.05 was considered significant.

Results: It was found that 45% of women had none/low symptom severity and 55% had medium/high symptom severity. The women's KHQ first part subscale mean score was found to be "general health condition" 41.09±20.48; "incontinence effect" 56.46±28.47; "role limitation" 41.04±33.43; "physical limitation" 46.67±33.01; "social limitation" 31.94±30.26; "personal relationship" 15.94±25.72; "emotions" 43.61±34.82; "sleep energy level" 27.71±27.97; "severity measurements" 38.46±24.56; KHQ second part (symptom severity scale) mean score was 9.56±5.97. It was found that women with medium/high symptom severity had statistically significant higher scores from all subscales of KHQ's quality of life part than women with none/low severity (p<0.01).

Conclusion: It was concluded that incontinence in women affected quality of life at a medium level, quality of life decreased as incontinence's symptom severity increased, and many UI risk factors affected quality of life. This study reveals that incontinence symptom severity has a negative effect on women's quality of life.

Keywords: Incontinence, lower urinary tract symptoms, quality of life, women

Öz

Amaç: Çalışma, üriner inkontinans (Üİ) tanısı alan kadınların semptom şiddeti ile yaşam kalitesi arasındaki ilişkiyi ve yaşam kalitesini etkileyen faktörleri belirlemek amacıyla yapılmıştır.

Yöntem: Araştırma tanımlayıcı, kesitsel ve karşılaştırmalı desende yapılmıştır. Veriler, bir üniversite hastanesinin ürojinekoloji polikliniği'ne başvuran 160 kadın ile "birey tanıtım formu" ve "King sağlık anketi (KHA)" kulanılarak yüzyüze görüşme tekniği ile toplanmıştır. Verilerin analizinde Number Cruncher Statistical System 2007 (Kaysville, Utah, ABD) programı kullanılmıştır. Veriler sayı, yüzde ve Mann-Whitney U testi ve doğrusal regresyon analizleri kullanılarak analiz edilmiştir. Anlamlılık düzeyi p<0,05 olarak kabul edilmiştir.

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Öz

Bulgular: Kadınların %45'inin semptom şiddetinin hiç/düşük, %55'inin orta/yüksek olduğu saptanmıştır. Çalışmaya katılan kadınların KHA birinci bölüm alt boyut puan ortalamaları; "genel sağlık durumu" 41,09±20,48; "inkontinans etkisi" 56,46±28,47; "rol limitasyon" 41,04±33,43; "fizik limitasyon" 46,67±33,01; "sosyal limitasyon" 31,94±30,26; "kişisel ilişki" 15,94±25,72; "emosyonlar" 43,61±34,82 "uyku enerji düzeyi" 27,71±27,97, "ciddiyet ölçümleri" 38,46±24,56; KHA ikinci bölüm (semptom ciddiyet skalası) puan ortalaması 9,56±5,97 olarak saptanmıştır. Semptom ciddiyeti orta ya da çok olan kadınların KHA yaşam kalitesi bölümünün tüm alt boyutlarından aldıkları puanlar, hiç ya da az olan kadınlara göre istatistiksel olarak anlamlı düzeyde yüksek bulunmuştur (p<0,01).

Sonuç: Kadınlarda inkontinansın yaşam kalitesini orta düzeyde etkilediği, inkontinansın semptom şiddeti arttıkça yaşam kalitesinin düştüğü ve birçok Üİ risk faktörünün yaşam kalitesini etkilediği sonucuna varılmıştır. Bu çalışma inkontinans semptom şiddetinin kadınların yaşam kalitelerini olumsuz etkilediğini ortaya koymaktadır.

Anahtar Kelimeler: İnkontinans, alt üriner sistem semptomları, yaşam kalitesi, kadın

Introduction

In the first standardization report (2002), the International Continence Society (ICS) defined urinary incontinence (UI) as involuntary UI, which can cause social and hygienic problems and can be objectively exhibited[1]. As being a problem that concerns every age group, its frequency increases with increasing age, and it is seen 2-5 times more in women than men[2].

It is estimated that on average, 250 million women suffer from incontinence around the world[3]. Very different numbers were obtained in the studies on UI prevalence in Turkey. In our country, the UI frequency is stated to be 20-25%[4].

Although UI is not a disease that threatens an individual's life, it causes psychosocial problems and deterioration in life quality[2]. UI leads to psychosocial effects such as constant urinary incontinence and fear of smelling bad, feeling insufficient and dirty, decrease in self-esteem, disturbance in body image, stigmatization, shame, unhappiness, anger, stress, anxiety, depression, sleep disorders, skin problems, limitation in physical activity, social isolation, decrease in libido, and avoiding sexual activity and causes a decrease in quality of life[2,5]. In the conducted studies, it was found that the incontinence problem plays an important role in the decrease in the quality of life decrease[6,7]. This decrease affects women not only from the aspect of symptoms but also from social, economic and medical aspects[8,9].

It was found that women spent a long time before applying to a health institution due to reasons such as perceiving UI as a natural result of aging, lacking information, disregarding complaints, being ashamed/afraid of examination, not finding any time for examination[2,5]. This situation disturbs the patient's psychosocial health and increases the treatment cost[2,10]. Although studies have revealed that every aspect of the quality of life is affected in women with UI, a limited number of studies have examined the effect of UI symptom severity on the quality of life[6,7]. For this reason, this studyaimed to examine the effect of symptom severity on quality of life in women with UI and to raise awareness of health professionals and society on this issue. Thus, it is thought that women will start treatment early before their symptoms worsen, control symptoms, and improve their quality of life.

Materials and Methods

This descriptive, cross-sectional, and comparative study was conducted at the urogynecology polyclinic of a university hospital.

Participant Selection

The target population of the research consisted of women (n=242), applied to the polyclinic in a year. The sample of study was determined at a 95% confidence interval by using the population known formula, and it was found that 149 women should be included in the sample. One hundred sixty (n=160) women who applied to the polyclinic on the given dates and filled out the data collection forms participated in the study.

Data Collection

Data were collected using the individual description form and king's health questionnaire (KHQ). The individual description form was created by the researcher according to the literature to determine the women's socio-demographic/obstetric-gynecologic characteristics, health history, and the characteristics related to the complaint of incontinence and had 26 questions[4,11]. The KHQ is a scale developed by Cardozo in 1991 to determine quality of life specifically

regarding urinary incontinence and consists of 32 items and two parts[12]. A Turkish validity and reliability study was conducted by Kaya et al.[12] (Cronbach alpha=0.72-0.89). Determination of the given score high indicates that life quality has deteriorated[12,13]. The Cronbach's alpha value was found to be 0.78-0.95 in the study. In the study, the women who answered "none or low" to the symptom evaluation question of the questionnaire were grouped as the first group (n=72, 45%), and those who answered "medium or high" were grouped as the second group (n=88, 55%), and the relationship between symptom severity and quality of life was compared accordingly.

Before data collection, this study was approved by the Ethics Committee of Ege University Medical Faculty (17-3/9) in accordance with the Declaration of Helsinki Research Principles. To conduct the study, an institutional permit and written informed consent were obtained from each participant. The data were collected using the face-to-face interview method by the researcher in 15-20 minutes. The women who were illiterate, in the lactational period, and had a radiotherapy history and a psychiatric disorder were excluded from the study.

Statistical Analysis

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for data analysis. Neither scale score had a normal distribution (Kolmogorov-Smirnov and Shapiro-Wilk $p<0.05$). The data were analyzed using numbers, percentages, Mann-Whitney U test, and linear regression analyses. $P<0.05$ was considered significant.

Results

It was found that the women's average age was 52.78±10.89 (min-max: 22-87 years), 41.9% of them were elementary school graduates, 61.3% of them were housewives, and 82.5% of them said the location where they lived was a province. It was found that 20% of the women had stress incontinence, 13.1% had urge incontinence, 65.0% had mixed incontinence, and 1.9% had nocturnal incontinence.

When the risk factors related to incontinence that the women had been taken into consideration, it was determined that 36.9-45.0% of them were overweight and obese, and 70.6% of them consumed caffeinated and acidic drinks. It was found that 97.5% of the women had given birth, and more than 89.1% of the birth-giving women had more than one, while 74.4% of them had vaginal delivery, 21.2% of them had given birth to a baby at four kilograms and above, and 66.9% of them were in menopause. The other risk factors are given in Table 1.

The first subscale mean score of the first part of the KHQ is given in Table 2. When all of the subscales were examined, it was found that the life qualities of the women suffering from UI were affected at the medium level.

The second group of women (having medium/high symptom severity), compared to the first group of women (having none/low symptom severity), had higher scores in all subscales, and the difference between them was found to be statistically significant. Accordingly, it was found that the higher the incontinence symptom severity, the more negative the quality of life was affected (Table 3).

In the linear regression analysis, made to determine the factors affecting KHQ subscales, while KHQ subscale scores were included in the study as dependent variables, the UI risk factors, questioned in the individual description form, were included as independent variables. The model was created using the backward elimination method. The statistical significance of the obtained model and the percentages of the variables included in the model for the variance belonging to the result variable are given in Table 4.

In this study, it was found that normal BMI and not having a chronic cough increased general health perception positively and having had three childbirths and advanced age decreased this perception.

While having had a lower abdominal operation and consuming caffeinated drinks increased the effect of UI-related incontinence, having a C-section as the delivery method decreased the effect of incontinence. The existence of a chronic disease and an active lifestyle increased the role limitation. Having three childbirths, the existence of a chronic disease, and an active lifestyle increased physical limitations due to incontinence; frequently not lifting heavy objects and not having a chronic cough decreased the incontinence-related physical limitations.

The women who had a vaginal delivery, a lower abdominal operation, and an active lifestyle experienced more social limitations.

The personal relationships were affected more in those who had more and above number of childbirths, a chronic cough, and an active lifestyle; emotions were affected negatively in those who had three childbirths, a lower abdominal operation, and a chronic disease; and having a

Table 1. Distribution of incidence-related risk factors in women		
Incontinence-related risk factors	**Number (n)**	**Percentage (%)**
BMI (kg/m²)		
Normal	29	18.1
Overweight	59	36.9
Obese	72	45.0
BMI mean ± SD (min-max)	29.36±5.29 (15.84-60.55)	
Caffeinated, acidic drink consumption		
Has	113	70.6
Does not have	47	29.4
Having childbirth		
No	4	2.5
Yes	156	97.5
Amount of childbirth (n=156)		
One	17	10.9
Two	70	44.9
Three	28	17.9
Four and above	41	26.3
The type of childbirth (n=156)		
Vaginal	116	74.4
C-section	18	11.5
Vaginal and C-section	22	14.1
Delivering an overweighted newborn (>4 kg) (n=156)		
Did	33	21.2
Did not	123	78.8
Menopause status		
Entered	107	66.9
Not entered	53	33.1
Lower abdominal operation		
Had	76	47.5
Did not have	84	52.5
Frequently lifting and pushing heavy objects		
Yes	110	68.8
No	50	31.3
Constipation		
Has	75	46.9
Does not have	85	53.1
Chronic disease		
Has	97	60.6
Does not have	63	39.4
Chronic cough		
Has	23	14.4
Does not have	137	85.6
Sedentary lifestyle		
Has	38	23.8
Does not have	122	76.3
Total	160	100

SD: Standard deviation, BMI: Body mass index

Table 2. Distribution of the king health questionnaire subscale scores

King health questionnaire subscales	Number (n)	Mean ± SD	Cronbach's alpha
General health status	160	41.09±20.48	-
Incontinence effect		56.46±28.47	-
Role limitation		41.04±33.43	0.87
Physical limitation		46.67±33.01	0.82
Social limitation		31.94±30.26	0.93
Personal relationship		15.94±25.72	0.86
Emotions		43.61±34.82	0.95
Sleep energy level		27.71±27.97	0.91
Severity measurements		38.46±24.56	0.82
King quality of life		-	0.95
King symptom severity scale		9.56±5.97	0.78

SD: Standard deviation

Table 3. Relationship between the king health questionnaire subscales and symptom severity

King health questionnaire subscales	Incontinence effect		U	p
	1. Group (n=72)	2. Group (n=88)		
	Min-max (median)	Min-max (median)		
General health status	25-75 (25)	0-100 (50)	-3.05	**0.002**
Incontinence effect	0-33.33 (33.33)	66.67-100 (66.67)	-11.53	**<0.001**
Role limitation	0-83.33 (16.67)	0-100 (66.67)	-7.18	**<0.001**
Physical limitation	0-100 (33.33)	0-100 (66.67)	-6.39	**<0.001**
Social limitation	0-100 (0)	0-100 (44.44)	-7.19	**<0.001**
Personal relationship	0-100 (0)	0-100 (0)	-2.62	**0.009**
Emotions	0-100 (22.22)	0-100 (66.67)	-5.60	**<0.001**
Sleep energy level	0-100 (16.67)	0-100 (33.33)	-4.32	**<0.001**
Severity measurements	0-86.67 (26.67)	0-100 (40.00)	-5.02	**<0.001**
Symptom severity	2-73 (6)	1-29 (10.50)	-5.63	**0.000**

Table 4. Risk factors affecting quality of life

General health perception	Beta	t	p	F	Model (p)	R^2
Stable	48.62	10.78	<0.001**	F: 6.684	p<0.001	0.128
Age (40-59)	7.96	2.42	0.016*			
BMI (normal)	-8.81	-2.15	0.033*			
Amount of childbirths (3)	11.19	2.74	0.007**			
Chronic cough (no)	-15.34	-3.41	0.001**			
Incontinence effect						
Stable	43.72	9.83	<0.001**	5.600	P=0.001	0.082
The type of childbirth (C-section)	-14.68	-2.05	0.042*			
Lower abdominal operation (yes)	13.99	3.06	0.003**			
Consumption of a caffeinated drink (yes)	11.15	2.29	0.023*			

Table 4. Continued

General health perception	Beta	t	p	F	Model (p)	R^2
Role limitations						
Stable	17.86	2.89	0.004**	8.761	p<0.001	0.091
Chronic disease (yes)	14.76	2.80	0.006**			
Sedentary lifestyle (no)	19.01	3.17	0.002**			
Physical limitations						
Stable	31.82	3.78	<0.001**	5.275	p<0.001	0.121
Amount of childbirths (3)	14.06	2.10	0.037*			
Lifting heavy objects (no)	-18.16	-3.25	0.001**			
Chronic disease (yes)	11.99	2.32	0.022*			
Chronic cough (no)	-16.90	-2.25	0.026*			
Sedentary lifestyle (no)	18.04	3.00	0.003**			
Social limitations						
Stable	5.33	0.63	0.52	4.403	p=0.005	0.062
The type of childbirth (vaginal)	12.61	2.06	0.04*			
Lower abdominal operation (yes)	16.35	3.08	0.00**			
Sedentary lifestyle (no)	12.34	2.20	0.02*			
Personal relationships						
Stable	11.82	1.91	0.05	4.137	0.003	0.075
Amount of childbirths (3)	11.63	2.12	0.03*			
Amount of childbirths (4 and above)	11.75	2.48	0.01*			
Chronic cough (no)	-11.84	-2.00	0.04*			
Sedentary lifestyle (no)	12.16	2.55	0.01*			
Emotions						
Stable	26.71	5.70	<0.00**	7.525	p<0.001	0.112
Amount of childbirths (3)	15.75	2.25	0.02*			
Lower abdominal operation (yes)	12.23	2.22	0.02*			
Chronic disease (yes)	14.21	2.56	0.01*			
Sleep/energy level						
Stable	15.56	4.09	<0.00**	7.563	0,001	0.078
Lower abdominal operation (yes)	9.55	2.14	0.03*			
Chronic disease (yes)	12.34	2.70	0.00**			
Severity measurements						
Stable	18.11	3.35	0.00**	6.520	p<0.001	0.097
The type of childbirth (vaginal)	11.35	2.36	0.01*			
Lower abdominal operation (yes)	10.77	2.50	0.01*			
Chronic disease (yes)	10.76	2.71	0.00**			
Symptom severity						
Stable	9.54	10.28	<0.00**	7.959	p<0.001	0.119
BMI (normal)	-3.13	-2.60	0.01*			
Constipation (no)	-2.26	-2.49	0.01*			
Chronic disease (yes)	2.89	3.12	0.00**			

BMI: Body mass index

lower abdominal operation and a chronic disease in the past affected UI-related sleep/energy level negatively.

It was found that the incontinence-related symptoms, existing in the women who had a vaginal delivery, a lower abdominal operation, and a chronic disease, were more severe; that keeping BMI in a normal range and not having constipation decreased the UI-related symptom severity, and the existence of a chronic disease affected the UI-related symptom severity.

Discussion

In this study, which was conducted to determine the relationship between urinary incontinence symptom severity and quality of life and the factors affecting it, it was found that women with medium/high symptom severity had statistically significant higher scores from all subscales of KHQ's quality of life part than women with none/low severity. It was determined that among the UI risk factors, advanced age, BMI, number of childbirths, pelvic surgery history, constipation, chronic diseases, chronic cough, sedentary lifestyle, lifting heavy objects, and consumption of caffeinated drinks decreased quality of life at a significant level. The obtained results are discussed in this section.

Relationship Between Urinary Incontinence Symptom Severity and Quality of Life

Urinary incontinence symptoms negatively affect the quality of life and cause emotional problems, leading to feelings of insufficiency and depression, even if they do not threaten life[1,14]. In a study examining the relationship between the severity of incontinence and quality of life, it was found that as the severity of symptoms increased, the quality of life decreased[7]. In a study conducted in China[6], it was found that the quality of life of those who had medium or severe urinary inconsistence was lower than those who had lesser inconsistence, and in a study conducted in Malaysia[14], it was found that the quality of life decreased as the incontinence severity increased. Alshammari et al.[9] concluded that the quality of life of women who had urinary incontinence at a higher volume was lower than those who had few incontinences per day. The studies that were conducted on incontinence in our country also show that there is a relationship between incontinence severity and quality of life. Gokkaya et al.[13] applied KHQ to the women, having applied to the urology polyclinic, and found that there is a significant difference in terms of general health, incontinence effect, role limitation, physical limitation, social limitation, emotional status, sleep energy level, and symptom severity. It was found that the quality of life of the group with high symptom severity, was lower. Kocaoz et al.[15], Shah and Rathod[16] and Orhan et al.[4] found that there is a negative relationship between quality of life and UI severity; symptom severity negatively affected quality of life. Demir and Beji[11] found that among women, the quality of life of those who generally and always had urinary incontinence was affected more negatively compared to those who had urinary incontinence from time to time. In studies that were conducted with women in the climacteric period and the advanced age groups, it was found that the increase in UI frequency and incontinence negatively affected quality of life negatively[5,7]. In the study of Karaca and Demir[17], it was found that the mean scores of being affected from urinary complaint and incontinence were the highest in those suffering from severe incontinence, and quality of life decreased as the frequency of incontinence increased. Moreover, it was found that the higher the number of pads that women used for incontinence, the lower their quality of life got[17]. In the conducted studies[18], it was found among women that the quality of life of those using pads because of incontinence was lower compared to those who did not usepads. As the duration of pad usage and incontinence amount increased, quality of life decreased because of the experienced difficulties[18]. The result in our study that the quality of life decreases as the severity of symptoms increases confirms the literature.

Discussion of Incontinence Risk Factors and Subscales

Because UI is a problem affecting women's family and social lives from physical and psychological aspects at a significant rate, it is a problem that needs to be approached with care[3]. It was found that the general health status of the women participating in the study was affected at a medium level and showed similarity to the results of the study that were made inside[12] and outside our country[19,20]. It was found that advanced age, increased BMI, having had three childbirths, and existence of chronic cough negatively affected the general health status negatively, and it was suggested in the literature that these variables increased the frequency of UI, and this situation affected general health negatively[21,22].

In the study, it was found that the incontinence effect was high, and it was seen that the results complied with other study findings[23]. Baykus and Yenal[24] stated that more than half of the women felt discomfort due to incontinence. Due to the damage that it causes to the pelvic fascia support, having

a vaginal delivery and a lower abdominal operation increases the impact of incontinence on the patient[24]. In addition, as a result of caffeine's diuresis effect, stimulation of the central nervous system, and contractions in the smooth muscles in the lower urinary system, it increases the negative effects on incontinence[25,26].

It was found that women's role limitation, physical limitation, and social limitations were affected at the medium level, and it was determined that role limitation had a similar exposure to Oh and Hyeon Ku's[27] and Oz and Altay[23] and studies and that the exposure was higher compared to the studies of Bakarman and Al-Ghamdi[28] and Tien et al.[29]. The fact that the study results show differences suggests that the factors that affect role limitation must be studied in a more detailed manner. It is thought that chronic disease existence negatively affects performing the roles, and with the addition of incontinence, difficulties in performing these roles were experienced. It was found that physical limitations were similar to those of Uemura and Homma[20] study, while being higher according to some others[19,28]. It is believed that the difference between the physical limitation points originated from the study groups' incontinence types and age differences. The incontinence problem negatively affects physical activities (running, swimming, doing exercise, traveling) negatively, and for this reason, it limits women's physical movements. It was found that social limitations were affected similarly to the studies of Kaya et al.[12] and Uemura and Homma[20]. However, there are also studies in which social limitations were experienced less[25,29,30].

It was observed that the personal relationships of the women participating in the study were affected more compared to other studies[19,20,23]. It can be thought that women's self-reflexive negative emotions due to incontinence reflect on their personal relationships. Women who cannot control their urinary functions may limit their personal relationships by seeing themselves as faulty and insufficient, and their sexual lives and relations with their partners may be affected negatively by thinking that they have lost their attractiveness and sexuality[8].

It was found that the women were affected at a medium level from the emotional aspect. Pereira et al.[8] suggested that there is less exposure from the emotional aspect. In the study, it was observed that there were more women at the end of their reproductive periods and in the postmenopausal period, and these results were in compliance with the literature. Women with UI may feel worthless, bad, uneasy, depressive and angry[11]. When it is considered that urinary incontinence is also a chronic disease, it is of the essence that women must be protected from UI from the aspect of psychological health and that symptom management must be made effectively.

In the study, it was found that the sleep/energy level was affected at a similar level with the study of Bakarman and Al-Ghamdi[28] and was affected less compared with the studies of Kaya et al.[12], Oz and Altay[23], and Uemura and Homma[20]. It can be said that the study results underline that women's waking up due to the necessity of frequently going to the toilet negatively affects their sleep/energy levels, and it is important to teach women effective coping methods (e.g., restricting liquid intake an hour before sleeping).

In this study, regarding severity measurements, it was found that the women were affected at a medium level in a manner that confirmed the study of Uemura and Homma[20]. However, there are also studies that indicate that incontinence-related severity situations were affected less[3,28]. In the conducted studies, it was determined that having to change underwear in relation to incontinence, being concerned of having a bad smell, experiencing incontinence to such a rate that requires using a pad, and increasing the number of pads used decrease women's quality of life[17,20].

Similar to the literature, incontinence-related symptom severity in women was affected at a medium rate[12,23]. To provide protection against UI and decrease symptom severity, it is thought that teaching such health protection behaviors as keeping BMI in a normal range, avoiding constipation, and protecting against chronic diseases is important to both lead a healthy life and control the effect of incontinence.

The more the symptom severity of the women diagnosed with UI increases, the more negative the quality of life is affected. Among the incontinence risk factors, advanced age, BMI and several childbirths, having a vaginal delivery, a lower abdominal operation, a chronic disease, constipation, chronic cough, consuming caffeinated drinks, and sedentary lifestyle negatively affect quality of life. To decrease the effect of urinary incontinence on the quality of life, early diagnosis and treatment are important and necessary. In order to increase the quality of life of women diagnosed with incontinence, it is important to provide consultancy about the methods to cope with the symptoms as well as treatment and to integrate these to the treatment/health care and to provide education toward the changeable factors (lifting heavy an object, sedentary lifestyle etc.). This study provides

important data for understanding the effect of urinary incontinence symptom severity on quality of life and the incontinence risk factors affecting quality of life.

Study Limitations

This study was a single-center study, and for this reason, generalizations cannot be made. The type of treatment that women received and their satisfaction with the treatment were not questioned. The large age difference between the participants also affected the level of being affected by urinary incontinence symptoms experienced during menopause and youth. In addition, the lack of comparison with urinary incontinence types is another limitation.

Conclusion

Findings of the study showed that the quality of life of women with urinary incontinence affected symptom severity. In addition, the study results show that women's quality of life is influenced by some urinary incontinence risk factors. The results will help raise the awareness of health care workers involved in the care of women about UI and help the design of education programs about the prevention of UI. It can be suggested that this study should be multi-centered with a larger sample in a similar age group.

Ethics

Ethics Committee Approval: Before data collection, this study was approved by the Ethics Committee of Ege University Medical Faculty (17-3/9) in accordance with the Declaration of Helsinki Research Principles.

Informed Consent: To conduct the study, an institutional permit and written informed consent were obtained from each participant.

Authorship Contributions

Concept: F.K., S.E.G., Design: F.K., S.E.G., Data Collection or Processing: F.K., Analysis or Interpretation: F.K., S.E.G., Literature Search: F.K., Writing: F.K., S.E.G.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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The Histopathological Findings of High-grade Serous Ovarian Carcinomas in Patients with BRCA Germline Mutations, Single Center Experience

BRCA Germline Mutasyonu Olan Hastalarda Yüksek Dereceli Seröz Over Karsinomlarının Histopatolojik Özellikleri; Tek Merkez Deneyimi

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Abstract

Objective: The current study aims to contribute to the identification of distinctive histomorphological findings of BRCA-associated high-grade ovarian carcinomas.

Methods: The study was planned to include high-grade serous carcinoma cases diagnosed in 2020-2021. The histopathological features of the groups with and without BRCA mutation were evaluated comparatively in the tumor slides of the cases.

Results: Solid/pseudo-endometrioid/transitional cell carcinoma-like growth pattern and high mitotic rates were observed more frequently in the BRCA mutation group than in those without mutations, which was statistically significant. There was no significant difference between the two groups in terms of significant nuclear pleomorphism, frequency of necrosis, and prominent tumor infiltrating lymphocytes.

Conclusion: Pathologists may play a crucial role in detecting BRCA mutations in patients without a family history of carcinoma. In this respect, it should be kept in mind that BRCA mutations may be present in high-grade serous ovarian carcinoma cases with solid/pseudo-endometrioid/transitional carcinoma-like growth pattern, necrosis, prominent nuclear pleomorphism, high mitotic activity and prominent tumor-infiltrating lymphocytes.

Keywords: BRCA, high-grade serous ovarian cancer, histopathology

Öz

Amaç: Çalışmamız BRCA ile ilişkili yüksek dereceli over karsinomlarının ayırt edici histomorfolojik bulgularının belirlenmesine katkı sağlamayı amaçlamaktadır.

Yöntem: Çalışma 2020-2021 yıllarında tanı alan yüksek dereceli seröz karsinom olgularını kapsayacak şekilde planlanmıştır. BRCA mutasyonu saptanan ve saptanmayan gruplarda histopatolojik özellikler arşivden tümör lamları çıkarılarak karşılaştırmalı olarak değerlendirilmiştir.

Bulgular: Solid/psödo-endometrioid/transizyonel karsinom benzeri büyüme paterni ve yüksek mitoz sayısı BRCA mutasyonu olan grupta mutasyon olmayanlara göre istatistiksel açıdan anlamlı olacak şekilde daha sık izlenmiştir. Belirgin nükleer pleomorfizm, nekroz sıklığı, belirgin tümör infiltre edici lenfositler açısından iki grup arasında anlamlı fark bulunmamıştır.

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Öz

Sonuç: Ailesinde karsinom öyküsü olmayan hastalarda BRCA mutasyonlarının saptanmasında patologlar çok önemli bir rol oynayabilir. Bu açıdan solid/psödo-endometrioid/transizyonel karsinom benzeri büyüme paterni, nekroz, belirgin nükleer pleomorfizm, yüksek mitotik aktivite ve belirgin tümör infiltre edici lenfositler gösteren yüksek dereceli seröz over karsinom olgularında BRCA mutasyonları olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: BRCA, yüksek dereceli seröz yumurtalık kanseri, histopatoloji

Introduction

Germline BRCA1 or BRCA2 mutations are detected in approximately 15% of all ovarian epithelial neoplasia patients[1]. The distinctive histopathological diagnosis of ovarian cancer associated with hereditary breast and ovarian cancer syndrome (HBOC) due to BRCA mutations is high-grade serous carcinoma (HGSC), and the frequency of BRCA1 and BRCA2 germline mutations increases to approximately 25% in patients diagnosed with these neoplasms[1-3]. The detection rate of somatic mutations is around 3-7%[4,5]. Apart from the BRCA genes, several other tumor suppressor genes and oncogenes are associated with hereditary ovarian cancer.

Tumor cells that have homologous recombination deficiency show high sensitivity to platinum-based chemotherapy regimens, and these tumors can be treated with poly adenosine diphosphate ribose polymerase (PARP) inhibitors. PARP inhibitors are a new treatment option that has been reported to prolong progression-free survival in patients with HGSC, particularly those with BRCA1 and BRCA2 mutations[6-8]. To determine which HGSC patients are likely to carry BRCA1 or BRCA2 mutations will provide cost-effective results for genetic testing applications.

Previous studies have shown a relationship between BRCA status and histological growth pattern, nuclear pleomorphism, necrosis, mitotic rates, and tumor-infiltrating lymphocytes (TILs) in breast tumors and high-grade serous ovarian tumors[9-12].

This study, examining patients with HGSC who applied to our center, was conducted to contribute to the definition of the distinctive histomorphological features of tumors associated with BRCA mutation.

Materials and Methods

Between January 1, 2020 and December 31, 2021, the records of patients diagnosed with HGSC in our institution were examined and 130 patients were identified. Among these cases, 72 patients for whom BRCA1/2 hereditary cancer risk panel could not be applied, 12 patients whose primary tumor was not of ovarian origin, and 20 patients who received neoadjuvant chemotherapy were excluded from the study. Twenty-six patients whose primary tumor originated from the ovary and who underwent genetic analysis were included in the study. Germline BRCA1 mutation was found in 6 of the patients, and BRCA2 mutation was found in 3.

Tumor slides of the cases were re-evaluated by a specialist pathologist (GA). Evaluation was made from the primary tumor localization (ovary). Metastatic foci were not included in the evaluating slides. Tumor growth patterns were assessed in terms of the architectural features of the tumor. Cases showing solid, pseudo endometrioid, and transitional cell carcinoma-like (SET) features more than 25% were noted as positive for SET morphology[9,13]. When more than one SET patterns were together, the ratios were summed and the calculation was made.

Initially, tumor slides were evaluated at low magnification (x40) for necrosis (comedo-like or geographic), nuclear pleomorphism, mitotic index, TILs, and tumor growth patterns. Tumors containing comedo-like or geographic necrosis were evaluated for the presence of necrosis. Marked nuclear pleomorphism has been determined as a prominent nuclear aberration in tumor cells compared to the surrounding tissue, such as clear irregular nuclear contours, vesicular nuclei, hyperchromatic, bizarre or coiled nuclei, macronucleoli, abundant eosinophilic cytoplasm)[14]. It was considered as positive when necrosis and nuclear pleomorphism were easily detectable in the majority of slides[9,14].

Although there are various publications on the mitotic rate and TILs evaluation in ovarian cancers, definite criteria have not been determined. In the literature review, it was seen that the criteria determined in breast cancers tend to be used in general. Mitotic rate assessment was made according to the modified Nottingham grading system. Accordingly, in

the evaluator microscope with a field diameter of 0.65 mm, mitosis was counted in 10 consecutive high magnification fields (400x) in the most mitotic active area of the tumor and scored as low (≤12)/medium (13-24)/high (≥25)[14]. Mononuclear infiltrate within the borders of the invasive tumor was taken into account while performing TILs evaluation. Lymphocytes in the intercellular areas and cores of the papillary structures of the tumor were included in the count. Immune infiltrates outside the tumor margins, areas of tumor necrosis, and lymphocytes within the blood vessels were excluded. Prominent TILs were considered positive when >40 intraepithelial lymphocytes in a single high-power field[14].

Ethics committee approval was obtained from University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Commitee (decision no: 2021/11, date: 11.2021).

Statistical Analysis

SPSS 22.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of the variables. Quantitative variables are shown in the tables as mean ± standard deviation and median range (maximum-minimum), while categorical variables are shown as n (%). The Mann-Whitney U test was used in the comparison of two independent groups in which quantitative data were evaluated. Fisher's Exact test was used to compare categorical variables in which qualitative data were evaluated. The results of the analysis were accepted as significant with a p-value less than 0.05 at a confidence level of 95%.

Results

The descriptive and histopathological features of the cases included in the study are presented in Table 1. The mean age of the group was 53.9 (±10.5). It was observed that 34.6% of the included cases had *BRCA* gene mutations; 66.7% of those with mutations are BRCA1 and 33.3% are BRCA2. Considering the tumor location, it was determined that 61.5% were bilateral and 38.5% were unilateral. While 26.9% of the patients showed extraovarian spread, it was observed that capsular rupture was observed in 50% of them. Lymph node metastasis was observed in 42.3% of the cases. Considering the histopathological features, SET growth pattern was detected in 65.4% of the cases (Figures 1, 2). Significant nuclear pleomorphism is present in 69.2% of cases. The proportion of tumors with significant mitotic activity was 34.6%; the rate of tumors with significant TILs is 23.1%. Necrosis was detected

Table 1. Descriptive clinical and histopathological features of the cases included in the study

	Count	%
BRCA mutation		
Present	9	34.6
Absent	17	65.4
BRCA mutation type		
BRCA-1	6	66.7
BRCA-2	3	33.3
Capsule rupture		
Present	13	50.0
Absent	13	50.0
Lymph node metastasis		
Present	11	42.3
Absent	15	57.7
Lymphovascular invasion		
Present	16	61.5
Absent	10	38.5
Necrosis		
Present	14	53.8
Absent	12	46.2
High mitotic activity		
Present	9	34.6
Absent	17	65.4
Extraovarian spread		
Present	7	26.9
Absent	19	73.1
SET pattern		
Present	17	65.4
Absent	9	34.6
Significant TILs		
Present	6	23.1
Absent	20	76.9
Ovarian side		
Unilateral	10	38.5
Bilateral	16	61.5
Prominent nuclear pleomorphism		
Present	18	69.2
Absent	8	30.8
Total	**26**	**100.0**

TILs: Tumor-infiltrating lymphocytes, SET: Solid, pseudo endometrioid

in 53.8% of the cases and lymphovascular invasion was found in 61.5% of the cases.

The histopathological features of the groups with and without *BRCA* gene mutation are given in Table 2. While 66.7% of the tumors are bilateral in the group with *BRCA* gene mutation, this rate is 58.8 in the group without mutation. There was no statistically significant difference in tumor localization in the group with and without *BRCA* gene mutation. Extraovarian spread was observed more frequently in the group with mutations (77.8%), but there was no statistically significant difference between the group without mutation (70.6%). The frequency of capsular rupture was also seen more frequently in the group with mutation (55.6%) than in the group without (47.1%), but it was not statistically significant. The frequency of lymph node metastases was not statistically different in the group with and without *BRCA* gene mutation.

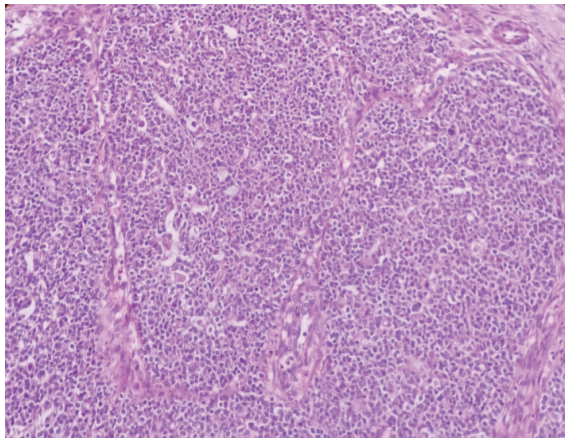

Figure 1. Solid growth pattern in one case with BRCA mutation

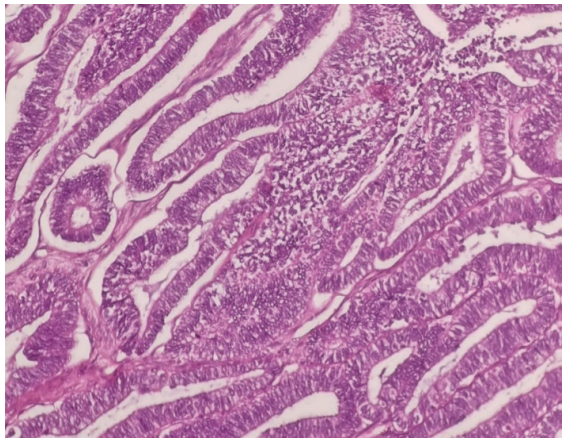

Figure 2. Pseudo-endometrioid growth pattern in one case with BRCA mutation

SET growth pattern was observed with a frequency of 66.7% in the group with *BRCA* gene mutation, and this rate was 17.6% in the group without gene mutation. The difference between the two groups was statistically significant (p=0.02). Marked nuclear pleomorphism was observed at a frequency of 88.9% and 58.8% in the group with and without *BRCA* gene mutation, respectively. However, this difference is not statistically significant. High mitotic activity was observed more frequently in the group with *BRCA* gene mutation (66.7%) than in the group without mutation (17.6%), which was statistically significant (p=0.02). Prominent tumor infiltrating lymphocytes were observed at a rate of 22.2% in the group with *BRCA* gene mutation, while it was observed at a rate of 23.5% in the group without mutations. This difference is not statistically significant. The incidence of necrosis was 55.6% in the group with *BRCA* gene mutation and 52.9% in the group without mutation. Although lymphovascular invasion was observed more frequently in the mutation group (77.8%), this difference was not statistically significant.

Discussion

Ovarian cancer ranks 8th among the causes of cancer-related death in women worldwide[15]. Epithelial ovarian tumors constitute 95% of all ovarian tumors[16]. Histological subtypes of epithelial ovarian tumors, in order of frequency; HGSC (75%), low-grade serous carcinoma (10%), endometrioid

Table 2. Histopathological features according to *BRCA* gene mutation status

		***BRCA* gene mutation**		
		Present	**Absent**	
		%	**%**	***p**
Capsule rupture	Present	55.6	47.1	0.50
Lymph node metastasis	Present	55.6	35.3	0.19
Lymphovascular invasion	Present	77.8	52.9	0.39
Necrosis	Present	55.6	52.9	0.61
Prominent nuclear pleomorphism	Present	88.9	58.8	0.19
High mitotic activity	Present	66.7	17.6	**0.02**
Extraovarian spread	Present	77.8	70.6	0.53
SET	Present	66.7	17.6	**0.02**
Significant TILs	Absent	77.8	76.5	0.66
	Present	22.2	23.5	

TILs: Tumor-infiltrating lymphocytes, SET: Solid, pseudo endometrioid, and transitional cell carcinoma-like

carcinoma (10%), clear cell carcinoma (5%), and mucinous carcinoma (2.4%)[16].

BRCA1 and BRCA2 are the most common mutations in HGSC. Together with *BRCA1* and *BRCA2*, *ATM*, *BARD1*, *NBN* and some other genes, they are important elements of the homologous recombinant (HR) DNA repair system[17]. Germline and somatic mutations in *HR* genes are seen in approximately 30% of patients with ovarian cancer, while 75% of them are in *BRCA1* and *BRCA2* genes[18]. 54-74% of BRCA1/2 mutations are germline and 27-46% are somatic type[4,5,17,19].

BRCA1 and *BRCA2* genes are located in chromosome 17q21 and 13q 12.3 regions, respectively, and are tumor suppressor genes that have important roles in DNA repair, cell cycle checkpoints, protein ubiquinization and chromatin rearrangement[20-22]. They encode proteins required for DNA double-strand break repair by HR[23,24]. Mutations across both genes are widely distributed. "Second hit" cells that cause HR repair deficiency in women with HBOC rely on error-prone alternative DNA repair mechanisms that lead to an increased risk of developing various malignancies, including the ovary and breast, as well as the tuba uterina and peritoneum[25]. Tumor cells showing HR repair deficiency show high sensitivity to platinum-based chemotherapy regimens, and these tumors can be treated with PARP inhibitors. PARP inhibitors are a new treatment option that has been reported to prolong progression-free survival in patients with HBOC, especially those with BRCA1 and BRCA2 mutations[6-8]. Besides BRCA1/2 mutations, other mutations in homologous recombination repair (*HRR*) genes such as RAD51, ATM, ATR, BRIP1, PALB2, RB1, NF1, CDKN2A confer homologous recombination deficiency and increased susceptibility to PARP inhibitors. HGSCs are associated with recurrent somatic mutations in the *NF1*, *BRCA1*, *BRCA2*, *RB1* and *CDK12* genes at a rate of approximately 5-8%[16].

Detection of BRCA mutation creates important prognostic and predictive effects in patients with HGSC. Current guidelines recommend a number of approaches to molecular testing. Guidelines from working groups such as the National Comprehensive Cancer Council and the American Society of Clinical Oncology (ASCO) recommend that all patients diagnosed with epithelial ovarian cancer undergo germline genetic testing at diagnosis for the *BRCA1/2* genes as well as other known ovarian cancer susceptibility genes[26,27]. ASCO also recommends that patients without germline BRCA1/2 mutations undergo genetic tumor testing for somatic mutations in BRCA1/2 and other commonly mutated genes[27]. The Society of Gynecological Oncology recommends the BRCA1/2 test for all patients with epithelial ovarian, tuba uterine and peritoneal cancers, even if there is no family history[28]. Joint guidelines of the European Society of Gynecological Oncology and the European Society of Medical Oncology recommend BRCA1/2 mutation testing for all patients with non-mucinous ovarian cancer[29].

Although it is recommended to apply genetic testing to all patients diagnosed with ovarian cancer, from a cost/effectiveness perspective, evaluating patients in terms of BRCA mutation risk and identifying patients who will benefit most from testing may be the ideal management plan. One way to classify patients, other than family history, is tumor histomorphology. For BRCA-associated ovarian tumors, the characteristic histopathological findings need to be better defined. As the identification of these morphological features increases, it becomes easier to predict which ovarian cancer cases may have BRCA1 and/or 2 mutations during routine pathological examinations. Similarly, reporting morphology suspicious for BRCA1 and/or 2 mutations in pathology reports may facilitate and accelerate clinical-genetic studies on a case-by-case basis.

Soslow et al.[9] examined tumors from patients with germline BRCA1/2 mutations in addition to tumors with somatic BRCA1/2 mutations or promoter hypermethylation. That study described a distinct morphological pattern, defined as SET morphology, in tumors with BRCA mutations. This morphological appearance consists of "solid", "pseudo-endometrioid" and "transitional cell carcinoma-like" patterns. Defined histologically, the solid pattern consists of large tumor islands without a specific growth pattern. In the pseudo-endometrioid pattern, gland-like structures composed of tubular cells and round cavities forming a cribrifoming-like appearance are observed. The transitional cell carcinoma-like type includes tumor cells that form an insular or trabecular architecture similar to the epithelium of the bladder[9,13]. According to this study, it was determined that BRCA1-associated HGSCs showed high mitotic rates, prominenet TILs, geographic/comedo-type necrosis and SET features, while tumors with BRCA2 mutations had SET features but tended to show relatively lower rates of TILs and necrosis.

Tubo-ovarian carcinomas in a cohort of BRCA1 germline mutation carriers [Fujiwara et al.[14]]; it has been shown that it tends to exhibit high-grade and serous/undifferentiated

histology, prominent TILs, marked nuclear atypia with giant/bizarre forms, and abundant mitotic figures.

In this study, which was conducted to compare the histopathological features according to the *BRCA1/2* gene mutation status in HGSCs of the ovary, 130 patients who applied to our center for a year were evaluated. *BRCA1/2* gene mutations were detected in more than a quarter of the patients who underwent genetic analysis. This rate was found to be compatible with previous studies[30-32].

In this study, SET growth pattern was found to be significantly higher in the group with BRCA mutation. In the study of Soslow et al.[9] in which BRCA1/2 mutations were examined, it was shown that HGSCs associated with BRCA1 and BRCA2 mutations tended to show SET features at a high rate[20].

In our study, mitotic activity was found to be high in patients with BRCA1/2 mutation according to the Nottingham grading system, which is consistent with the literature. In a study conducted in Canada in 2020 by Fujiwara et al.[14], who evaluated mitotic activity according to the same grading system, it was shown that ovarian carcinomas carrying BRCA mutations tend to exhibit significant mitotic activity[14,20]. Similarly, Soslow et al.[9] found high mitotic rates in their studies in which they examined HGSCs carrying the BRCA1/2 mutation.

It has been reported in many studies that HGSCs carrying BRCA1 mutations contain significant TILs[9,14,20]. In this sense, when we examined our cases, TILs were detected in all tumors, but when the groups with and without mutations were compared, no significant difference was found between the groups in terms of prominent TILs.

The prominent nuclear pleomorphism observed in tumor cells is defined as a characteristic histological feature in HGSC with BRCA mutation[9,14]. In our study, marked nuclear pleomorphism was found at a higher rate in the group with BRCA mutation than in the group without it. However, the difference was not significant. This may be because the study group was small.

The presence of necrosis is one of the more frequently expected characteristic findings, especially in HGSCs carrying the BRCA1 mutation[9]. In our study, necrosis was found to be slightly higher in the group carrying the BRCA mutation, but the difference was not significant.

Study Limitations

The fact that genetic analysis could not be performed on all patients diagnosed with HGSC in this study was a limiting factor. We think that the more detailed and reliable evaluation of the characteristic histopathological features described in the literature in HGSCs carrying *BRCA1/2* gene mutations may be possible by increasing the number of cases.

Conclusion

The pathologists play a key role in detecting cases with BRCA mutations, while they examine the tumor morphology, microscopically. It is particularly important for cases with no family history for carcinoma. In this respect, it should be kept in mind that high grade serous ovarian carcinoma cases that show SET pattern, necrosis, prominent nuclear pleomorphism, high mitotic activity and TIL may have BRCA mutations.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Commitee (decision no: 2021/11, date: 11.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: İ.Ç., Concept: C.K.T., Design: G.A., C.K.T., Data Collection or Processing: G.A., Ö.Ö.K., T.R.Ö., Analysis or Interpretation: G.A., C.K.T., Literature Search: G.A., Writing: G.A.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Single-center Experience of Therapeutic Plasma Exchange in Children with Neuroimmunological Disorders: Indications, Efficacy, and Safety

Nöroimmünolojik Hastalıkları Olan Çocuklarda Terapötik Plazma Değişiminde Tek-merkez Deneyimi: Endikasyonlar, Etkinlik ve Güvenilirlik

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Abstract

Objective: Therapeutic plasma exchange (TPE) is frequently employed to treat neurological conditions with known or presumed immune pathogenesis in adults, however knowledge and experience in children remains insufficient. The purpose of this study is to perform a retrospective assessment of the indications, long-term efficacy, safety, and complications of TPE in children with various neuroimmunological conditions.

Methods: This investigation was a single-center, retrospective cohort study conducted at a tertiary hospital, analyzing pediatric patients with neuroimmunological diseases who were subjected to TPE.

Results: The median age of the patients was 74.5 (22-180) months, and 60% (n=6) of the patients were female. The indications for TPE included acute disseminated encephalomyelitis, Guillain-Barré syndrome, autoimmune encephalitis, acute necrotizing encephalopathy of childhood, transverse myelitis, acute flaccid myelitis, thrombotic thrombocytopenic purpura, and febrile infection-related epilepsy syndrome. The median number of TPE sessions per patient was five, with a median duration of 8.5 (5-14) days. The study found that two (20%) patients exhibited a complete response to TPE, while partial response was observed in remaining eight (80%) patients. There was neither mortality nor serious adverse events associated with the TPE procedure. At the most recent follow-up, 80% of the patients exhibited neurological sequelae.

Conclusion: TPE was observed to be an effective and well-tolerated treatment modality for children with various neuroimmunological disorders, resulting in a partial response in the majority of cases without any life-threatening complications. The rate of neurological sequelae was high despite positive clinical response, albeit in varying degrees.

Keywords: Therapeutic plasma exchange, Guillain-Barré syndrome, acute disseminated encephalomyelitis, efficacy, safety

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Öz

Amaç: Terapötik plazma değişimi (TPD), yetişkinlerde bilinen veya varsayılan immün patogenezi olan nörolojik durumları tedavi etmek için sıklıkla kullanılmasına rağmen çocuklarda bilgi ve deneyim yetersizdir. Bu çalışmanın amacı, çeşitli nöroimmünolojik hastalıkları olan çocuklarda TPD'nin endikasyonları, uzun süreli etkinliği, güvenliği ve komplikasyonlarının retrospektif bir değerlendirmesini yapmaktır.

Yöntem: Bu araştırma, üçüncü basamak bir hastanede nöroimmünolojik hastalıklara yönelik TPD yapılan pediyatrik hastaları inceleyen, tek merkezli, retrospektif bir kohort çalışmasıydı.

Bulgular: İlk TPD işleminde ortanca yaş 74,5 (22-180) ay olup, hastaların %60'ı (n=6) kızdı. TPD endikasyonları arasında akut dissemine ensefalomiyelit, Guillain-Barré sendromu, otoimmün ensefalit, çocukluk çağı akut nekrotizan ensefalopatisi, transvers miyelit, akut flask miyelit, trombotik trombositopenik purpura ve febril enfeksiyonla ilişkili epilepsi sendromu vardı. Hasta başına ortanca TPD seansı sayısı beşti ve ortanca süre 8,5 (5-14) gündü. Çalışmada iki (%20) hastanın TPD'ye tam bir yanıt gösterdiği, geri kalan sekiz (%80) hastada ise kısmi yanıtın gözlendiği bulundu. TPD prosedürüyle ilişkili mortalite ya da ciddi yan etki yoktu. En son takipte, hastaların %80'inde nörolojik sekel izlendi.

Sonuç: TPD'nin, çeşitli nöroimmünolojik bozuklukları olan çocuklar için etkili ve iyi tolere edilen bir tedavi yöntemi olduğu ve hastaların çoğunda yaşamı tehdit eden herhangi bir komplikasyon olmaksızın kısmi yanıtla sonuçlandığı gözlendi. Değişen derecelerde pozitif klinik yanıta rağmen nörolojik sekel oranı yüksekti.

Anahtar Kelimeler: Terapötik plazma değişimi, Guillain-Barré sendromu, akut dissemine ensefalomiyelit, etkinlik, güvenlik

Introduction

Therapeutic plasma exchange (TPE) is a procedure that lowers the levels of circulating autoantibodies, alloantibodies, monoclonal proteins, and immune complexes by centrifugation and replacement of the plasma with albumin solution or fresh frozen plasma[1-3]. In recent decades, TPE has emerged as a widely recognized therapeutic modality for various pediatric immune-mediated disorders. Among which, neurological disorders are the most common indications[4,5]. However, there still exists only a restricted set of case series and a dearth of randomized controlled trials examining the efficacy and safety of TPE in pediatric patients with neurological disorders, probably due to relative scarcity of these disorders and the technical challenges associated with implementing TPE in pediatric patients[6-8]. Consequently, knowledge pertaining to the acute and long-term outcomes of TPE in the pediatric population remains insufficient and further reports are warranted to establish the effectiveness of TPE in the context of neurological disorders among pediatric patients. Progress in this area of inquiry may pave the way for improved management of neurological disorders and may, in turn, help mitigate the occurrence of chronic neurological sequelae. We therefore conducted a retrospective study of the medical records of pediatric patients with neurological disorders who underwent TPE, with the aim of evaluating the indications, safety, complications, and outcomes of TPE in children.

Materials and Methods

The present study is a retrospective cohort analysis conducted in a single-center on pediatric patients who had undergone TPE due to neurological disorders events between 2015 and 2023. The medical records were perused to gather demographic and clinical data, types of neurological disorders, immunotherapies, length of stay in intensive care units and hospitals, and procedure details including replacement fluid, vascular access, intubation status, number of procedures and courses, duration of the courses, complications, efficacy, and overall outcome.

Determining the Indication of TPE

The criteria for indicating TPE encompassed an inadequate response to first line or standard treatments and the abrupt progression of clinical symptoms, such as marked muscular impairment or respiratory failure. According to the American Society for Apheresis (ASFA) 2019 guidelines, which provide a list of evidence-based indications for TPE in pediatric neurological diseases, all patients were reclassified into four categories based on the quality of published evidence and the strength of recommendations[9]. For patients without a recommendation level in ASFA, the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence were used to categorize[10].

TPE Procedures

A double-lumen venous catheter was inserted into the internal jugular (preferred) or femoral veins for TPE procedures, which were performed every other day at a rate of 1.5 times the predicted plasma volume using Teruma BCT Spectra Optia® Apheresis Sysytem (Tokya, Japan). The plasma volume for each patient was calculated using body surface area, gender, and hematocrit. Fresh frozen plasma

was used as the volume replacement fluid, and acid citrate dextrose-A (dilution 1:10-1:20) was used for anticoagulation during TPE as previously decribed[11]. Vital signs were closely monitored for adverse events during the procedure. Procedure time, whole blood flow rate, processed and removed plasma volumes were recorded. Ionized calcium levels were measured before and after TPE to prevent severe hypocalcemia. All procedures were performed by experienced physicians specialized in apheresis and written informed consent was obtained from all patients after detailed explanation of the procedural risks.

Ethical Approval

The present study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Local Ethics Committee of Dokuz Eylül University (number of approval: 2021/30-12).

Statistical Analysis

All statistical analyses were conducted using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL). The variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they were normally distributed. Continuous variables were expressed as mean ± standard deviation, median (minimum-maximum) and interquartile range (IQR), as appropriate.

Results

Demographic and Clinical Data

A total of 92 children received TPE treatment in the specified time period. In 10 of whom, an acute neurological condition was certified as an indication for TPE. Majority of the patients (n=6, 60%) were female and the median age at first procedure of TPE was 74.5 (range: 22-180, 93.8±53.6, IQR: 72-139) months. The indications of TPE encompassed acute disseminated encephalomyelitis (ADEM; n=2, %20), Guillain-Barré syndrome (GBS; n=2, %20), and autoimmune encephalitis (AE), acute necrotizing encephalopathy of childhood, transverse myelitis, acute flaccid myelitis, thrombotic thrombocytopenic purpura (TTP), and febrile infection-related epilepsy syndrome in one patient each (10%). The decision of TPE was based on an inadequate response to first-line or standard treatments in majority of the cohort (n=8, 80%). In contrast, two (20%) patients underwent TPE due to sudden progression of clinical findings, such as severe muscle weakness or respiratory failure. Based on the 2019 guidelines set forth by the ASFA, four individuals, constituting 40% of the cohort, were categorized under group I, whereas two participants, comprising 20% of the sample, were categorized under group II. The roles of TPE in the remaining four (40%) patients were not covered by the ASFA recommendations, but had Oxford level 4 evidence which represents case-series and poor cohort studies. Demographic and clinical features, treatment modalities and outcomes of the study population are summarized in Table 1.

Procedures and Other Treatment Modalities

The number and frequency of TPE procedures were determined based on the clinical scenario. A total of 58 procedures were administered to ten patients. The median number of TPE sessions per patient was five and ranged between five and seven (mean: 5.8±1.03, IQR: 5-7). The median duration of procedures was 8.5 days (range: 5-14, mean: 8.5±2.79, IQR: 7-10). The time interval from the onset of the acute condition to the first TPE intervention varied between 1-10 days (with a median value of 4.5 days, mean value of 4.4±2.75 days, and an IQR of 2.5-5 days).

TPE was first-line therapy in only one (10%) patient with TTP, in whom steroid treatment was given adjunctively. In one of the GBS patients, TPE and intravenous immunoglobulin (IVIg) were applied in combination and sequentially (zipper method) due to rapidly progressive muscle weakness and respiratory failure. A total of seven (70%) patients received IVIg, of which four (40%) were administered prior to TPE. The duration of IVIg treatments ranged from two to five days, with a total dose of 2 g/kg. Out of the total number of patients, 80% (n=8) received corticosteroids, with 70% of whom (n=7) having taken it before undergoing TPE. Corticosteroid regimens consisted of pulse methylprednisolone 30 mg/kg/dose, maximum 1 g) given for 5-10 days followed by a gradual reduction in dosage over a period ranging from 7 to 30 days using oral maintenance taper. While five (50%) patients were administered both IVIg and corticosteroid therapy, none of the patients were subjected to second-line immunotherapy.

Adverse Events and Complications

There was no mortality associated with TPE procedure. The procedures were not terminated due to adverse events in any of the patients. A slight and easily rectifiable electrolyte imbalance was detected in a combined group of four (40%) patients, with three of them (30%) experiencing hyponatremia.

Table 1. Demographic and clinical features, treatment modalities and outcomes of the study population

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (months)	156	37	72	76	73	22	72	161	180	89
Gender	F	F	M	M	M	F	F	F	F	M
Diagnosis	GBS	GBS	ADEM	ADEM	AE	ANEC	TM	AFM	TTP	FIRES
Evidence level of indication	ASFA I, 1A	ASFA I, 1A	ASFA II, 2C	ASFA II, 2C	ASFA I, 1C	Oxford level 4, grade D	Oxford level 4, grade D	Oxford level 4, grade D	ASFA I, 1A	Oxford level 4, grade D
Disease duration before TPE (days)	1	4	5	4	10	5	7	5	1	2
Treatments	IVIg (zipper method)	IVIg (after TPE)	IVIg (before TPE) MP (before IVIg)	IVIg (before TPE) MP (before IVIg)	IVIg (before TPE) MP (before IVIg)	IVIg (before TPE) MP (before IVIg)	MP (before TPE)	IVIg (before TPE) MP (before IVIg)	MP (adjucvant)	MP (before TPE)
PIM3 score	3.90%	4.05%	10.10%	10.05%	3.5%	5.01%	3.09%	4.08%	1.50%	2.60%
PRISM3 score	4	11	12	12	5	5	6	5	2	5
Vascular access	Jugular vein	Jugular vein	Jugular vein	Jugular vein	Subclavian vein	Jugular vein	Jugular vein	Jugular vein	Jugular vein	Subclavian vein
Intubation time with/ without TPE (days)	10/26	10/36	7/2	5/6	0/0	1/7	10/10	14/4	0/0	0/0
Number of TPE procedures/courses	1/5	1/5	1/7	1/5	1/7	1/5	1/5	1/7	1/5	1/7
Length of TPE course (days)	10	10	7	5	7	5	10	14	10	7
Complications related to TPE	Hyponatremia	Hyponatremia	None	None	None	None	None	Hyponatremia	Hypocalcemia	None
Improvement with TPE	Partial response	Partial response	Partial response	Partial response	Complete response	Partial response	Partial response	Partial response	Complete response	Partial response
Length of stay in the intensive care unit/ hospital (days)	36/65	46/56	12/37	15/32	11/21	14/34	20/23	18/26	9/14	9/12
Follow-up duration (months)	8	60	5	156	12	60	24	36	12	48
Outcome										
Motor impairment	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Cognitive impairment	No	No	Yes	Yes	No	Yes	No	No	No	Yes
Epilepsy	No	No	No	No	No	Yes	No	No	No	Yes

TPE: Therapeutic plasma exchange, PIM3: Pediatric index of mortality, PRISM3: Pediatric risk of mortality 3, F: Female, M: Male, GBS: Guillain-Barré syndrome, ADEM: Acute disseminated encephalomyelitis, AE: Autoimmune encephalitis, ANEC: Acute necrotizing encephalopathy of childhood, TM: Transverse myelitis, AFM: Acute flaccid myelitis, TTP: Thrombotic thrombocytopenic purpura, FIRES: Febrile infection-related epilepsy syndrome, ASFA: American Society for Apheresis, IVIg: Intravenous immunoglobulin, MP: Methylprednisolone

Efficacy and Outcome

After undergoing TPE, two patients (20%) exhibited a complete response in signs and symptoms. Patients with a complete response to TPE had underlying etiologies of AE and TTP. Although partial response was observed in eight (80%) patients, no patient demonstrated a complete lack of response.

The study findings indicate that patients spent a median of 14.5 days in the intensive care unit (range: 9-46, mean: 19±12.35, IQR: 11.25-19.5). Furthermore, the median hospital stay duration was 29 days, with a range of 12 to 65 days and an IQR of 21.5-36.25 (mean: 32±17.7). The overall clinical follow-up duration varied from 6 to 156 months, with a mean of 42.1±36.17 months and a median of 30 months (IQR: 12-57). At the most recent follow-up examination, eight out of ten patients (80%) exhibited neurological sequelae, including motor impairment (n=4, 40%), cognitive and motor impairment (n=2, 20%), and cognitive-motor impairment and epilepsy (n=2, 20%). Regarding the two patients who achieved full recovery, one had AE and the other had TTP.

Discussion

Rapid clearance of pathogenic molecules in immune-mediated or autoimmune disorders is anticipated to accelerate the recovery process or provide sufficient time for alternative therapies to take effect. TPE is most frequently used for neurological disorders in adults, whereas its application in children poses greater challenges due to a lack of consensus regarding the indications, more frequent technical issues concerning vascular access, reduced blood volume, higher incidence of adverse events, and relatively poor cooperation[12-14]. Nonetheless, recent technical advancements and the availability of different types of central venous catheters and ports have improved safety and encouraged the use of TPE in in pediatric patients[15,16]. This modality is now utilized as a primary intervention or as an ancillary or substitute therapy for neurological disorders based on the ASFA 2019 guidelines which regularly revise evidence-based suggestions[9]. Due to the paucity of randomized controlled trials investigating the efficacy and safety of TPE in pediatric populations, the literature has largely relied on the retrospective analysis of small cohorts of patients from various centers, with each center contributing its own experiences to the body of knowledge[6,7,17]. Therefore, the objective of this study is to provide a comprehensive description of the experience of a tertiary pediatric center regarding the use of TPE. Our investigation identified GBS and ADEM as the predominant indications for TPE in our cohort. These findings are in line with those reported in previous studies that have specifically evaluated the use of TPE in pediatric neurology[6,18]. Moreover, it is noteworthy that GBS was initially reported as the most frequent indication for TPE in a study that encompassed a broader range of diseases beyond neurological conditions in the pediatric population[19].

After the diagnosis of ADEM, the therapeutic goal is to promptly mitigate the inflammatory response in the central nervous system to facilitate clinical recovery. Although there have been no randomized controlled trials for the treatment of ADEM, the available therapies are derived from anecdotal evidence presented in case reports and case series. Given the presumed immune-mediated mechanism of ADEM, immunomodulatory agents remain the primary treatment form. The use of high-dose steroids may benefit ADEM patients with early intervention of inflammatory response, but this has not been validated by randomized controlled trials. Intravenous immunoglobulin is advocated for children who are unresponsive to steroids or in whom a contraindication is identified. TPE is recommended for patients with refractory fulminant disease. There is no established standard for determining the optimal TPE regimen in ADEM. In most studies, clinical improvement was observed within days, usually after 2-3 TPE sessions. Most published experiences describe 5-7 TPE treatments. Overall, according to the ASFA 2019 guidelines, ADEM is classified as a category II indication[9]. Our patients diagnosed with ADEM received pulse methylprednisolone and IVIG as the initial treatment regimen. However, due to the lack of clinical improvement with these therapies, we proceeded with TPE. Although our patients exhibited some partial response after undergoing 5-7 TPE sessions, they continued to experience residual deficits, such as motor and cognitive impairments. In contrast, other studies have reported moderate to marked improvements in 50-75% of ADEM patients with a similar history of prior steroid and IVIG treatments[6,7,20]. Hence, there is abundant room for further progress in determining the role of TPE in ADEM.

Published data presents conflicting findings regarding the efficacy, response to treatment, and neurological sequelae of treatment options in GBS. Both TPE and IVIg have demonstrated superiority over conservative treatment for disability recovery, making them the most efficacious treatments for both pediatric and adult populations[9,21,22]. Aside from studies indicating no substantial difference

between TPE and IVIg in treating GBS, there is also evidence suggesting that TPE may be somewhat more effective in children with GBS who require mechanical ventilation[9,23-25]. Lower incidence of adverse effects and readily availability of IVIG makes it commonly employed first-line therapy in GBS[6,7,9,21]. In GBS, the standard TPE protocol involves exchanging 1-1.5 plasma volumes 5-6 times during a 10-14 day period, with some patients requiring further treatment sessions[9]. According to the ASFA 2019 guidelines, TPE in GBS belongs to ASFA category I as primary treatment. In our study population, we treated our two GBS cases in accordance with the ASFA-recommended number and timing of TPE procedures. We administered IVIg treatment sequentially (via the zipper method) in one patient, while in the other patient, we provided IVIg treatment after observing only a partial response to TPE. Although GBS typically carries a favorable prognosis, the presence of motor sequelae in our patients could be attributed to the administration of TPE in individuals with pre-existing severe clinical manifestations.

In the present study, two patients underwent TPE in accordance with the ASFA recommendations under category I for AE and TTP, and both were associated with complete recovery. The number of published pediatric patients of AE treated with TPE has been increasing steadily, but due to a lack of consistent data, it is difficult to estimate the proportion of TPE usage compared to other immune interventions[26]. Once diagnosed, immunotherapy should be initiated promptly. High-dose corticosteroids, IVIG, or TPE are considered first-line therapies, and a search for underlying tumors should be conducted. However, there is no consensus on the exact order in which to apply these treatments or when to initiate a combined multimodal approach. There are no systematic comparisons available between the modalities. TPE removes pathophysiologically relevant antibodies and is an adjunct to immunotherapy for suppressing active inflammation and antibody production[9,26]. The rate of full recovery demonstrated a steady increase over time, from immediately after TPE (21.1%) to the last follow-up (64.2%). In children with a similar median length of follow-up, a trend towards a higher rate of full recovery was observed with a first-line immune therapy strategy consisting of TPE, steroids, and IVIG (67.1%), or TPE and steroids (65.2%), compared to TPE and IVIG (50%) or TPE alone (42.8%)[26]. For AE, 5-12 TPE treatments over 1-3 weeks with individually adjusted intervals between treatments are recommended[9]. The strategy of using all three first-line immune therapies associated with the best prognosis in the literature was applied in our patient with AE (seven procedures of TPE over seven days), who had full recovery in line with the literature[26].

Acquired TTP is a rare and potentially life-threatening hematological disorder in pediatric patients, characterized by the formation of microthrombi throughout the body[27]. The current routine initial treatment involves a combination of TPE, corticosteroids, and rituximab. The rationale for TPE is based on its ability to remove the patient's deficient plasma and replace it with donor plasma containing normal levels of ADAMTS13, thereby preventing further thrombus formation and promoting resolution of the disease[9,27]. Corticosteroids are commonly used as an adjunctive therapy, either as daily prednisone or pulsed methylprednisolone for a few days, or a combination; however, the comparative efficacy of these approaches has not been definitively established by clinical trials. Rituximab is frequently used to treat refractory or relapsing cases[9]. The prompt initiation of treatment is crucial in pediatric patients with acquired TTP, as even in the absence of neurological symptoms at presentation, there is a significant risk of subsequent major stroke[28]. As per the recommended guidelines, TPE was initiated expeditiously along with adjuvant pulse methylprednisolone in our pediatric, leading to an excellent clinical outcome. Although TPE has been shown to increase the survival rate of pediatric patients with acquired TTP from 10-20% to 80-90%, as evidenced by our case, further randomized controlled trials are warranted to establish standard therapeutic modalities for pediatric TTP.

Study Limitations

Among the remaining four patients in our study, diagnosed with acute necrotizing encephalopathy of childhood, transverse myelitis, acute flaccid myelitis, and febrile infection-related epilepsy syndrome, the level of evidence for TPE was supported by case series and low-quality cohort studies, rather than by established guidelines from the ASFA[29-33]. While our study found partial benefit of TPE in these patients, the simultaneous use of immunomodulatory agents, antibiotic-antiviral treatments, anti-seizure medications, and other supportive treatments may have contributed to the recovery. Even though our findings suggest that TPE may be a viable treatment option for these conditions in children, given the diverse etiologies and clinical presentations of these diseases, more research is needed to clarify the exact role, efficacy, and safety of TPE in pediatric patients.

Conclusion

The current study provides evidence that TPE is a safe and effective treatment option for immune-mediated neurological diseases, leading to substantial neurological recovery in a significant proportion of the pediatric patients with severe manifestations. The limited availability of established guidelines and experience derived from a large number of cases in the adult population, coupled with the prolonged neurological sequelae experienced by pediatric patients, underscores the need for further research in this topic.

Ethics

Ethics Committee Approval: The present study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Local Ethics Committee of Dokuz Eylül University (number of approval: 2021/30-12).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ç.G., G.A., Ö.Ö., G.S.U., D.A., T.B., S.H.K., A.A., U.Y., Concept: Ç.G., G.A., G.S.U., T.B., A.A., Design: Ç.G., Ö.Ö., D.A., S.H.K., U.Y., Data Collection or Processing: Ç.G., G.A., Ö.Ö., G.S.U., D.A., T.B., Analysis or Interpretation: Ç.G., G.A., S.H.K., A.A., U.Y., Literature Search: Ç.G., Ö.Ö., G.S.U., D.A., T.B., Writing: Ç.G., G.A., Ö.Ö., G.S.U., D.A., T.B., S.H.K., A.A., U.Y.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Efficiency of Preoperative 64-Channel Multidetector Computed Tomography in Detection of Hepatocellular Carcinoma in Patients Undergoing Liver Transplantation due to Liver Cirrhosis: A Comparison of Radiological and Pathological Findings

Karaciğer Sirozu Nedeniyle Karaciğer Nakli Yapılan Hastalarda Hepatosellüler Karsinomun Saptanmasında Ameliyat Öncesi 64 Kanallı Çok Dedektörlü Bilgisayarlı Tomografinin Etkinliği: Radyolojik ve Patolojik Bulguların Karşılaştırılması

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Abstract

Objective: The aim of this study is to demonstrate the efficiency of preoperative 64-channel multidetector computed tomography in detection in detecting hepatocellular carcinoma (HCC) in patients who underwent transplantation due to cirrhosis.

Methods: The study was designed retrospectively, and data were obtained by reviewing patient records at the organ transplant clinic. A total of 37 patients who met the specified criteria were included in the study.

Results: In the study, 9 (24.3%) of the 37 included patients were female. There was no significant difference between the two observers. The correlation between both observers and pathology regarding the presence of lesions showed a strong correlation for both Observer 1 and Observer 2, with r-values of 0.799 and 0.510, respectively. The correlation between Observer 2 and pathology was moderate, with an r-value of 0.441. For Observer 1, the sensitivity of CT was 100% for lesions larger than 2 cm and 64.2% for lesions smaller than 2 cm. For Observer 2, the sensitivity was 100% for lesions larger than 2 cm and 50% for lesions smaller than 2 cm.

Conclusion: Especially in our study, although the sensitivity of CT is low in lesions smaller than 2 cm (50-64%), it is quite successful in lesions larger than 2 cm (100%). However, due to the high spatial and temporal resolution of contrast-enhanced CT, a high false-positive rate should be considered, and patients should not be unnecessarily removed from the transplantation list.

Keywords: Cirrhosis, hepatocellular carcinoma, liver transplantation

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Öz

Amaç: Bu çalışmanın amacı siroz nedeniyle transplantasyon yapılan hastalarda preoperatif 64 kanallı multidedektör bilgisayarlı tomografinin hepatosellüler karsinomu (HCC) saptamadaki etkinliğini göstermektir.

Yöntem: Çalışma retrospektif olarak tasarlandı ve veriler organ nakli kliniğindeki hasta kayıtları incelenerek elde edildi. Belirlenen kriterleri karşılayan toplam 37 hasta çalışmaya dahil edildi.

Bulgular: Çalışmaya dahil edilen 37 hastanın 9'u (%24,3) kadındı. İki gözlemci arasında anlamlı bir fark yoktu. Her iki gözlemci ve patoloji arasında lezyonların varlığına ilişkin korelasyon, sırasıyla 0,799 ve 0,510 r-değerleri ile hem Gözlemci 1 hem de Gözlemci 2 için güçlü bir korelasyon gösterdi. Gözlemci 2 ile patoloji arasındaki korelasyon 0,441 r-değeri ile orta düzeydeydi. Gözlemci 1 için bilgisayarlı tomografinin (BT) duyarlılığı 2 cm'den büyük lezyonlar için %100 ve 2 cm'den küçük lezyonlar için %64,2 idi. Gözlemci 2 için duyarlılık 2 cm'den büyük lezyonlar için %100 ve 2 cm'den küçük lezyonlar için %50 idi.

Sonuç: Çalışmamızda özellikle BT'nin duyarlılığı 2 cm'den küçük lezyonlarda düşük olmasına rağmen (%50-64), 2 cm'den büyük lezyonlarda oldukça başarılıdır (%100). Ancak kontrastlı BT'nin yüksek uzaysal ve zamansal çözünürlüğü nedeniyle yüksek yanlış pozitiflik oranı göz önünde bulundurulmalı ve hastalar gereksiz yere transplantasyon listesinden çıkarılmamalıdır.

Anahtar Kelimeler: Siroz, hepatoselüler karsinom, karaciğer transplantasyonu

Introduction

About 80-90% of primary liver cancers are hepatocellular carcinoma (HCC), accounting for approximately 5% of all malignant cancers. HCC ranks as the fourth leading cause of cancer-related deaths. More than 90% of these patients also have liver cirrhosis[1]. In our country, the incidence in 2008 was 2.5 per 100,000, with a mortality rate of 2.3 per 100,000[2]. HCC can be treated with surgical, percutaneous, and transarterial interventions; however, curative treatment options are resection or transplantation. Unfortunately, curative treatment can be applied to less than 20% of patients due to reasons such as tumor size, presence of metastatic disease, and limited liver reserve[3,4].

HCC diagnosis, according to the European Association for the Study of Liver (EASL) guidelines, can be classified into two categories: Pathological or non-invasive. The role of radiology is mainly in the non-invasive diagnostic field. According to the EASL guidelines, non-invasive diagnosis can only be performed in cirrhotic patients using 4-phase multidetector computed tomography (MDCT) or dynamic magnetic resonance imaging (MRI)[5]. Typical HCC findings for diagnosis include hypervascularity in the arterial phase and washout of contrast material in the portal or late phase. The diagnostic value of contrast-enhanced ultrasound and angiography remains controversial, while positron emission tomography-computed tomography (PET-CT) is considered unhelpful[1-5]. Most of the studies comparing CT and MRI for HCC diagnosis have not shown statistically significant differences, and MDCT and MRI have been reported to exhibit similar diagnostic performance[6-9]. However, there are publications suggesting that MRI may be superior, especially for detecting small lesions[6]. Baek et al.[6] reported that MDCT and MRI had similar diagnostic power but MRI was more successful in detecting lesions smaller than 1 cm. On the other hand, Pitton et al.[7] stated that dynamic MRI was superior to MDCT in detecting HCC, and Hwang et al.[8] claimed that MRI was more effective than MDCT in detecting lesions smaller than 2 cm in their study. The reported sensitivity for HCC diagnosis with CT ranged widely between 44% and 93% in the studies[9].

The aim of this study is to demonstrate the efficiency of preoperative 64-channel MDCT in detecting HCC in patients who underwent transplantation due to cirrhosis.

Materials and Methods

This study was conducted at Dokuz Eylül University Faculty of Medicine Organ Transplantation Clinic between April 2008 and June 2011. The study included adult patients (18 years and older) who had undergone liver transplantation and had undergone dynamic MDCT scanning before transplantation. The study was designed retrospectively, and data were obtained by reviewing patient records at the organ transplant clinic. A total of 37 patients who met the specified criteria were included in the study. Patients who did not meet the criteria or had missing information were excluded from the study.

Ethics committee approval was obtained from the Local Ethics Committee (Dokuz Eylül University; date: 04.10.2012, number: 2012/32-05).

CT Procedure

All patients underwent contrast-enhanced biphasic or triphasic 64-channel MDCT imaging of the liver using a Brilliance CT scanner (Philips Medical Systems) before

operation at the Department of Radiology, Dokuz Eylül University Faculty of Medicine. An 18/20 G angiocath was placed in the right or left antecubital vein for intravenous contrast administration. The CT examination covered the region from the superior diaphragm to the superior iliac crest. A "bolus tracking" technique was employed for contrast-enhanced CT imaging. A trigger was set at the level of the diaphragm, placed in the aorta, and adjusted to initiate the scan when the attenuation reached 150 HU. A total of 120 mL of non-ionic iodinated contrast material at 350 mgI/mL was used for intravenous contrast administration. The injection rate was 4 mL/s, and the scan began when the contrast attenuation in the aorta reached 150 HU. The CT scan was performed with the following parameters: 120 kV, gantry rotation time of 0.5 seconds, and a parameter of 250 mAs. The arterial phase images were acquired with an 8-second delay after reaching the 150 HU attenuation level in the aorta. For the portal phase, a delay of 45 seconds was used, and for the late phase, a delay of 180 seconds was applied. The pitch factor ranged from 0.89 to 1.1, and the detector collimation was 64x0.625.

Analysis of the Images

The MDCT images were evaluated independently by two different radiologists, one being an experienced abdominal radiologist, without knowledge of the patient records or information. During the assessment, the radiologists were aware that the patients had undergone liver transplantation surgery, but they had no access to any clinical information, AFP levels, or pathological data related to the operation. The CT images were reviewed on the picture archiving and communication system, and all lesions with different densities within the liver parenchyma were assessed for the possibility of HCC. The size, number, and location of detectable lesions were noted for each case. The longest dimension of the lesions seen in any plane was recorded. In the literature, a four-point confidence level has been determined for the detection of HCC[6]. However, in this study, a separate category (Category 3) was specified for uncertain lesions. The radiologists classified the lesions in a five-point scale based on their confidence level regarding the presence of HCC; Category 1: Definitely not HCC, Category 2: Probably not HCC, Category 3: Uncertain, Category 4: Probably HCC, Category 5: Definitely HCC. Lesions falling into Category 4 demonstrated contrast enhancement in the arterial phase and were isodense with the parenchyma in the portal and late phases, whereas those in Category 5 showed contrast enhancement in the arterial phase and washout of contrast material in the portal or late phase, appearing hypodense compared to the parenchyma. Categories 4 and 5 were considered significant for HCC.

The EASL diagnostic criteria were used for HCC diagnosis[5]. In the diagnosis of HCC, contrast characterization and morphological features of the lesion are important. The typical contrast enhancement pattern includes hyperdensity in the arterial phase for nodular lesions, washout of contrast material in the portal and late phases, or hyperdensity in the arterial phase, isodensity in the portal phase, and hypodensity due to washout in the late phase. Morphologically, features such as mosaic pattern, peritumoral capsule formation, and fat infiltration are observed in HCC. The mosaic pattern refers to the presence of different contrast-enhanced areas, nodules, and septa with varying densities within the tumor. The peritumoral capsule is a thin, well-defined tissue surrounding the tumor. Fat infiltration is characterized by the presence of low-density gross fat tissue within the tumor.

Histopathological Evaluation

The pathology evaluation is performed without knowledge of the CT findings. Native liver is sectioned in the coronal plane with a thickness of 7-10 mm. The transplanted liver specimens are fixed in formalin immediately after surgery and examined. The location, size, and number of visually identifiable nodules are recorded, and samples are taken for microscopic examination. The microscopic examination is used to assess the presence of HCC findings.

Measurements

The nodular lesions observed on CT were compared with pathology reports in terms of the number, location, and size of the lesions on a lesion-by-lesion basis. Lesions seen on CT in the liver were recorded, and those lesions whose location and size were confirmed by pathology data were considered true positives. Lesions that were detected in pathological evaluation but missed on CT were considered false negatives, while lesions that were classified as HCC on CT but determined to be benign in pathological evaluation were considered false positives. Sensitivity was calculated as the ratio of the number of nodules defined as HCC on CT to the number of HCC nodules confirmed by pathology. Specificity was calculated as the ratio of the number of CT-negative cases for HCC to the number of cases negative for HCC according to pathology. The false positive rate represents the ratio of false positive cases on CT to the total number of true and false positive cases. Positive predictive value is the

ratio of the number of true HCC nodules detected in imaging to the total number of lesions detected in imaging. Negative predictive value is the ratio of true negatives to the sum of true and false negative lesions.

Statistical Analysis

In the evaluation of the findings in the study, statistical analyses were performed using the SPSS (Statistical Package for Social Sciences) for Windows 15 program. Chi-square test, McNemar's test for paired proportions, Fisher's Exact test, and correlation analysis were used for statistical analysis. A p-value less than 0.05 was considered statistically significant for all tests. Descriptive statistics, such as counts and percentages, were provided for categorical variables.

Results

In the study, 9 (24.3%) of the 37 included patients were female, and 28 (75.7%) were male. The ages of the patients ranged from 23 to 65 years, with a mean age of 50.02. Among the 37 patients, 20 (54.1%) had undergone biphasic CT examination, while 17 cases (45.9%) had undergone triphasic CT examination. The time interval between the preoperative CT examination and the surgery ranged from 0 to 345 days, with a mean of 64.1 days. Out of the 37 cases, 31 had preoperative AFP values, which ranged from 1.12 to 321, with a mean of 23.9.

When assessing the agreement between Observer 1 and Observer 2, the McNemar's test yielded a p-value of 0.687, indicating no significant difference between the two observers. The Kappa value was 0.797, representing "excellent correlation". Regarding the pathological data, among the 37 patients, 20 (54.1%) had no lesions consistent with HCC, while 17 (45.9%) had HCC. The size of these lesions ranged from 10 to 70 mm, with a mean of 23.5 mm. According to the evaluations made by the observers based on CT, Observer 1 identified 16 lesions consistent with HCC in 16 out of the 37 patients. The size of these lesions ranged from 6 to 55 mm, with a mean of 21.7 mm. On the other hand, Observer 2 identified 35 lesions consistent with HCC in 16 out of the 37 patients, with lesion sizes ranging from 8 to 65 mm and a mean of 22.8 mm (Table 1).

When the pathological results were considered as the gold standard, the sensitivity of CT according to Observer 1 was 88% (15/17), with a specificity of 95% (19/20). The positive predictive value was 93% (15/16), and the negative predictive value was 90% (19/21). The overall accuracy rate of CT at the patient level was 91.8% (34/37), with a diagnostic odds ratio of 147.1. For Observer 2, the sensitivity of CT was 82.3% (4/17), with a specificity of 90% (18/20). The overall accuracy rate of CT at the patient level was 86.4% (32/37), with a diagnostic odds ratio of 41.2 (Table 2).

The correlation between both observers and pathology regarding the presence of lesions showed a strong correlation for both Observer 1 and Observer 2, with r-values of 0.799 and 0.510, respectively. The correlation between Observer 2 and pathology was moderate, with an r-value of 0.441 (Table 3).

The ROC curve for the detectability of HCC by CT revealed an area under the curve of 0.749 for Observer 1 and 0.718 for Observer 2. Both values fell within the range of 0.70 to 0.80, indicating moderate success of the method (Table 4, Figure 1).

Table 1. HCC distribution and lesion sizes in patients according to pathology and observers

Parametre	Pathology	Observer 1	Observer 2
HCC (n, %)			
Yes	17 (45.9%)	16 (43.2%)	16 (43.2%)
No	20 (54.1%)	21 (56.8%)	21 (56.8%)
Lesion size [mm, (avarage, min, max)]	23.5 (10-70)	21.7 (6-55)	23.43 (8-65)

HCC: Hepatocellular carcinoma

Table 2. Comparison of observers with gold standard

	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	Diagnostic OR
Observer 1	88 (62-97)	95 (73-99)	93 (67-99)	90 (68-98)	91	147.1
Observer 2	82 (55-95)	90 (66-98)	87 (60-97)	85 (62-96)	86	41.2

PPV: Positive predictive value, NPV: Negative predictive value, OR: Odds ratio

Table 3. Correlation analysis for the presence of lesions

	Observer 1	Observer 2	Pathology
Observer 1 (p-value)	-	0.799 0.000	0.510 0.000
Observer 2 (p-value)	0.799 0.000	-	0.441 0.000
Pathology (p-value)	0.510 0.000	0.441 0.000	-

Table 4. Evaluation of HCC detectability with CT

	Area	Std. mistake	95% confidence interval	
			Lower value	Top value
Observer 1	0.749	0.065	0.622	0.877
Observer 2	0.718	0.067	0.586	0.850

HCC: Hepatocellular carcinoma, CT: Computed tomography

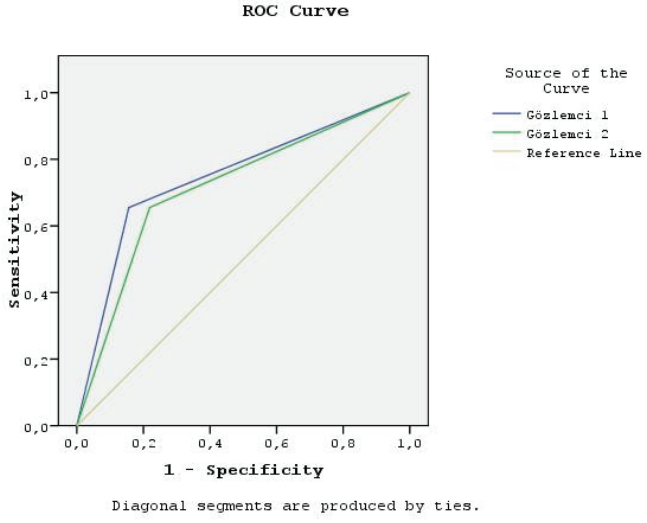

Figure 1. Evaluation of HCC detectability with CT

HCC: Hepatocellular carcinoma, CT: Computed tomography

Considering lesion sizes, evaluations were performed for lesions smaller or larger than 2 cm. For Observer 1, the sensitivity of CT was 100% for lesions larger than 2 cm and 64.2% for lesions smaller than 2 cm. For Observer 2, the sensitivity was 100% for lesions larger than 2 cm and 50% for lesions smaller than 2 cm.

Discussion

Cirrhosis is defined as a chronic liver disease characterized by fibrosis and regeneration. Curative treatment for this patient group is liver transplantation. In patients with cirrhosis who undergo transplantation, the prevalence of HCC not detected during the preoperative period can reach up to 8%[10]. This high rate is observed in advanced cirrhosis patients requiring transplantation, and it is not considered applicable to all cirrhosis patients. In fact, the true prevalence of HCC in cirrhosis patients is unpredictable due to difficulties in imaging small HCC lesions.

Although there are different alternatives in radiological evaluation, some studies have reported that contrast-enhanced CT is the most valuable method for detecting malignancy in cirrhotic patients[11,12]. Since the liver morphology changes in cirrhosis, the normal radiological appearance of the liver also changes significantly on CT. On the other hand, non-tumoral small arteriovenous shunts may create a false nodule appearance, making evaluation challenging[13]. While arterial phase images in CT are more useful for detecting hypervascular tumors like HCC, portal venous and delayed phases are more useful for evaluating less vascular tumors with good differentiation or early HCC.

In previous studies, the sensitivity of CT ranged widely from 50% to 99% at the patient level, while specificity ranged from 75% to 96%. Some studies suggested that the reported low sensitivity values may be due to early arterial phase imaging and thicker (5-10 mm) sections. Francis et al.[14] indicated that the best lesion distinction was achieved in delayed arterial phase images (at 30-35 sec delay).

Lopez Hänninen et al.[15] reported the sensitivity of biphasic helical CT in diagnosing HCC as 76% in patients who underwent liver transplantation. In their study, sensitivity values for HCC nodules based on lesion size were 20% for lesions of 0.5-1.0 cm, 82% for 1.1-2.0 cm, 86% for 2.1-3.0

cm, and 100% for lesions larger than 3 cm. Lim et al.[16] reported the patient-based sensitivity of helical CT as 80% and the lesion-based sensitivity as 71%. In their study, 60% of HCCs smaller than 2 cm and 82% of lesions larger than 2 cm were detected. Noguchi et al.[17,18] reported the overall sensitivity of helical CT in diagnosing HCC as 66%, with 98% for lesions larger than 2 cm and 50.3% for lesions smaller than 2 cm[19]. In another series, Zacherl et al.[20] reported a sensitivity of 75% and a positive predictive value of 72% for pre-transplantation patients who underwent biphasic helical CT. In this series, a high false-positive rate (27.7%, 15/54) was found, but the authors did not specify the reason for this[19,20].

In our study, CT data was compared with pathological data, and evaluations were made at the patient and lesion levels by two observers. Looking at the patient-based data, the sensitivity of CT was found to be 88-82%, specificity 95-90%, positive predictive value 93-87%, and negative predictive value 90-85%. Studies on this subject in the literature have reported sensitivity values for lesion-based HCC detection ranging from 37% to 82% with helical CT. In studies using contrast-enhanced CT, lesion-based sensitivity has been reported between 64% and 89%[10,21-30].

Brancatelli et al.[31] and Valls et al.[9] reported false-positive rates of 8% and 12%, respectively. In our study, this rate was higher (27-28%). A possible explanation for this could be that the other two studies used single-detector helical CT, while we used contrast-enhanced CT. Indeed, Addley et al.[32] reported false-positive rates of 30-50% with contrast-enhanced CT. Nadarevic et al.[33] showed that 22.5% of people with HCC would be missed and 8.7% of people without HCC would have a positive diagnosis. Seo et al.[34] reported that overall diagnostic accuracy with imaging ranged from 81.5% to 83.3%.

Study Limitations

Limitations in the use of imaging modalities may be that in the setting of cirrhosis, fibrosis surrounding regenerative or dysplastic nodules may mimic the appearance of a "strengthening capsule" and may lead to misinterpretation of benign lesions as HCC.[35] The high spatial and temporal resolution of contrast-enhanced CT leads to the identification of more lesions, which in turn increases the false-positive rate. Although our study found sensitivity and specificity within the previously reported range, the specificity was lower than sensitivity due to false-positive lesions.

Addley et al.[32] conducted a study on the role of contrast-enhanced CT in the diagnosis of HCC, including 39 patients, and reported the sensitivity of contrast-enhanced CT to be 65-75% for all lesions and 48-57% for lesions smaller than 2 cm. In this study, as in our study, a diagnosis scale ranging from one to five was used. With evaluation based on confidence levels, as the confidence level increased towards five (i.e., lesions more likely to be HCC), the sensitivity in larger lesions was 26-70%, while it was 4-26% in lesions smaller than 2 cm.

Our study demonstrates that contrast-enhanced CT has an overall acceptable sensitivity for diagnosing HCC and can be used for imaging patients who will undergo transplantation during the preoperative period. Especially, although the sensitivity of CT is low in lesions smaller than 2 cm (50-64%), it is quite successful in lesions larger than 2 cm (100%). Contrast-enhanced CT achieves a general sensitivity of 78-84% and a positive predictive value of 73-71% for the imaging of HCC before liver transplantation. However, due to the high spatial and temporal resolution of contrast-enhanced CT, a high false-positive rate should be considered, and patients should not be unnecessarily removed from the transplantation list.

Conclusion

Our study demonstrates that contrast-enhanced CT has an overall acceptable sensitivity for diagnosing HCC and can be used for imaging patients who will undergo transplantation during the preoperative period. Especially in our study, although the sensitivity of CT is low in lesions smaller than 2 cm (50-64%), it is quite successful in lesions larger than 2 cm (100%). However, due to the high spatial and temporal resolution of contrast-enhanced CT, a high false-positive rate should be considered, and patients should not be unnecessarily removed from the transplantation list.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Local Ethics Committee (Dokuz Eylül University; date: 04.10.2012, number: 2012/32-05).

Informed Consent: Retrospective study.

Authorship Contributions

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

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Denosumab Discontinuation Rate in Patients Who Presented with Osteoporotic Vertebral Fracture During Pandemic

Pandemi Sırasında Osteoporotik Vertebral Kırıkla Başvuran Hastalarda Denosumab Bırakma Oranı

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Abstract

Objective: Social distancing mitigates transmission of Coronavirus disease-2019 but also can delay access to parenteral osteoporosis therapy. After discontinuation of denosumab therapy without concomitant biphosphanate use results with increased rate of multiple vertebral fractures within 2 to 10 months.

Methods: In this study, we wanted to evaluate whether restrictions during the pandemic resulted in an increased fracture rate due to denosumab discontination. For this, we compared the data between 2020-2021, when the restrictions were the most intense, and 2022-2023, when the restrictions were relaxed. Prospectively collected data of patients who applied to the neurosurgery clinic with osteoporotic vertebral fractures between 2020-2021 and 2022-2023 were retrospectively analyzed.

Results: A total of 49 patients were met the inclusion criteria, denosumab discontinuation was detected in five patients who presented with osteoporotic fractures during the period of intense restrictions, there was no patients with denosumab discontinuation during the period when the restrictions were relaxed. Discontinuation reasons was due to fear of access to hospital and mobility restriction in all patients. Mean time interval between treatment discontinuation and fracture occurrence was 12.6 months (10-15 months).

Conclusion: Patients should be warned about the durability of denosumab treatment, and if there is doubt about the durability, oral bisphosphonate therapy should be temporarily switched in pandemic.

Keywords: Pandemic, denosumab, vertebral fracture

Öz

Amaç: Sosyal mesafe, Koronavirüs hastalığı-2019'un bulaşmasını azaltır ancak aynı zamanda parenteral osteoporoz tedavisine erişimi geciktirebilir. Eş zamanlı bifosfanat kullanımı olmaksızın denosumab tedavisinin kesilmesi, iki ila on ay içinde çoklu vertebral kırık oranlarında artış ile sonuçlanır.

Yöntem: Bu çalışmada pandemi sırasındaki kısıtlamaların denosumab tedavisini kesilmesine bağlı olarak kırık oranında artışa yol açıp açmadığının değerlendirilmesi amaçlandı. Bunun için kısıtlamaların en yoğun olduğu 2020-2021 ile kısıtlamaların gevşetildiği 2022-2023 arasındaki veriler karşılaştırıldı. 2020-2021 ve 2022-2023 yılları arasında nöroşirürji kliniğine osteoporotik vertebra kırığı ile başvuran hastaların prospektif olarak toplanan verileri retrospektif olarak incelendi.

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Öz

Bulgular: Toplam 49 hasta dahil edilme kriterlerini karşıladı, kısıtlamaların yoğun olduğu dönemde osteoporotik kırıkla başvuran beş hastada gecikmiş denosumab enjeksiyonu saptandı, kısıtlamaların gevşetildiği dönemde denosumab tedavisinin kesildiği hasta yoktu. Tedaviyi bırakma nedenleri tüm hastalarda hastaneye erişim korkusu ve sokağa çıkma kısıtlılığıydı. Tedavinin kesilmesi ile kırık oluşumu arasındaki ortalama süre 12,6 ay (10-15 ay) idi.

Sonuç: Hastalar denosumab tedavisinin devamlılığı konusunda uyarılmalı ve devamlılık konusunda şüphe varsa pandemide oral bifosfonat tedavisine geçici olarak dönülmelidir.

Anahtar Kelimeler: Pandemi, denosumab, omurga kırığı

Introduction

Osteoporotic fracture is a public health issue affecting thirty percent of women and is associated with high morbidity and mortality rates[1]. Vertebral fracture-associated pain and limitation of function can cause decreased health-related quality of life in the elderly population[1].

Healthcare systems are overstretched during the pandemic, resulting in reduced hospital and doctor visits. In addition, social distancing mitigates transmission of Coronavirus disease-2019 (COVID-19) and can delay access to parenteral therapies. The management of osteoporosis is largely performed in outpatient settings. The prescribing and administration of anti-osteoporosis drugs may have been disrupted by the COVID-19 pandemic. A retrospective analysis using Google Analytics data found that access to the online FRAX® fracture risk assessment tool was almost 60% lower in April than in February 2020, which may indicate the neglect of osteoporosis assessment during the pandemic[2]. In another study, as concrete proof of this, it was shown that only 29% of the patients could perform follow-up bone mineral density assessment with dual energy X-ray absorptiometry (DXA) during the pandemic period, and only 60% of the patients could continue their parenteral anti-osteoporosis treatment[3].

Agents used for treating osteoporosis can simply be divided into two groups: Anabolic and antiresorptive. Bisphosphonates and denosumab are currently used as antiresorptive agents. After discontinuation of bisphosphonates, the antiresorptive effect lasts for 1-5 years; however, discontinuation of denosumab therapy without concomitant bisphosphonate use results in accelerated bone loss and an increased rate of multiple vertebral fractures within 2 to 10 months[4-6]. Therefore, patients must be informed that denosumab therapy should not be discontinued without concomitant bisphosphonate use. Restricting access to parenterally administered denosumab during the pandemic period may increase the risk of fracture due to drug discontinuation[7].

In this study, we aimed to evaluate whether restrictions during the pandemic resulted in an increased fracture rate due to denosumab discontinuation. For this, we compared the data between 2020 and 2021, when the restrictions were the most intense, and 2022 and 2023, when the restrictions were relaxed.

Materials and Methods

Patients with an osteoporotic vertebral fracture who were admitted to the Neurosurgery Clinic between 2020 and 2021 and 2022-2023 in am and University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital were retrospectively analyzed. Patients were grouped as admitting to hospital between 2020 and 2021, when the restrictions were the most intense, and 2022 and 2023, when the restrictions were relaxed. The two groups compared their demographic data, clinical and laboratory findings, and osteoporotic treatment discontinuation.

Study Group

Postmenopausal women aged 50 years or older were included in the study. The other inclusion criteria were a conclusive clinical and radiological diagnosis of osteoporotic fracture with recent onset of back pain (less than one month).

Patients who were immobile and diagnosed with chronic inflammatory or oncologic diseases or with a history of neuroendocrine disorders (thyroid, parathyroid disorders, anticonvulsant- thiazolidinedione usage, etc.), chronic renal or liver diseases, and excessive use of systemic corticosteroids and alcohol were excluded. Male patients were also excluded to avoid bias because secondary predisposing factors for osteoporosis can be identified in 40-60% of men with osteoporotic fractures[8].

Definition of Osteoporotic Vertebral Fracture

Clinic definition: Occurring a fall from a standing height or less without significant trauma[9].

Radiological definition: Alteration appears in the shape and size of the vertebral body, associated or not with vertebral height loss, resulting as a wedge, end-plate (mono-or biconcave), or collapse vertebral deformity[9].

Identification Methods for Vertebral Fractures

All patients in the study group had DXA images. In addition, all patients underwent thoracic or lumbar magnetic resonance or computed tomography imaging at hospitalization.

Statistical Analysis

The patients' files were reviewed retrospectively, and the demographic data, imaging and laboratory results, concomitant disease, and drug use were recorded. Analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL). Normally distributed continuous variables are presented as mean ± standard deviation and compared using Student's t-test. A p-value <0.05 was considered statistically significant for all statistical evaluations.

Results

Between 2020 and 2021, a total of 41 patients presented with osteoporotic vertebral fractures, and 24 patients met the inclusion criteria. The mean age was 73.3±6.7 years, mean 25-hydroxy vitamin D level was 18.3±8.1 ng/mL, and mean femoral neck BMD was 0.663±22.42 g/cm^2. Regarding concomitant diseases, 16 (66.6%) patients had hypertension, two had type 2 (8.3%) diabetes, and four (16.6%) had anxiety disorder. Four patients (16.6%) had fractures in more than one vertebra. The T12 vertebra was the most common fracture site [six (25%) patients]. Vertebroplasty was performed in 10 patients and kyphoplasty in five patients. Other patients were followed up conservatively.

Between 2022 and 2023, a total of 43 patients presented with osteoporotic vertebral fractures, and 25 patients met the inclusion criteria. The mean age was 72.1±6.2 years, mean 25-hydroxy vitamin D level was 19.1±7.1 ng/mL, and mean femoral neck BMD was 0.658±18.33 g/cm^2. There were 14 (56%) patients with hypertension, four (16%) with type 2 diabetes, six (24%) with anxiety disorder, and two (8%) with coronary arterial disease. Six patients (24%) had fractures in more than one vertebra. The L1 vertebra was the most common fracture site [eight (32%) patients]. Vertebroplasty was performed in 12 patients and kyphoplasty in six patients. Other patients were followed up conservatively. There was no previous vertebral fracture history in either group. Comparison of the continuous variables summarized in Table 1.

When evaluated regarding medication use for osteoporosis, none of the patients in the 2022-2023 group had antiresorptive or anabolic agent use before admission. In the 2020-2021 group, two patients were using intravenous ibandronate, and five were using denosumab before presentation, and all patients had stopped using denosumab and ibandronate after the pandemic because of fear of access to hospital and mobility restriction. None of the patients in the denosumab discontinuation group were informed before treatment that denosumab therapy should not be discontinued without concomitant bisphosphonate use. The duration of antiresorptive therapy and time elapsed between the occurrence of vertebral fracture and antiresorptive therapy discontinuation are reported in Table 2.

Clinical and laboratory findings of the treatment discontinuation group are summarized in Table 3.

None of the patients in the study groups had a previous history of vertebral fracture or oral bisphosphonate and teriparatide usage. In addition, no other antiresorptive therapy or teriparatide was used before the current therapy in the discontinuation group.

Table 1. Comparison of age, 25-hydroxy vitamin D level, and femur BMD score between the groups

Variables	2020-2021	2022-2023	p-value
Age (years)	73.3±6.7	72.1±6.2	0.545
25-hydroxy vitamin D level (ng/mL)	18.3±8.1	19.1±7.1	0.599
Mean femoral neck BMD (g/cm^2)	0.663±22.42	0.658±18.33	0.433
Number of multiple fractures (n)	4	6	0.634
The most common fractured vertebra	T12	L1	-
Number of vertebraplas	10	12	0.678
Number of kyphoplasty procedures	5	6	0.712

Table 2. Length of antiresorptive therapy and time elapsed between vertebral fracture and antiresorptive therapy discontinuation

Patient	Age	Drug	Length of therapy (months)	Time interval between treatment discontinuation and fracture occurrence (months)
1	65	Ibandronate	12	14
2	74	Ibandronate	15	15
3	83	Denosumab	18	11
4	72	Denosumab	24	13
5	77	Denosumab	12	10
6	74	Denosumab	12	15
7	76	Denosumab	30	14

Table 3. Clinical and laboratory findings of the treatment discontinuation group

Age (years)	74.4±5.4
Mean femoral neck BMD (g/cm²)	0.621±113
25-hydroxy vitamin D level (ng/mL)	19.14±5.42
Concomitant diseases (n)	
Hypertension	1
Type 2 diabetes mellitus	2
Having a fracture in more than one vertebra (n)	0
Fracture manangement (n)	
Vertebroplasty	2
Conservatively	3
Average duration of denosumab use (months)	20±8
Average duration of ibandronate use (months)	24±11

Discussion

In our study, we detected denosumab discontinuation in five patients who presented with osteoporotic fractures during intense restrictions; there were no patients with denosumab discontinuation during the period when the restrictions were relaxed. Delayed denosumab dosing due to patient non-compliance is common in clinical practice, especially as the treatment extends beyond the first 1 to 2 years[10,11]. The average duration of denosumab use was 20±8 months in our study, but discontinuation was due to fear of access to hospital and mobility restriction in all patients, which are the main problems arising with the pandemic. It has been reported that there may be problems in accessing injectable osteoporosis treatments during the pandemic; therefore, the American Society for Bone and Mineral Research recommends the temporary transition to an oral bisphosphonate for patients at risk for delayed denosumab injection[7,12].

The increased risk of bone loss and fracture after denosumab discontinuation without concomitant bisphosphonate use is a well-known complication. Lyu et al.[11] found that delayed denosumab administration by more than 16 weeks is associated with an increased risk of vertebral fracture. In another study examining the effect of delayed denosumab injection on BMD during the pandemic, BMD loss was evident nine months after the last injection[13]. Minisola et al.[14] reported 12 patients admitted with osteoporotic vertebral fracture due to delayed denosumab injection during the pandemic. There were only eight cases the seven years before the pandemic[14]. In our study, the mean time interval between treatment discontinuation and fracture occurrence was 12.6 months (10-15 months).

Beneficial effects on bone mass persist 1-2 years after ibandronate discontinuation[15]. In our study, there were two patients with ibandronate discontinuation, and the time interval between treatment discontinuation and fracture occurrence was 14.5 months. Therefore, it may be unrealistic to attribute vertebral fracture development to ibandronate discontinuation in these patients.

We restricted inclusion criteria in order not to create bias, exclude secondary osteoporosis and etiologies other than discontinuation of denosumab, and balance continuous variables between groups. Although it was clearly seen in our study that the fracture rate due to denosumab discontinuation increased during intense restrictions, it is necessary to conduct a cohort study with a wider time interval to reach a definite conclusion.

Study Limitations

The major limitations of this study are its limited time period, its conduct only in osteoporotic patients presenting with fractures, and its retrospective design.

Conclusion

Patient compliance and treatment durability should be considered when choosing drugs during the pandemic. Patients should be warned about the durability of denosumab treatment, and if there is doubt, they should be temporarily switched to oral bisphosphonate therapy.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (no: 2022.04.120, KAEK/2022.04.120).

Informed Consent: Retrospective study.

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Rational Laboratory Practice in the "Savings and Revenue Enhancement Program" Perspective: Calculated LDL

"Tasarruf ve Gelir Artırıcı Program" Perspektifinde Akılcı Laboratuvar Uygulaması: Hesaplanmış LDL Kullanımı

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Abstract

Objective: Rational laboratory practices can provide significant savings in hospital expenses. In recent years, the use of Friedewald formula has been accepted as a cost-effective calculation method in the measurement of lipid parameters of a patient in the risk group screened for hypercholesterolemia. In patients with triglyceride (TG) ≤400 mg/dL, it can be said that measurements using the direct-low density lipoprotein (LDL) kit instead of this formula bring unnecessary testing costs to laboratories.

Methods: In our study, the test orders of registered outpatients between 01.01.2022-31.12.2022 were examined and 112,649 patient results were obtained with measurement of total cholesterol (TC), high density lipoprotein (HDL), TG and direct-LDL or at least one of them. After exclusion of patient results for TC, TG, HDL and direct-LDL tests not ordered together, results with TC >400 mg/dL and results with non-numeric test results, 720 patient results were included in the study. The ratio of the unnecessary test order cost to the SUT package reimbursement fee and the package fee excluding the examination fee was calculated.

Results: Of the 720 patient results included in the study, the highest number of unnecessary direct-LDL orders belonged to the internal medicine outpatient clinic with 261 (36.25%), while the lowest number of orders belonged to the dermatology, pulmonology, hematology and psychiatry outpatient clinics with one order each (0.14%). Since the tender price of the direct-LDL test was fixed at 4.75 TL per unit test, the unnecessary test cost ratio is proportional to the number of orders is 36.25% and 0.14%, respectively.

Conclusion: With this study, it can be said that it is more cost-effective in terms of institutions and national economy to use computational LDL test instead of direct-LDL test ordering when requesting lipid profile in individuals with risk factors and who are met for the first time, and then to request targeted test ordering.

Keywords: Low-density lipoprotein, cost-effectiveness analysis, clinical laboratory techniques

Öz

Amaç: Sağlık harcamalarının verimli kullanılması, devlet politikası olarak hedeflenmiştir. Akılcı laboratuvar uygulamaları ile hastane giderlerinde önemli kazanç sağlanabilir. Hiperkolesterolemi taraması yapılan risk grubundaki bir hastanın lipit parametreleri ölçümünde maliyet etkin bir hesaplama yöntemi olarak son yıllarda Friedewald formülünün kullanımı kabul görmüştür. Trigliserit (TG) ≤400 mg/dL olan hastalarda bu formül yerine direkt-düşük yoğunluklu lipoprotein (LDL) kiti kullanılarak yapılan ölçümlerin laboratuvarlara gereksiz test maliyeti getirdiği söylenebilir.

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Öz

Yöntem: Çalışmamızda 01.01.2022-31.12.2022 tarihleri arasında kayıtlı poliklinik hastalarının test istemleri incelenmiş olup, total kolesterol (TK), HDL, TG ve direkt LDL veya bunlardan en az birisinin ölçümü olan 112.649 hasta sonucu elde edildi. TK, TG, HDL ve direkt LDL testleri beraber istenmeyen hasta sonuçları; TK değeri >400 mg/dL olan sonuçlar ve test sonuçları numerik olmayan sonuçlar çalışma dışı bırakıldığında 720 hasta sonucu çalışmaya dahil edildi. Gereksiz test istem maliyetinin, SUT paket (poliklinik) geri ödeme bedeli ve muayene ücreti dışı paket ücretine oranı hesaplandı.

Bulgular: Çalışmaya dahil edilen 720 hasta sonucundan en çok gereksiz direkt LDL istemi, 261 (%36,25) adet ile dahiliye polikliniğine aitken en az istem birer adet (%0,14) ile dermatoloji, göğüs hastalıkları, hematoloji ve psikiyatri polikliniklerine aittir. Direkt LDL testinin birim test başına ihale bedeli 4,75 TL ve sabit olduğundan gereksiz test maliyet oranı meblağ olarak istem sayısıyla orantılı ve sırasıyla %36,25 ve %0,14'tür.

Sonuç: Bu çalışma ile risk faktörü bulunan ve ilk kez karşılanan bireylerde lipid profili istenirken direkt LDL test istemi yerine hesaplamalı LDL testinin kullanılmasının, daha sonra ise hedefe yönelik test isteminin yapılmasının kurumlar ve ülke ekonomisi açısından daha maliyet etkin olduğu söylenebilir.

Anahtar Kelimeler: Düşük dansiteli lipoprotein, maliyet etkinlik, klinik laboratuvar teknikleri

Introduction

The medium-term program was published in Official Gazette no. 30541 dated September 20, 2018, with Presidential Decree No. 108. In this context, it has been decided to establish the Public Finance Transformation and Change Office within the Ministry of Treasury and Finance to use public resources efficiently, reduce costs and expenditures, and increase the quality of revenues. The savings and revenue enhancement program (SREP) to be prepared and monitored by this office aims to make permanent improvements in public finance.

The SREP, which is also implemented by the Ministry of Health, is an action plan that seeks to prevent unnecessary expenditures of central and provincial institutions by taking necessary measures and, where possible, increasing their revenues.

Medical biochemistry laboratories are units that positively affect the revenues of hospitals, even if they do not have direct income. In this sense, significant savings can be made in laboratory test costs by organizing the tests within the scope of rational laboratory practices in accordance with current medical science.

In patients at cardiovascular risk, clinical status is associated with low-density lipoprotein (LDL) levels. Therefore, LDL levels are one of the most important target parameters in cholesterol-lowering treatment regimens worldwide. In biochemistry laboratory practice, LDL is usually a member of a group of tests called the "lipid profile". Other tests in this panel are total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL).

Medical laboratories are units that adopt the principle of cost-effective operation and fast and accurate delivery of test results. Scientists have begun to develop new laboratory tests and methods for many reasons, especially increasing health expenditures. Since it was developed in 1972 by Friedewald, the LDL calculation equation [LDL=TC-(HDL+TG/5)] has been widely used in clinical practice for several decades[1]. Recently, many new formulas have entered the literature that have been shown to calculate more successfully than the Friedewald formula, especially at low LDL levels. Although the calculation methods developed by Martin-Hopkins and Sampson et al.[2] have been used in many centers, the most widely used formula is still the Friedewald formula[3]. Therefore, it can be said that measurements using a direct-LDL kit in patients with TG ≤400 mg/dL in hospitals incur unnecessary testing costs to laboratories.

In today's health policies, cost-effectiveness is another consideration for laboratories trying to respond appropriately to expanded test panels and increasing patient populations. Therefore, reflex testing practices and test panels programed together with clinicians may be a good first step to have a positive impact on health expenditures[4]. "Reflex testing" refers to the ordering and running of a new test based on the result of the first test if the criteria are provided[5]. A reflex test can be created according to the criteria set at the beginning in accordance with the needs of the hospital and laboratory. With reflex testing, unnecessary test ordering may be avoided because not all tests are ordered at the first time but only when needed according to the algorithms. Therefore, reflex testing has become an important tool that provides timely, cost-effective, and quality care to patients. When the literature is reviewed, many publications can be noticed regarding the positive effect of reflex testing in laboratories[6,7].

Thus, we aimed to reveal the cost to the laboratory of not performing the direct LDL test as a "reflex test" in a training and research hospital with a capacity of 910 beds.

Materials and Methods

Data Collection and Formation of Groups

In our study, we obtained the results of 112,649 outpatients registered in the Hospital Information Management System (HIMS) of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital between 01.01.2022 and 31.12.2022, who had TC, HDL, TG, and direct LDL test orders (at least one of which was available). According to the Social Security Institution reimbursement regulation, the results of patients admitted to emergency, oncology and hematology outpatient clinics whose reimbursement conditions differed from those of other outpatient clinics; results of patients who did not want TC, TG, HDL and direct LDL tests together; results with TC value >400 mg/dL and non-numeric test results were excluded from the study. After the exclusion criteria, 720 patient results, including duplicate test results, were included in the study.

Statistical Analysis

This study was planned as a retrospective descriptive study. The ratio of unnecessary test ordering cost to the SUT (health practice regulations in Turkey) package (outpatient clinic) reimbursement fee and outpatient package fee was calculated. Calculations and statistics were performed using Microsoft Excel© 2019 (USA) program.

Ethics Committee Approval

Our study was initiated with the permission of the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (ethics committee permission date and number: 06/06/2023-2023/05-17).

Cost Analysis of Unnecessary Direct LDL Orders

The LDL test results were calculated using the Friedewald formula from test results with TG levels ≤400 mg/dL. Therefore, the number of patients included in the study and the distribution of the ordering clinics was calculated. The additional cost of this test was calculated by determining the number of unnecessary tests ordered, the tender test price valid on the relevant dates, and the social security institution (SSI) reimbursement amount (SUT Annex-2b). The percentile of the amount paid for direct LDL and the other three parameters in outpatients was calculated according to the package fee. In addition, the percentage expression of the changed cost if computed LDL was used instead of the unnecessary direct LDL test was calculated.

Measurement Principles for Related Tests

All lipid profile parameters were measured on Beckman Coulter AU 5800 (Brea, California, USA) automated chemistry analyzers in the biochemistry laboratory of the hospital. TC was calculated using the enzymatic cholesterol esterase/oxidase method, and TG was calculated using the enzymatic glycerol phosphate oxidase method. HDL was measured by direct homogeneous assays without precipitation, and LDL was measured by a direct homogeneous assay using a selective preservative to separate LDL from chylomicrons, HDL, and VLDL and then calculated by the cholesterol esterase/oxidase method. All assays were performed using Beckman Coulter AU reagents and calibrators and Bio-Rad© (California, USA) internal quality control material.

Results

In the "Biochemistry Service Procurement for Results" tender dated and numbered 2021/202539 for our hospital, the HDL test purchase cost was determined as 4.704 TL, the TG test purchase cost as 3.535 TL, the TC test purchase cost as 3.227 TL, and the direct LDL test purchase cost as 4.75 TL. The SUT reimbursement costs of these tests were 3.98, 2.99, 3.0, and 6.23 TL, respectively. Outpatient clinic package fees were obtained from the SUT Annex-2A list. When the results of 720 patients included in the study were analyzed, the highest number of unnecessary direct LDL orders belonged to internal medicine outpatient clinic with 261 (36.25%), while the lowest number of orders belonged to dermatology, pulmonology, hematology, and psychiatry outpatient clinics with one order each (0.14%). Since the tender price per unit of direct LDL test was 4.75 TL and fixed, the unnecessary test cost ratio between 2022 and 2023 was proportional to the number of claims in terms of amount and was 36.25% and 0.14%, respectively.

Dermatology and anesthesia had lower SSI reimbursement outpatient clinic package fees than other outpatient clinics and had the highest unnecessary order cost/polyclinic package fee ratio (5.16%) as their examination fees were fixed at 31.75 TL for each outpatient clinic. Therefore, 7.88% of the amounts allocated for examinations in these two branches were allocated to unnecessary test orders. Among the tests that include lipid profile, direct LDL accounts for 41% of the cost of this test. Among outpatient clinics that ordered unnecessary LDL, anesthesia and dermatology outpatient clinics had the lowest package fee (TL 92.0), while cardiology outpatient clinic had the highest package fee with TL 146.00 (Table 1). Package fees defined for radiology and nuclear

Table 1. Distribution of tests in lipid panel according to polyclinics and cost analysis

Polyclinic	Number of LDL orders	% Distribution according to polyclinics	Lipid profile total tender price (Tl)	Direct LDL total cost (Tl)	Polyclinic SSI package fee (Tl)	Direct LDL cost/ package ratio (%)	SSI examination fee (Tl)	Lipid panel cost/ examination budget ratio (%)	Direct LDL cost/ examination budget ratio (%)
Internal medicine	**261**	**36.25**	11.51	**1239.75**	123.00	3.86	31.75	12.61	5.21
Endocrinology	79	10.97	11.51	375.25	122.00	3.89	31.75	12.75	5.26
Pediatrics	71	9.86	11.51	337.25	101.00	4.70	31.75	16.62	6.86
Gastroenterology	57	7.92	11.51	270.75	122.00	3.89	31.75	12.75	5.26
General surgery	54	7.50	11.51	256.50	122.00	3.89	31.75	12.75	5.26
Cardiology	53	7.36	11.51	251.75	146.00	3.25	31.75	10.07	4.16
Obstetric	44	6.11	11.51	209.00	132.00	3.60	31.75	11.48	4.74
Family medicine	31	4.31	11.51	147.25	99.00	4.80	31.75	17.12	7.06
Radiology	14	1.94	11.51	66.50	99.00	4.80	0.00	11.63	4.80
Eye diseases	7	0.97	11.51	33.25	96.00	4.95	31.75	17.91	7.39
Neurology	6	0.83	11.51	28.50	112.00	4.24	31.75	14.34	5.92
Urology	6	0.83	11.51	28.50	122.00	3.89	31.75	12.75	5.26
Infectious disease	6	0.83	11.51	28.50	122.00	3.89	31.75	12.75	5.26
Nephrology	6	0.83	11.51	28.50	123.00	3.86	31.75	12.61	5.21
Neurosurgery	5	0.69	11.51	23.75	122.00	3.89	31.75	12.75	5.26
Otolaryngology	5	0.69	11.51	23.75	96.00	4.95	31.75	17.91	7.39
Orthopedics	4	0.56	11.51	19.00	109.00	4.36	31.75	14.90	6.15
Anesthesiology	3	0.42	11.51	14.25	**92.00**	**5.16**	**31.75**	**19.10**	**7.88**
Genetics	2	0.28	11.51	9.50	99.00	4.80	31.75	17.12	7.06
Nuclear medicine	2	0.28	11.51	9.50	99.00	4.80	0.00	11.63	4.80
Dermatology	1	0.14	11.51	4.75	**92.00**	**5.16**	**31.75**	**19.10**	**7.88**
Pulmonology	1	0.14	11.51	4.75	109.00	4.36	31.75	14.90	6.15
Hematology	1	0.14	11.51	4.75	123.00	3.86	31.75	12.61	5.21
Psychiatry	1	0.14	11.51	4.75	109.00	4.36	31.75	14.90	6.15
Mean					**112.13**	**4.30**	**29.10**	**14.30**	**5.90**
Total	**720**	**100**		**3420**					

LDL: Low density lipoprotein, SSI: Social security institution

medicine units were reimbursed only if interventional procedures were performed.

Discussion

When our study results were analyzed, it was observed that the use of direct LDL measurements together with lipid parameters as reflex tests unnecessarily increased laboratory costs. Internal medicine specialists ranked first and endocrinology specialists ranked second with the highest number of unnecessary direct LDL orders. This ranking is not surprising when considering the patient profiles of the clinics and SSI reimbursement.

Two of the most important steps in the prevention of coronary heart disease are lifestyle modification and identification of risk factors. The most important risk factors are hypertension and hypercholesterolemia[8]. Cardiology, cardiovascular surgery, and endocrine and metabolism specialists are mainly involved in the detection and treatment of these risks. In addition to these disciplines, it should not be forgotten that hypercholesterolemia treatment can be arranged by

all specialist physicians in terms of preventive medicine. In parallel with this situation, the reimbursement conditions of the drugs to be used for treating hypercholesterolemia are periodically updated in the SUT. The latest drug reimbursement conditions are as follows:

According to the SUT dated 08/01/2019, all specialist physicians can issue a low-dose statin group (<40 mg for atorvastatin, <20 mg for rosuvastatin) drug report.

1. According to the SUT dated 24/06/2020, atorvastatin ≥40 mg and rosuvastatin ≥20 mg doses can be reported by cardiology, cardiovascular surgery, endocrinology, geriatrics, and neurology specialists in adults and pediatric metabolism, pediatric endocrinology, and pediatric cardiology specialists in children.

2. According to the SUT dated 18/05/2018, drugs with active ingredients fenofibrate and gemfibrozil can be reported by cardiology, cardiovascular surgery, endocrinology, internal medicine, and neurology physicians.

It is quite natural for physicians in these specialties to order lipid panel tests in the health centers where they work and thus to make erroneous orders. Similarly, in our study, the highest number of erroneous orders were made by internal medicine physicians. Endocrinology specialists ranked second. It can be said that patients cannot be examined directly by subspecialty physicians because of the health policies in our country; therefore, the data in our study are compatible with the results of the current health policies. Another factor contributing to the relatively lower number of erroneous orders by subspecialists specialized in treatment might be that patients whose lipid profile had been ordered by internal medicine were then referred to subspecialists, and these physicians had focused on the treatment of patients with elevated lipid profile tests (frequently LDL and TG) that were already estimated.

Of the 112,649 patient results obtained at the beginning of the study, only 720 patient results remained after the exclusion criteria. There may be several reasons for this situation. Because patients with hypercholesterolemia are frequently followed up by specialist family physicians at family health centers or secondary health care institutions, patients admitted to our hospital for treatment are mostly complicated cases (patients with acute coronary syndrome on the background of hypercholesterolemia, etc.). Because lipid profiles are often included in the periodic controls of these patients performed in external centers, only the elevated lipid parameter may have been requested. In addition, because our hospital is a hospital with A1 group training and research status, it is expected that the relevant clinics apply rational test ordering procedures in their test requests because they are training clinics and closely follow the current treatment guidelines. The fact that the number of test orders per patient was 4.01 tests between 2022 and 2023 in our hospital could be considered as an indicator of the success of this practice.

Unnecessary test requests are one of the most important reasons for increasing laboratory and therefore institutional resources to be used more than necessary[9]. These unnecessary requests are usually due to the physician's concern that the diagnosis may be overlooked or the desire to present the diagnosis/condition in uncertain situations[10]. In particular, training clinics that order LDL and organize the treatment of hypercholesterolemia should focus more on rational test ordering, which may provide significant savings in hospital costs. In emergency services (yellow and red areas) and oncology services, which were not included in the study, tests are charged outside the package when appropriate conditions are provided. While the cost per direct LDL test is 4.75 TL, the SUT reimbursement is 6.23 TL. Although the return to the hospital per test is +1.48 TL, it costs the social security institution -6.23 TL/test in real terms.

In addition, the use of machine learning algorithms from artificial intelligence technologies is increasing. These algorithms are particularly used to help predict the result of a target laboratory test using other laboratory tests. There are studies that have achieved successful results in predicting the LDL test, which is the subject of our article[11,12]. In the future, the costs of producing more accurate results can be further minimized by calculating the results from other parameters using classical methods or artificial intelligence instead of analyzing the tests.

Study Limitations

The limitations of this study include the inability to compare the reduction in the number of unnecessary test requests and costs with the reflex test application established according to certain rules compared with the previous situation.

Conclusion

As a result of this study, it can be said that the use of computational LDL test (Friedewald, Martin-Hopkins, Sampson, etc. formulas) instead of direct LDL test ordering

when requesting lipid profile in individuals with risk factors and who are provided for the first time, and then targeted test ordering (TG for hypertriglyceridemic patients and/or direct LDL for hypercholesterolemic patients) is more cost-effective in terms of institutions and national economy.

Ethics

Ethics Committee Approval: Our study was initiated with the permission of the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (ethics committee permission date and number: 06/06/2023-2023/05-17).

Informed Consent: No specific patient or patient results were used. Only test order numbers were received from clinics.

Authorship Contributions

Concept: F.D., Design: F.D., M.Z.K., Data Collection or Processing: F.D., M.A., Analysis or Interpretation: F.D., M.A., M.Z.K., Literature Search: F.D., Writing: F.D.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Measurement Uncertainty of HbA1c and Glucose Parameters, Which Are Diabetes Mellitus Diagnostic Tests

Diabetes Mellitus Tanı Testleri Olan HbA1c ve Glukoz Parametrelerinin Ölçüm Belirsizliği

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Abstract

Objective: In this study, it was aimed to calculate the measurement uncertainties of HbA1c and glucose parameters, which have important roles in the diagnosis and treatment of diabetes, and to evaluate the possible effects of these uncertainty values on clinical decision limits.

Methods: The measurement uncertainties of HbA1c and glucose tests were calculated according to ISO/TS 20914 guidelines. In 2022, the results of patients in whom HbA1c and glucose were ordered simultaneously were retrospectively analysed and the results were evaluated according to measurement uncertainty.

Results: The calculated measurement uncertainty values of HbA1c and glucose tests were 2.41% and 7.92% for level 1 and 1.37% and 7.68% for level 2, respectively. When the HbA1c results of the patients were evaluated according to the measurement uncertainty calculated for level 1 and level 2, 2493 (8.1%) and 1845 (5.9%) were in the grey zone according to negative uncertainty and 2816 (9.1%) and 2120 (6.9%) were in the grey zone according to positive uncertainty, respectively. When glucose results were evaluated according to negative and positive uncertainty at both levels, 3959 (12.8%) and 5934 (19.2%) patients were in the grey zone, respectively.

Conclusion: In our laboratory, uncertainty values calculated for the HbA1c parameter were below the TEa% values determined by all three international organizations. Although the uncertainty of the glucose test was below the CLIA and rilibak TEa% values, it was found to be higher than the BV TEa% value. It should be kept in mind that measurement uncertainty in values at medical decision levels may affect the diagnosis and treatment of DM.

Keywords: Diabetes, glucose, HbA1c, measurement uncertainty

Öz

Amaç: Bu çalışmada diyabetin tanı ve tedavisinde önemli yeri olan HbA1c ve glukoz parametrelerinin ölçüm belirsizliklerinin hesaplanması ve bu belirsizlik değerlerinin klinik karar limitlerine olası etkilerinin değerlendirilmesi amaçlanmıştır.

Yöntem: HbA1c ve glikoz testlerinin ölçüm belirsizlikleri ISO/TS 20914 kılavuzuna göre hesaplandı. 2022 yılında eş zamanlı olarak HbA1c ve glukoz istenen hastaların sonuçları retrospektif olarak incelendi ve sonuçlar ölçüm belirsizliğine göre değerlendirildi.

Bulgular: HbA1c ve glukoz testlerinin hesaplanan ölçüm belirsizliği değerleri seviye 1 için sırasıyla %2,41 ve %7,92, seviye 2 için ise %1,37 ve %7,68 olarak hesaplandı. Hastaların HbA1c sonuçları seviye 1 ve seviye 2 için hesaplanan negatif belirsizliğe göre değerlendirildiğinde sırasıyla 2493'ü (%8,1) ve 1845'i (%5,9), pozitif belirsizliğe göre ise 2816'sı (%9,1) ve 2120'si (%6,9) gri bölgedeydi. Glukoz sonuçları her iki seviyede negatif ve pozitif belirsizliğe göre değerlendirildiğinde sırasıyla 3959 (%12,8) ve 5934 (%19,2) hasta gri bölgede bulundu.

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Öz

Sonuç: Laboratuvarımızda HbA1c parametresi için hesaplanan belirsizlik değerleri her üç uluslararası kuruluş tarafından belirlenen TEa% değerlerinin altında kalmıştır. Glukoz testinin belirsizliği ise CLIA ve rilibak TEa% değerlerinin altında olmasına rağmen BV TEa% değerinden yüksek bulunmuştur. Tıbbi karar düzeylerindeki değerlerde ölçüm belirsizliğinin DM'nin tanı ve tedavisini etkileyebileceği unutulmamalıdır.

Anahtar Kelimeler: Diyabet, glukoz, HbA1c, ölçüm belirsizliği

Introduction

Diabetes mellitus (DM), a disease characterized by high blood glucose levels, affects important organs such as the heart, blood vessels, eyes, kidneys, and nerves, causing complications such as kidney failure, blindness, lower extremity amputation, and cardiovascular diseases, and seriously affects the quality of life[1,2]. It is estimated that approximately 463 million individuals in the adult population aged 20-79 years worldwide in 2019 have diabetes, and this number is predicted to increase to 700 million in 2045. In this case, it is estimated that the proportion of diabetic patients will increase from 9.3% to 10.9%[3]. It has been suggested that diabetes and its complications cause 4.2 million deaths worldwide between the ages of 20 and 79, and approximately half of these (46.2%) are observed in people under 60 years of age[4].

According to the American Diabetes Association (ADA); each of the criteria for fasting plasma glucose ≥126 mg/dL, plasma glucose at 2nd hour of 75 g oral glucose tolerance test (OGTT) ≥200 mg/dL, HbA1c ≥6.5% [National Glycated Hemoglobin Standardization Program (NGSP) certified method] or random plasma glucose ≥200 mg/dL (In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis) alone is sufficient for the diagnosis of DM[5]. Medical laboratories are very important in the diagnosis of diseases and the follow-up of treatment. Because the precise accuracy of the test result may be limited, the concept of measurement uncertainty plays an extremely critical role in the evaluation process of test results. Measurement uncertainty is a statistical parameter that shows the quality of the analytical result and expresses the limits within which the measured value may vary. In this way, it provides the opportunity to evaluate the reliability of the measurement result. Knowing the level of uncertainty, especially in measurements at the border of medical decisions, is of great importance in the correct interpretation of test results and in providing valuable contributions to the treatment processes of patients[6].

In our study, it was aimed to calculate the measurement uncertainties of HbA1c and glucose parameters, which have important roles in the diagnosis and treatment of diabetes, and to evaluate the possible effects of these uncertainty values on clinical decision limits.

Materials and Methods

For our retrospective study, approval was obtained from the ethics committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital with the decision dated June 6, 2023, and numbered 2023/05-04. To calculate the measurement uncertainty, 6-months (July-December 2022) internal quality control (IQC) and 12-months (January-December 2022) external quality control (EQC) data of HbA1c and glucose tests were used.

EQC data of the tests were obtained from the External Quality Assurance Services (EQAS) (Bio-Rad Laboratories Inc., Irvine, CA, USA) quality control program. HbA1c levels were analyzed by ion exchange high-performance liquid chromatography (HPLC) method on the BIO-RAD Variant II instrument (Bio-Rad Laboratories, Marnes-la-Coquette, France), which was certified by the NGSP. The glucose test was measured by the hexokinase method using the AU5800 autoanalyzer device (Beckman Coulter Inc., CA, USA). The measurement uncertainty of HbA1c and glucose tests was calculated according to the ISO/TS 20914 uncertainty of measurement guide[7]. Desirable bias values were obtained from Westgard's biological database (www.westgard.com/biodatabase1.htm). Since the bias(%) values calculated from EQC data were lower than the desirable bias(%) values, they were not included in the uncertainty calculation.

Standard deviation (SD) of the IQC results was calculated. The SD was accepted as long-term precision (uRw). Calibrator uncertainty (Ucal) data was obtained from the manufacturer. The combined uncertainty calculation used the formula "$\sqrt{(URW^2 + UCAL^2)}$". Uncertainty calculations were made separately for both IQC levels. The expanded uncertainty was calculated by multiplying the combined uncertainty by coverage factor (The coverage factor was taken as 2 at the 95 confidence interval). The expanded uncertainty values were compared with the total allowable

error (TEa%) values of international organizations [Clinical Laboratory Improvement Amendments (CLIA) 2024, Desirable specifications for allowable total error, based on biological variability (BV), and rilibak][8-10].

In order to evaluate the possible effects of measurement uncertainty on clinical decision limits, the results of 31,030 patients who were requested simultaneous HbA1c and glucose tests in our hospital in 2022 were obtained from the hospital information management system. One hundred and sixty patients whose HbA1c and/or glucose test could not be studied due to preanalytical error (insufficient sample, clotted sample, inappropriate tube, etc.) were excluded from the evaluation. The HbA1c and glucose results of the patients were evaluated according to the ADA criteria, taking into account the measurement uncertainty, and the number of patients in the grey zone was determined.

Statistical Analysis

Data were analyzed using Microsoft Excel 2010, Statistical Package for Social Sciences (SPSS) version 25.0 software (IBM Corp., Armonk, USA), and MedCalc version 12 (MedCalc Software, Ostend, Belgium). In the statistical analyses, the chi-square test was used for categorical data. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Results

Statistical values and measurement uncertainty of HbA1c and glucose tests are shown in Table 1. In our study, the measurement uncertainty values calculated of HbA1c and glucose tests were calculated as 2.41% and 7.92% for level 1 and 1.37% and 7.68% for level 2, respectively (Table 1). The uncertainty values calculated for the HbA1c parameter were below the TEa% values determined by all three international organizations. Although the uncertainty of the glucose test was below the CLIA and rilibak TEa% values, it was found to be higher than the BV TEa% value (Table 2).

The mean age of 30870 patients analysed retrospectively was 55±15 years, with HbA1c values between 3-18% and glucose values between 10-945 mg/dL. When the patients were evaluated according to ADA criteria, 9473 (30.7%) had prediabetes and 15557 (50.4%) had DM. Considering the HbA1c measurement uncertainty ±2.41% for level 1 and ±1.37% for level 2, the grey zones for level 1 and 2 in the DM cut-off value of 6.5% were between 6.3-6.7%, 6.4-6.6%, respectively (Figure 1). When the HbA1c results of the patients were evaluated according to the measurement uncertainty calculated for level 1 and level 2, it was seen that a total of 5309 and 3965 patients were in the gray zone and were affected by the uncertainty values, respectively (Table 3).

Considering the glucose parameter measurement uncertainty ±7.92% for level 1 and ±7.68% for level 2, the grey zone was between 116 and 136 mg/dL for the clinical decision limit for DM, which is 126 mg/dL (Figure 2). When glucose results were evaluated according to measurement uncertainty, 3959 (12.8%) patients were in the grey zone according to negative uncertainty and 5934 (19.2%) patients according to positive uncertainty. It was determined that the results of a total of 9893 patients were affected by uncertainty values (Table 3).

Table 1. Statistical values and measurement uncertainty of HbA1c and glucose tests

	IQC material	n	Mean	SD	U_{RW}^2	U_{CAL}	U_{CAL}^2	Combined uncertainty	Expanded uncertainty	Bias (%)	Desirable Bias(%)
HbA1c (%)	Level 1	100	5.2	0.08	0.01	1.20	1.44	1.20	2.41	0.25	1.5
	Level 2	100	10.2	0.15	0.02	0.67	0.45	0.69	1.37		
Glucose (mg/dL)	Level 1	145	98	3.43	11.76	1.98	3.93	3.96	7.92	-2.13	2.34
	Level 2	145	237	3.29	10.82	1.98	3.93	3.84	7.68		

IQC: Internal quality control, SD: Standard deviation, U_{RW}: Long-term precision, U_{CAL}: Calibrator uncertainty

Table 2. The measurement uncertainty of the parameters and TEa values of international organizations

	Level 1 measurement uncertainty	Level 2 measurement uncertainty	CLIA TEa%	BV TEa%	Rilibak TEa%
HbA1c	2.41	1.37	8	3.0	18
Glucose	7.92	7.68	8	6.96	15

CLIA: Clinical Laboratory Improvement Amendments, BV: Desirable specifications for allowable total error, based on biological variability, TEa: Total allowable error

Table 3. The effect of measurement uncertainty of HbA1c and glucose tests on diagnostic performances in the diagnosis of DM

Test		Cut-off value		DM		PPV (%)	NPV (%)	Sensitivity % (95% CI)	Specificity % (95% CI)
				Negative	Positive				
HbA1c	Level 1	6.5%	Negative	15313	1357	100	91.9	91.3 (90.8-91.7)	100 (100-100)
			Positive	0	14200				
		6.3%	Negative	13817	997	90.7	93.3	93.6 (93.2-94.0)	90.2 (89.7-90.7)
			Positive	1496	14560				
		6.7%	Negative	15313	2816	100	84.5	81.9 (81.3-82.5)	100 (100-100)
			Positive	0	12741				
	Level 2	6.5%	Negative	15313	1357	100	91.9	91.3 (90.8-91.7)	100 (100-100)
			Positive	0	14200				
		6.4%	Negative	14638	1170	95.5	92.6	92.5 (92.1-92.9)	95.6 (95.3-95.9)
			Positive	675	14387				
		6.6%	Negative	15313	2120	100	87.8	86.4 (85.8-86.9)	100 (100-100)
			Positive	0	13437				
Glucose	Level 1&2	126 mg/dL	Negative	15313	4162	100	78.6	73.2 (72.5-73.9)	100 (100-100)
			Positive	0	11395				
		116 mg/dL	Negative	14236	2882	92.2	83.2	81.5 (80.9-82.1)	93.0 (92.6-93.4)
			Positive	1077	12675				
		136 mg/dL	Negative	15313	5934	100	72.1	61.9 (61.1-62.6)	100 (100-100)
			Positive	0	9623				

DM: Diabetes mellitus, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

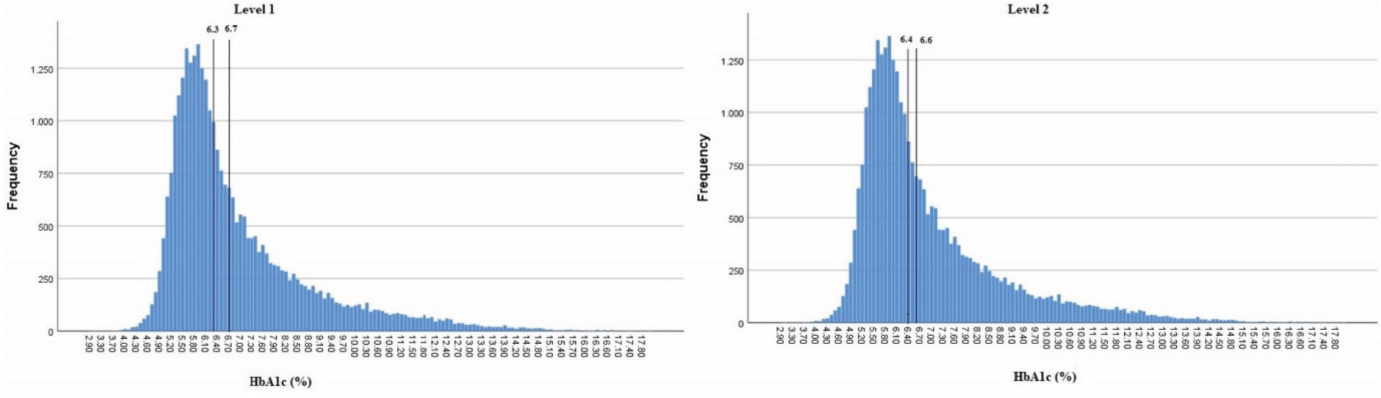

Figure 1. HbA1c values in the gray zone according to level 1 and level 2 measurement uncertainty

Discussion

Measurement uncertainty is a statistical parameter that evaluates the reliability and accuracy of the measurement result obtained. This parameter refers to the range containing the value of the measured quantity and quantitatively indicates the quality of the result. The measurement uncertainty is reported together with the measurement result, showing a distribution that is reasonably consistent with the value of the measured quantity. In this way, it provides information about the reliability and precision of the measurement result[11]. In our study, the measurement uncertainty values of HbA1c and glucose tests were 2.41% and 7.92% for level 1 and 1.37% and 7.68% for level 2 at 95% confidence interval, respectively. In our laboratory,

uncertainty values calculated for the HbA1c parameter were below the TEa% values determined by all three international organizations. Although the uncertainty of the glucose test was below the CLIA and rilibak TEa% values, it was found to be higher than the BV TEa% value. Even at these measurement uncertainty values, which are within acceptable limits for the clinical biochemistry laboratory, 12629 false negative results and 2573 false positive results were found for level 1 uncertainty, and 12106 false negative results and 1752 false positive results were found for level 2 uncertainty. Considering that the number of patients in the grey zone will increase as the measurement uncertainty value increases, the quality and reliability of the results are very important.

In the study of Dülgeroğlu[6] the expanded measurement uncertainty of HbA1c measured by the cation exchange chromatography method in the BIO-RAD D10 HPLC device was found to be 7.4%. It has been reported that there is a measurement uncertainty of ±0.4% for HbA1c at the level of 6% and it may affect the clinical decision[6].

In the study of Ayyildiz and Kalayci[12] the measurement uncertainty of HbA1c on the Trinity Biotech Premier Hb9210 device was found to be ±4.27% at 95% confidence interval, which is lower than the total allowable error determined by international organisations (clia, rilibak, Fraser rules). It was reported that the HbA1c threshold value of 6.5% had a measurement uncertainty between 6.2% and 6.8% and 1539 (11.5%) of 13329 patients had HbA1c results in the grey zone. Since the uncertainty value of each laboratory is different from each other, it has been suggested that the grey zones of parameters evaluated using cut-offs such as HbA1c should be determined according to the measurement uncertainty[12].

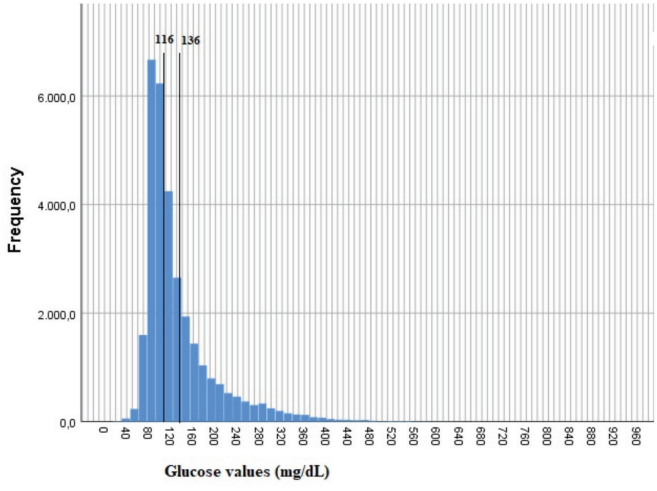

Figure 2. Glucose values in the grey zone

In the study of Unal and Atikeler[13] the measurement uncertainty (95% confidence interval) of HbA1c on the Trinity Biotech Premier Hb9210 device was calculated as ±4.6%. It was observed that the results of 1555 (15.2%) patients with HbA1c values between 6.2-6.8% were affected by the uncertainty value[13]. In the study by Galindo-Méndez et al.[14], HbA1c measurement uncertainty values were found to be significantly different from each other, ±0.19% and ±0.43%, respectively, due to different bias results obtained using two different EQC programmes (Unity Interlaboratory Programme and Randox International Quality Assessment Scheme). However, in both cases, the measurement uncertainty results were reported to be below the recommended maximum uncertainty of ±0.5%[14].

In the study by İnce et al.[15], the measurement uncertainty of the glucose parameter in the Abbott/Architect C8000 autoanalyser was found to be 3%. It has been suggested that the uncertainty value for the 126 mg/dL limit used in the diagnosis of diabetes is ±3.78 mg/dL and all error sources that may affect the result should be identified and given as uncertainty value[15]. In the study of Telo and Kaman[16] the measurement uncertainty of the glucose test performed on the Siemens Advia 2400 autoanalyser was similarly found to be 3.9%. In the study of Bal et al.[17], the measurement uncertainties of glucose parameters in three different devices of the same brand and model (DxC 800, Beckman Coulter) were found to be 3.22%, 5.81% and 3.74%, respectively. Celebiler et al.[18] reported the measurement uncertainty for glucose in the Roche/Hitachi Modular P800 autoanalyser as ±6% in the 95% confidence interval.

In the study of Öztürk et al.[19], investigating the effect of glucose measurement uncertainty in the diagnosis of gestational diabetes, 150 of 937 pregnant women had a 1st-hour glucose result ≥140 after 50 g OGTT. Sixty-six of these pregnant women were diagnosed with gestational diabetes after 100 g OGTT. The uncertainty of the glucose test performed on the Olympus AU2700 autoanalyzer was found to be 7.26% and it was reported that 77 patients were diagnosed with gestational diabetes according to negative uncertainty and 55 patients were diagnosed with gestational diabetes according to positive uncertainty[19]. In the study by Kütükçü et al.[20], investigating the importance of the use of measurement uncertainty and reference change value in the

diagnostic evaluation of biochemical tests, the measurement uncertainty of glucose was found to be 5.39 and 4.30 in Architect ci4100 and ci8200 devices, respectively. They stated that measurement uncertainty and reference change value should be given together with the test results to increase diagnostic accuracy[20].

In the study conducted by Çat and Uçar[21] in 2023, the measurement uncertainty of the glucose test was calculated separately for two levels of IQC in the same brand and model A and B devices (Roche Cobas 6000 c501). The uncertainty of glucose was found to be 5.3% and 3.8% for IQC-1 and 2 in device A and 13.7% and 4.4% in device B, respectively. It was noted that the calculated measurement uncertainty for IQC-2 in both instruments met the targeted quality specification (5%) but exceeded the permissible targets for IQC-1. It has been reported that different measurement uncertainty values can be obtained for the same analyte in different materials and different instruments[21].

Study Limitations

One of the strengths of our study is that it is the first study to simultaneously calculate the measurement uncertainty of HbA1c and glucose parameters, which have an important place in the diagnosis and treatment of DM, according to the ISO/TS 20914 guideline. The second is to evaluate the effect of measurement uncertainty in HbA1c and glucose tests on diagnostic performance in a large patient group.

Conclusion

Although the measurement uncertainty values of HbA1c and glucose tests in our laboratory are within acceptable limits, it has been observed that false negative and false positive results may occur. However, when glucose and HbA1c results at medical decision levels are evaluated together with measurement uncertainty, diagnosis and treatment modality may change. It should be taken into consideration that false negative results may lead to delay in diagnosis and related complications, while false positive results may cause unnecessary test and treatment costs.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital with the decision dated June 6, 2023, and numbered 2023/05-04.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: M.A., Design: M.A., Data Collection or Processing: M.A., F.D., Analysis or Interpretation: M.A., F.D., Literature Search: M.A., F.D., Writing: M.A., F.D.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Factors Affecting Length of Hospital Stay After Laparoscopic Adrenalectomy

Laparoskopik Adrenalektomi Sonrası Hastanede Kalış Süresine Etkili Faktörler

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Abstract

Objective: The aim of this study is to evaluate the factors affecting the length of hospital stay after surgery in patients who underwent laparoscopic adrenalectomy.

Methods: Patients who underwent laparoscopic adrenalectomy between 2012 and 2022 were retrospectively analyzed. The 75th percentile of the study population was set as the limit for the length of stay. Staying longer than this time was defined as prolonged hospital stay. Factors affecting prolonged hospital stay were analyzed with univariate and multiple logistic regression analyses. Variables with a p-value of <0.10 in univariate logistic regression analysis were included in the multiple regression model.

Results: A total of 86 patients were included in the study. Seventy-one (83%) of the patients were women. The median age was 54 (interquartile range, 45-61) years. The median hospital stay was 2 (interquartile range, 2-2) days. According to the 75th percentile of the population, the duration of stay longer than 2 days was determined as prolonged hospital stay. Prolonged hospital stay was detected in 14 (16%) patients. As a result of multiple regression analysis, operation time (odds ratio: 1.03; p-value: 0.017), conversion to open surgery (odds ratio: 4.79; p-value: 0.045), and male gender (odds ratio: 5.61; p-value: 0.022), was associated with prolonged hospital stay.

Conclusion: Laparoscopic adrenalectomy is a safe technique in the treatment of various adrenal pathologies. Operation time and conversion to open surgery were associated with prolonged hospital stay; however, studies with a high level of evidence are needed.

Keywords: Laparoscopic adrenalectomy, minimally invazive adrenalecomy, transabdominal approach, length of hospital stay

Öz

Amaç: Bu çalışmanın amacı laparoskopik adrenalektomi uygulanan hastalarda, ameliyat sonrasında hastanede kalış süresine etki eden faktörleri değerlendirmektir.

Yöntem: 2012-2022 yılları arası laparoskopik adrenalektomi uygulanan hastalar retrospektif olarak incelendi. Hastanede kalış süresi için çalışma popülasyonunun 75. yüzdelik dilimi sınır olarak belirlendi. Bu süreden daha uzun süre kalınması uzamış hastanede kalış olarak tanımlandı. Uzamış hastanede kalışa etkili faktörler tek değişkenli ve çoklu lojistik regresyon analizleriyle incelendi. Tek değişkenli lojistik regresyon analizinde p-değeri <0,10 olan değişkenler çoklu regresyon modeline dahil edildi.

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Öz

Bulgular: Çalışmaya toplam 86 hasta dahil edildi. Hastaların 71'i (%83) kadındı. Ortanca yaş 54 (çeyrekler arası aralık, 45-61) yıldı. Ortanca hastanede kalış süresi 2 (interkuartil aralık, 2-2) gündü. Popülasyonun 75. yüzdelik dilimine göre 2 günden uzun süren kalış süresi uzamış hastanede kalış olarak belirlendi. Buna göre 14 (%16) hastada uzamış hastanede kalış saptandı. Çoklu regresyon analizi sonucunda operasyon süresi (olasılık oranı: 1,03; p-değeri: 0,017), açık cerrahiye geçiş (odds oranı: 4,79; p-değeri: 0,045) ve erkek cinsiyet (olasılık oranı: 5,61; p-değeri: 0,022), uzamış hastanede kalış süresi ile ilişkili bulundu.

Sonuç: Laparoskopik adrenalektomi, bir çok adrenal patolojinin tedavisinde güvenilir bir yöntemdir. Operasyon süresi ve açık cerrahiye geçiş, uzamış hastanede kalış süresi ile ilişkili bulunmuştur; ancak kanıt düzeyi yüksek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Laparoskopik adrenalektomi, minimal invaziv adrenalektomi, transabdominal yaklaşım, hastanede kalış süresi

Introduction

Laparoscopic adrenalectomy (LA) has been defined as a safe and feasible treatment method for adrenal diseases since its introduction in 1992[1-4]. Gagner et al.[5] described lateral decubitus position for LA in 1994. LA offers various advantages over conventional adrenalectomy, such as less postoperative pain, reduced risk of bleeding, shorter hospital stay, and lower morbidity[1,6-8].

While LA is now a standardized procedure, there are significant differences in short-term outcomes such as hospital stay and morbidity among centers[9].

The aim of this study is to evaluate the factors affecting the duration of hospital stay following LA.

Materials and Methods

Patients and Study Design

This is a retrospective cohort study. Patients who underwent laparoscopic transabdominal adrenalectomy between 2012 and 2022 were included in the study. Patients who underwent bilateral adrenalectomy were excluded from the study. All patients were evaluated by an endocrinologist for possible functional adenomas before the operation. The operations performed using lateral transabdominal approach. A drain was placed in all patients at the end of the operation.

Demographic data, past medical history, adrenal tumor size (mm) and side, histopathological result, performing surgeon (specialist/resident under specialist supervision), operation time (minutes), postoperative length of hospital stay (days), and the occurrence of conversion to open surgery were retrospectively evaluated.

The hospital stay duration was defined as the time between the operation day and discharge. Discharge criteria included stable vital signs, absence of peritoneal irritation signs, oral intake tolerance, and discontinuation of intravenous analgesia. The desired length of hospital stay was determined as the 75th percentile of the study population. Accordingly, patients were divided into two groups: Hospital stay of two days or less, and hospital stay of more than two days. Histopathological examination results were categorized into three main groups: Benign, malignant, and pheochromocytoma.

Ethical Approval

Approval for the study was obtained from University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee (date: 03/05/2023, no: 2023/04-18). The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The data were analyzed using the IBM SPSS Statistics software package, Version 25.0, released by IBM Corp. Descriptive statistics included frequency (percentage) for categorical variables and median (minimum-maximum) values for numerical variables. Between-group comparisons for categorical variables were performed using the chi-squared test or Fisher's Exact test, while numerical variables were compared using the Mann-Whitney U test. Logistic regression analysis was conducted to identify factors influencing prolonged hospital stay. Variables with a p-value <0.10 in univariate logistic regression analysis were included in the multiple regression model.

Results

A total of 86 patients were included in the study. Among them, 15 were male (17%), and 71 were female (83%). The median age of the patients was 54 years (range: 20-78). The length of hospital stay ranged from 2 to 5 days, with a median hospital stay of 2 days. In Group 1, comprising patients with a hospital stay of two days or less, there were 72 patients (84%), while in Group 2, with a hospital stay of more than two days, there

were 14 patients (16%). The baseline characteristics of the patients are presented in Table 1.

The median operation duration was 145 minutes (range: 90-210). In Group 1, the median operation duration was 140 minutes (range: 90-205), whereas in Group 2, it was 175 minutes (range: 115-210) (p=0.031). Among the patients, 35 underwent right adrenalectomy, while 51 underwent left adrenalectomy. Among those who underwent right adrenalectomy, hospital stay was prolonged in five patients (14%), and among those who underwent left adrenalectomy, hospital stay was prolonged in nine patients (18%). However, this difference was not statistically significant (p=0.678). Fourteen operations were performed by surgical residents under specialist supervision, and 72 operations were conducted by general surgery specialists. Prolonged hospital stay was not observed in operations performed by residents, whereas prolonged hospital stay was observed in 14 cases (19%) performed by specialists. However, the difference was not statistically significant (p=0.113). A total of 10 patients required conversion from laparoscopic surgery to open surgery. Among those converted to open surgery, hospital stay was prolonged in four cases (40%), while among cases completed laparoscopically, prolonged hospital stay was observed in 10 cases (13%) (p=0.053). Five patients had a history of previous abdominal surgery. Among patients with a history of previous abdominal surgery, two (40%) required conversion to open surgery, while among those without such a history, eight (10%) required conversion to open surgery. However, the difference was not statistically significant (p=0.101).

The median tumor diameter was 70 mm (range: 30-160). In Group 1, the median tumor diameter was 70 mm (range: 30-160), while in Group 2, it was 61 mm (range: 45-108) (p=0.247). There was no significant difference between the two groups in terms of histopathological results (p=0.573) (Table 2).

Complications were observed in seven patients. All complications were classified as Clavien-Dindo grade 1. Among patients with complications, length of hospital stay was prolonged in two cases (29%), while among those without complications, length of hospital stay was prolonged in 12 cases (15%). However, the difference was not statistically significant (p=0.319).

According to the results of the multiple regression analysis, male gender, operation duration, and conversion to open surgery were found to be associated with prolonged hospital stay (Table 3).

Discussion

LA is considered the gold standard for the treatment of most adrenal tumors due to its low major complication rates

Table 1. Demographic data

Variable	Total	Group 1	Group 2	p-value
	n=86	n=72	n=14	
Age (years)	54 (20-78)	53 (20-78)	56 (37-69)	0.323
Sex				0.063*
Female	71 (83%)	62 (86%)	9 (64%)	
Male	15 (17%)	10 (14%)	5 (36%)	
Prior surgery				0.185*
No	81 (94%)	69 (96%)	12 (86%)	
Yes	5 (6%)	3 (4%)	2 (14%)	

*: Fisher's Exact test

Table 2. Histopathological results

Variable	Total	Group 1	Group 2	p-value
	n=86	n=72	n=14	
Histopathology				0.573
Benign	65 (100%)	54 (83%)	11 (17%)	
Malignant	4 (100%)	4 (100%)	0 (0%)	
Pheochromocytoma	17 (100%)	14 (82%)	3 (18%)	

Table 3. Factors affecting the length of hospital stay

Variable	Univariate analysis		Multiple analysis	
	OR	p-value	OR	p-value
Age	1.023	0.384		
Male gender	3.444	0.058	5.609	0.022
Prior surgery	3.833	0.164		
Operation time	1.022	0.029	1.030	0.017
Conversion to open surgery	4.400	0.042	4.786	0.045
Tumor size	0.983	0.306		
Right sided tumor	0.778	0.679		
Histopathology				
Benign (ref.)	1	-		
Malignant	0.000	0.999		
Pheochromocytoma	1.052	0.944		
Complication	2.233	0.368		

OR: Odds ratio

and safety. The length of hospital stay following a surgical procedure is influenced by patient-related factors and factors associated with the performed surgical procedure. It is generally accepted that length of hospital stay after minimally invasive interventions is shorter compared to conventional methods. Complications arising during or after surgical procedures are also well-known factors associated with prolonged hospital stay. The average postoperative hospital stay for LA has been reported as 2 to 8 days in the literature[10-17].

Various studies in the literature have investigated factors affecting postoperative hospital stay following adrenalectomy. In a series of 453 cases published by Pisarska et al.[16], the presence of postoperative complications, the need for drain usage, histopathological type, and the day of surgery (Thursday or Friday) were found to be associated with prolonged hospital stay. In this study, a correlation between histopathologically confirmed pheochromocytoma and prolonged hospital stay was reported. However, no relationship was found between the presence of complications and length of hospital stay. This could be attributed to the low complication rate and the fact that all complications were grade 1. Additionally, contrary to the literature, no significant relationship was found between histological subtypes and hospital stay. As routine drain usage was employed after LA in our clinic, the need for drainage could not be evaluated in our study.

In a large series published by Chen et al.[15], it was reported that tumor size is correlated with prolonged hospital stay. According to this study, adrenal masses with a size of 4 cm and above were associated with prolonged hospital stay. In another study by Rodríguez-Hermosa et al.[18] published in 2020, tumor size greater than 9 cm, the day of surgery (Thursday or Friday), and intraoperative blood loss were reported to be associated with prolonged hospital stay. However, in our study, no significant association was found between tumor size and prolonged hospital stay.

Study Limitations

Contrary to the results of the current study, Bergamini et al.[19] evaluated post-LA complications in a study where age, BMI, tumor diameter, and pheochromocytoma were indirectly associated with the rate of complications, and thus with the length of hospital stay. On the other hand, in the study of Aydin et al.[20], there was no observed disparity in the duration of hospital stay between the hormone-active and non-functional groups. However, upon conducting a subgroup analysis within the hormone-active group, a prolonged duration of hospitalization was noted specifically among patients diagnosed with Cushing's syndrome.

In our study, conversion to open surgery was associated with prolonged hospital stay. Consistent with this, Köstek et al.[21] reported similar results, as longer hospital stay in patients with conversion to open surgery.

Conclusion

LA is a safe surgical procedure in the treatment of various adrenal pathologies, with a low complication rate. According to this study, prolonged operation time, male gender, and conversion to open surgery were found to be associated with prolonged hospital stay. Since this study was limited because it was a single-center retrospective study, studies with a high level of evidence are needed.

Ethics

Ethics Committee Approval: Approval for the study was obtained from University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee (date: 03/05/2023, no: 2023/04-18). The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Informed consent was obtained.

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Quality of YouTube Videos About Cataracts and Surgical Management

Katarakt ve Cerrahi Tedavisi ile İlgili YouTube Videolarının Kalitesi

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Abstract

Objective: In recent years, YouTube has been frequently used as a source of information in the medical field. To clarify the quality of Turkish language YouTube videos about cataracts and surgical management.

Methods: Two experienced ophthalmologists searched for the terms "cataract", "cataract surgery", "phacoemulsification cataract surgery", and "intraocular lens" in YouTube. Queries were performed only in the Turkish language. Video characteristics were recorded, and quality and reliability of each video was analyzed with the global quality score (GQS), the modified DISCERN form, and the patient education materials assessment tool (PEMAT).

Results: A total of 184 YouTube videos were evaluated to for inclusion in the analysis, and 58 videos did not match with study inclusion criteria. The mean number of views was significantly higher in favor of professional videos (p=0.006). The duration on YouTube was significantly longer for non-professional videos (217.5 days vs. 400.0 days, p=0.005). Moreover, "like count" and "comment count" were significantly higher for professional videos (p=0.001 and p=0.003). Modified DISCERN score was 3.5 for professional videos and 2.1 for non-professional videos, and GQS was 3.4 for professional videos and 2.3 for non-professional videos (p=0.001 for both parameters). In addition, 75 (91.5%) videos uploaded by professional health care providers had PEMAT score >70, and 20 (58.8%) non-professional videos had PEMAT score >70 (p=0.001).

Conclusion: The present study demonstrated that view numbers, like count, and comment count were significantly higher for professional videos, but duration on YouTube was significantly longer for non-professional videos. Quality of professional YouTube videos about cataracts and surgical management were significantly better according to the modified DISCERN score, GQS, and PEMAT score.

Keywords: Cataracts, DISCERN, global quality score, PEMAT, YouTube

Öz

Amaç: Son yıllarda Youtube tıbbi bilgi kaynağı olarak sıklıkla kullanılmaktadır. Katarakt ve cerrahi tedavisiyle ilgili, Türkçe YouTube videolarının kalitesini netleştirmek amaçlanmıştır.

Yöntem: Deneyimli iki göz doktoru YouTube'da "katarakt", "katarakt ameliyatı", "fakoemülsifikasyon katarakt ameliyatı" ve "göz içi lens" terimlerini araştırdı. Sorgulamalar yalnızca Türkçe dilinde gerçekleştirilmiştir. Video özellikleri kaydedildi ve her videonun kalitesi ve güvenilirliği, küresel kalite puanı (GQS), değiştirilmiş DISCERN formu ve hasta eğitim materyalleri değerlendirme aracı (PEMAT) ile analiz edildi.

Bulgular: Toplam 184 YouTube videosu analize dahil edilmek üzere değerlendirildi ve 58 video çalışmaya dahil edilme kriterleriyle eşleşmedi. Ortalama izlenme sayısı, profesyonel videolar lehine anlamlı derecede yüksekti (p=0,006). Profesyonel olmayan videolarda YouTube'da kalma süresi anlamlı derecede

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Öz

daha uzundu (217,5 gün vs. 400,0 gün, p=0,005). Ayrıca profesyonel videolarda "beğeni sayısı" ve "yorum sayısı" anlamlı düzeyde daha yüksekti (p=0,001 ve p=0,003). Modifiye DISCERN puanı profesyonel videolar için 3,5, profesyonel olmayan videolar için 2,1, GQS ise profesyonel videolar için 3,4, profesyonel olmayan videolar için 2,3 olarak belirlendi (her iki parametre için de p=0,001). Ayrıca profesyonel sağlık hizmeti sağlayıcıları tarafından yüklenen videoların 75'inin (%91,5) PEMAT puanı >70 iken, profesyonel olmayan videoların 20'sinin (%58,8) PEMAT puanı >70 idi (p=0,001).

Sonuç: Bu çalışma, profesyonel videolarda izlenme sayısının, beğeni sayısının ve yorum sayısının anlamlı derecede yüksek olduğunu, ancak profesyonel olmayan videolarda YouTube'da kalma süresinin önemli ölçüde daha uzun olduğunu gösterdi. Katarakt ve cerrahi tedavisiyle ilgili profesyonel YouTube videolarının kalitesi; değiştirilmiş DISCERN puanı, GQS ve PEMAT puanına göre önemli ölçüde daha iyi bulundu.

Anahtar Kelimeler: Katarakt, DISCERN, global kalite puanı, PEMAT, YouTube.

Introduction

Cataracts are simply defined as clouding of the lens in the eye that deteriorates vision, and cataracts have become a serious and challenging health problem in the last century. Previous reports have demonstrated that cataracts are the reason for almost half of blindness cases[1]. Vision of 90% of individuals who live in developing countries is negatively affected due to cataracts[2]. The definitive treatment option for cataracts is surgery. Phacoemulsification cataract surgery is accepted as a surgical technique for the management of cataracts with a high success rate and acceptable complication rates. Moreover, multifocal intraocular lenses (IOL) were developed for cataract treatment, and the safety and efficiency of multifocal IOL were proven by *in vitro* and *in vivo* studies[3]. Many patients investigate their illness and treatment options from magazines, books, and the internet before attending the professional health care system, and many people obtain information from social media applications, including Instagram, Twitter, and YouTube[4].

YouTube is the largest social media application, and billions of videos are shared in this application. In a study by Freeman and Chapman[5] which evaluated the impact of content type on public attention, they revealed that public interest was significantly higher for visual content than for written content and audio sources. Video uploads are not restricted to the YouTube platform, and some videos can be misleading and others may include false information. Ergul[6] analyzed YouTube videos about uterine leiomyoma, and the author stated that despite high view rates, YouTube videos had insufficient and inadequate information about uterine leiomyoma. In another study, Cetin et al.[7] evaluated videos about coronary artery bypass grafting on YouTube and found that videos uploaded by professional health care providers were reliable and had good quality.

Although previous studies have evaluated the quality and reliability of YouTube videos about various medical conditions, no study has investigated the quality of YouTube videos about cataracts and surgical treatment. In this study, we aimed to clarify the quality of Turkish-language YouTube videos on cataracts and surgical management.

Materials and Methods

The present study was done between 15th February 2023 and 30th February 2023, and two experienced ophthalmologists searched for the terms "cataract", "cataract surgery", "phacoemulsification cataract surgery", and "multifocal intraocular lens" in YouTube. Queries were performed only in Turkish. Videos with 1-16 minutes in length were evaluated for inclusion, and YouTube videos with language other than Turkish, videos unrelated to cataracts and cataract surgical treatment, and personal advertising videos were excluded from analysis. A playlist was created from the selected YouTube videos, and each video was analyzed by two experienced ophthalmologists. The study was conducted after obtaining Local Ethics Committee of Dokuz Eylül University approval (number: E-87347630-659-848886).

Selected YouTube videos were classified into two groups: Professional and non-professional. Videos uploaded by professional healthcare providers and health institutions were accepted as professional videos. Personal experience videos and new update videos were classified as non-professional videos. For each video, the number of views, video length, and duration on YouTube were recorded. Moreover, counts of "likes", "dislikes", and "comments" and population targeted by the video (healthcare providers or patients) were noted. The quality and reliability of each video were analyzed using the global quality score (GQS), the modified DISCERN form, and the patient education materials assessment tool (PEMAT). Two ophthalmologists scored each video separately, and if

the ophthalmologists gave different scores for a video, the average of the two scores were accepted.

Evaluation of the Modified DISCERN Score, Global Quality Score and Patient Education Materials Assessment Tool Score

The modified version of DISCERN is a basic form of the 16-question DISCERN scale, which includes five yes or no questions. Each "yes" answer scores 1 point, and each "no" answer scores 0. Five points for the modified DISCERN score indicate the highest quality of video[8]. GQS consists of five questions, each question is scored between 1 and 5, and higher scores demonstrate high quality of video[9]. PEMAT is another form to analyze the applicability and understandability of videos, which includes 17 questions (13 questions for video intelligibility, and 4 questions for video applicability). Each answer is scored as 0 or 1, and a total PEMAT score higher than 70% is associated with high video quality[10].

To clarify and compare the quality and reliability of professional and non-professional videos, selected videos were categorized into two groups. The professional and non-professional video groups were compared with regard to video features, modified DISCERN score, GQS, and PEMAT score.

Statistical Analysis

The Statistical Package for the Social Sciences version 26 (SPSS IBM Corp., Armonk, NY, USA) program was used. The normality of variable distribution was analyzed using the Kolmogorov-Smirnov test. Normally distributed parameters were analyzed with the Student's t-test, and non-normal values were analyzed using the Mann-Whitney U test. Quantitative parameters are presented as mean ± standard deviation or median (interquartile range) values. Categorical variables were categorized and compared using the χ^2 test or Fisher's Exact test. The data were analyzed at a 95% confidence level, and a p-value <0.05 was set as statistically significant.

Results

A total of 184 YouTube videos were evaluated for inclusion in the analysis, and 58 videos did not match the study inclusion criteria. A total of 21 videos had irrelevant content, 10 videos were in another language than Turkish, and 32 videos had inappropriate duration. At the end of the evaluation, 116 videos matched the study inclusion criteria, 82 videos were categorized as professional videos, and 34 videos were categorized as non-professional videos. The flowchart of the study is presented in Figure 1.

Video features including "video length" and "dislike count" were similar between professional and non-professional videos (p=0.579 and p=0.077). The mean number of views was significantly higher in favor of professional videos (3522.5 vs. 2088.0, p=0.006). In contrast, the duration on YouTube was significantly longer for non-professional videos (217.5 days vs. 400.0 days, p=0.005). Moreover, "like count" and "comment count" were significantly higher for professional videos (p=0.001 and p=0.003) (Table 1).

The modified DISCERN score was 3.5 for professional videos and 2.1 for non-professional videos, and the GQS was 3.4 for professional videos and 2.3 for non-professional videos (p=0.001 for both parameters). In addition, 75 (91.5%) videos uploaded by professional health care providers or health institutions had a PEMAT score >70, and 20 (58.8%) non-professional videos had a PEMAT score >70 (p=0.001) (Table 2).

The correlation of video characteristics with the DISCERN score and GQS are summarized in Table 3. There was a significant correlation between the number of views, duration on YouTube, number of comments, and GQS score (p=0.001, p=0.001, and p=0.001; respectively). Also, the DISCERN score was significantly correlated with view numbers, duration on YouTube, like count, and comment count (p=0.001, p=0.001, p=0.014, and p=0.001, respectively).

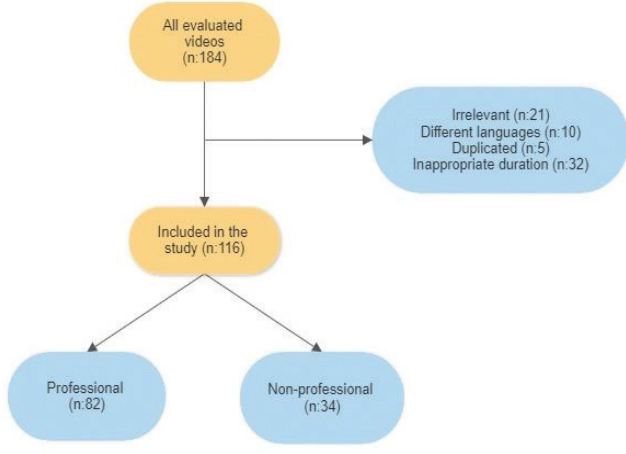

Figure 1. Flowchart for the YouTube video screening and selection process

Table 1. Comparison of video features between groups

	Professional	Non-professional	p-value
Number of videos	82 (70.7%)	34 (29.3%)	
Video features*			
Number of views	3522.5 (1956.3-5965.5)	2088.0 (476.0-4512.8)	**0.006**
Video length (min)	4.8 (2.5-9.3)	4.9 (3.2-8.2)	0.579
Duration on YouTube (days)	217.5 (120.0-367.5)	400.0 (150.0-590.0)	**0.005**
Like count	95.0 (19.0-107.0)	31.5 (9.8-59.5)	**0.001**
Dislike count	11.5 (3.0-24.5)	10.0 (0.8-12.6)	0.077
Comment count	35.0 (12.4-203.0)	20.5 (2.0-46.2)	**0.003**
Target group, n (%)			0.160
Healthcare providers	22 (26.8%)	5 (14.7%)	
Patients	60 (73.2%)	29 (85.3%)	

*: Median (interquartile range)

Table 2. Comparison of video quality scores between groups

	Professional	Non-professional	p-value
PEMAT score, n (%)			
(>70%)	75 (91.5%)	20 (58.8%)	**0.001**
(≤70%)	7 (8.5%)	14 (41.2%)	
Global quality score*	3.4±1.0	2.3±0.9	**0.001**
Modified DISCERN score*	3.5±1.0	2.1±1.0	**0.001**

*: Mean ± standard deviation, PEMAT: Patient education materials assessment tool

Table 3. Correlation of video features with DISCERN score and GQS score

	Number of views	Video length	Duration on YouTube	Likes	Dislikes	Comment
DISCERN						
CC	0.459	0.004	-0.494	0.228	0.138	0.568
p-value	**0.001**	0.965	**0.001**	**0.014**	0.140	**0.001**
GQS						
CC	0.309	0.042	-0.369	0.127	0.064	0.369
p-value	**0.001**	0.655	**0.001**	0.176	0.492	**0.001**

CC: Correlation coefficient, GQS: Global quality score

Discussion

Social media platforms have dramatically changed how people can obtain information about any issue, and health-related matters are significantly affected by this situation. Patients have access to accurate information on medical issues. Previous statistics revealed that more than 90% of internet users watch YouTube videos, and features such as being free and easy to access make this platform more popular[11]. Thus, we conducted a study to investigate the quality of YouTube videos about cataracts and the most common cataract surgeries, one of the most common disorders in the field of ophthalmology. Our findings revealed that view numbers, like counts, and comment counts were significantly higher for professional videos, but duration on YouTube was significantly longer for non-professional videos. Moreover, the quality and reliability of professional YouTube videos about cataracts and surgical management were significantly higher according to the modified DISCERN, GQS, and PEMAT scores.

The GQS and modified DISCERN score were developed to analyze the quality and reliability of the visual content. Yuksel and Ozgor[12] analyzed YouTube videos about pregnancy

during the COVID-19 pandemic, and the authors emphasized that most YouTube videos about pregnancy and COVID-19 had low quality according to the DISCERN score. In a study on general surgery, Ferhatoglu et al[13]. found low quality and reliability of YouTube videos on obesity surgery. However, Ferhatoglu et al.[13] found significantly higher DISCERN scores for YouTube videos uploaded by professional sources. In another study, Kılınç and Sayar[14] evaluated the quality of YouTube videos about orthodontic surgery using GQS and stated that YouTube videos about orthodontics had poor quality. In our study, we found significantly higher modified DISCERN scores and GQS for YouTube videos about cataracts and surgical management shared by professional sources.

The PEMAT tool was developed to evaluate the ease of understanding and practical applicability of information sources. Wong et al.[15] used PEMAT for evaluating YouTube videos about laryngeal cancer, and the authors showed the understandability of YouTube videos using the PEMAT score. Ji et al.[16] evaluated the intelligibility of YouTube videos about bladder overactivity and found that videos uploaded by professional healthcare workers had significantly better PEMAT scores. In this study, professional videos about cataracts and surgical management had significantly higher PEMAT scores.

For YouTube videos, "like number", "view number" and "comment count" are critical to stand out in the channel and achieve more interaction. Sevgili and Baytaroglu[17] analyzed YouTube video features of professional and non-professional videos about cardiovascular diseases, and the authors did not find any significant difference with regard to "comment count", and "number of views". Kumar et al. [11] emphasized that "view numbers" but not "like count" and "comment number" was significantly higher for professional YouTube videos about pregnancy and COVID-19. In the present study, "view number", "like number", and "comment count" were significantly higher for professional YouTube videos about cataracts and cataract surgery.

Study Limitations

Our analysis was performed only in the Turkish language, which could be accepted as a study limitation. However, we believe that conducting research using multiple languages can complicate data analysis. Additionally, we selected four keywords for analysis, but beyond these four terms, people could use other keywords while searching about cataracts and surgical treatment on YouTube. Finally, many resources continuously shared videos about cataracts and cataract surgery, and our study only included a certain duration.

Conclusion

We found that YouTube videos about cataracts and cataract surgery are popular and easily accessible sources for the public. In addition, the present study demonstrated that view numbers, like count, and comment count were significantly higher for professional videos, but duration on YouTube was significantly longer for non-professional videos. In addition, the quality and reliability of professional YouTube videos about cataracts and surgical management were significantly better according to the modified DISCERN, GQS, and PEMAT scores. Patients should be especially careful when obtaining information from unprofessional videos.

Ethics

Ethics Committee Approval: The study was conducted after obtaining Local Ethics Committee of Dokuz Eylül University approval (number: E-87347630-659-848886).

Informed Consent: There are no patients in our study evaluating cataract-related videos on the YouTube platform. Since it did not involve a patient, consent was not required.

Authorship Contributions

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

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Digital Infrared Thermal Imaging Assistance for Laryngectomy and Neck Dissection Flap Monitoring in Elderly Patients

Yaşlı Hastalarda Larenjektomi ve Boyun Diseksiyonu Flep İzlemesinde Dijital Kızılötesi Termal Görüntüleme Yardımı

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Abstract

Objective: In flap survival, close postoperatively monitoring of neck flaps is essential; instant action increases the rate of flap salvage. The purpose of this research was to assess the ability of digital infrared thermal Imaging and software during laryngectomy and neck dissection monitoring to detect failure of neck flaps.

Methods: Twelve elderly patients who required total laryngectomy and bilateral neck dissection for advanced laryngeal cancer participated in this study. The hourly clinical examination of skin colour, capillary refilling and turgor were evaluated for both flaps. In addition, thermal images were taken synchronously with the digital camera. Such images were processed and analyzed as an indication of flap failure on their additional value.

Results: Out of 12 flaps, one failed due to hematoma, and venous congestion formed in two flaps. The mean flap temperature demonstrated to be most predictive of flap failing relative to the adjacent control skin. In contrast to the uncompromised flaps, both failed flaps demonstrated lower temperatures after failure.

Conclusion: An efficient thermal camera imaging can possibly improve post-operative flap monitoring. It could play an additional part in the non-invasive early diagnosis of flap failure if used in conjunction with other modalities. By analyzing relative differences in temperature between the flap and reference tissue, vascular occlusion in flaps may be differentiated.

Keywords: Thermal camera, flap monitoring, laryngectomy, neck dissection

Öz

Amaç: Flep hayatta kalmasında ameliyat sonrası boyun fleplerinin yakın takibi önemlidir; anında harekete geçme flep kurtarma oranını artırır. Bu araştırmanın amacı, dijital kızılötesi termal görüntüleme ve yazılımın larenjektomi ve boyun diseksiyonu izlemi sırasında boyun fleplerinin başarısızlığını tespit etme yeteneğini değerlendirmektir.

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Öz

Yöntem: Total larenjektomi gerektiren 12 yaşlı hasta ve bilateral ileri evre larenks kanseri için boyun diseksiyonu yapılan hastalar bu çalışmaya katılmıştır. Her iki flep için deri rengi, kapiller dolum ve turgor saatlik klinik muayeneler ile değerlendirildi. Ayrıca termal görüntülemeler de çekildi. Dijital kamerayla eş zamanlı olarak, bu tür görüntüler, flep başarısızlığının bir göstergesi olarak kaydedilerek analizleri yapıldı.

Bulgular: On iki flepten biri hematom nedeniyle başarısızlıkla sonuçlandı ve iki flepte venöz konjesyon oluştu. Ortalama flep sıcaklığı, flep başarısızlığı açısından en tahmin edici veri olmuştur ve yanındaki kontrol derisine göre değerlendirilmiştir. Başarısız flepler başarısızlıktan sonra sağlam fleplere kıyasla daha düşük sıcaklıklar göstermiştir.

Sonuç: Verimli bir termal kamera görüntüleme, postoperatif flep takibinde daha yararlıdır. Diğer modalitelerle birlikte kullanıldığında, flep başarısızlığının non-invaziv erken teşhisinde ek bir rol oynayabilir. Flep ve referans dokusu arasındaki sıcaklık farkları analiz edilerek, fleplerde vasküler oklüzyon ayırt edilebilir.

Anahtar Kelimeler: Termal kamera, flep monitörizasyonu, larenjektomi, boyun diseksiyonu

Introduction

Flaps have been commonly used over the decades for the repair or coverage of significant defects and the removal of tumours. Part of the flap circumference is completely isolated from the blood supply. Although apron flap success rate is high, due to circulatory failure, surgical revision is often required. Venous and arterial thrombosis are responsible for the majority of failures, usually occurring during the first 3 days[1]. The overall tolerable time for ischemia depends on type of flap. That being said, it is normally just a few hours before permanent tissue damage happens. It is mainly possible to monitor flaps by clinical examination. The explanation for these results; however, is highly reliant on the clinical experience of the healthcare staff[2].

More advanced technical methods, such as handhelds Ultrasonography with Doppler, tissue oximetry have been practiced over the past years. These techniques have both advantages and disadvantages. One of the oldest measures of surface temperature is postoperative monitoring techniques. A body's emittance of infrared light is proportional to its temperature. A contactless approach for the surface temperature can be calculated. Some medical trials have shown that flap temperature can be associated with flap failure obtained with an infrared surface thermometer[3,4]. The objectives of this research was to determine the feasibility of combining the use of an infrared thermal digital camera with postoperative monitoring imaging tools to detect flap failure.

Materials and Methods

This was performed in the Department of Otolaryngology at a Medical Tertiary Centre. The study was performed in accordance with the ethical standards of the Institutional and National Research Committee and was approved by the Ethics Committee of University of Health Sciences Turkey, Antalya Training and Research Hospital (17th July 2020-protocol number 14/1). Additionally, patient consents were obtained. Twelve patients participated in this study who needed a total laryngectomy and bilateral functional neck dissection for advanced laryngeal cancer. All of the study group's patients were male and over 60 years of age. We performed the Apron flap incision described by Latyschevsky and Freund to all patients[5]. Only a horizontal incision gently curving inferiorly up to the upper border of the thyroid cartilage from mastoid to mentum was used bilaterally.

Every hour, postoperative flap monitoring was done on the first postopertative day and subsequent days 4 times a day by clinical examination of skin colour, capillary refilling and turgor. Normal mode digital photographs and thermal photographs were taken simultaneously with the Nikon D3100 DSLR Camera (made in Japan) and FLIR E8 (made in USA) high resolution infra-red thermal camera, respectively. Digital infrared thermal imaging was performed for the skin temperature mapping in automatic self-calibration mode. The spectral range of this camera lies between 7.5 and 13 µm.

After a time of 5 minutes, the photographs were made in a room with a stable temperature of 25 °C, 60 per cent humidity, used to suit the room temperature and environmental conditions. On all available visual images, including thermal data from the actual thermal image, the entire flap and reference skin were demarcated. The thermal and visual images were verified and matched. As an indication of flap failure, these images were analyzed for their additional value.

Statistical Analysis

Categorical variables are given as percentage distribution. Microsoft Excel and manual statistical formulas were used for analysis.

Results

In order to find interrelationship between the thermal images, digital photographs and clinical findings flaps data were retrospectively analyzed. Of the 12 flaps, nine had no postoperative complications. The mean temperature for each point of time was measured to serve as the basis for examination and clinical signs (skin color, turgor, and capillary refilling) were reported for the healthy flaps.

Three of the flaps had postoperative complications. Two have shown clinical symptoms of venous congestion. The healthy flaps, according to both the reference point and the mean temperature, this finding was associated with the overall lower temperature of this flap, as shown in the Figure 1, drop in temperature difference from 0.5 °C to-1.5 °C was revealed by thermal data.

One flap presented 12 h postoperatively with discolored, purple regions. Moreover, in contrast to the top, the flap was pinker in the middle. Fluctuation was felt on palpation in this area. A decrease in temperature was already detected. Hematoma was drained from the incision edge and the hemovac drain was checked. In the following days the colour appeared to improve spontaneously.

Discussion

Flaps have been widely used for the repair or coverage of critical defects and tumour removal. Apron flap is one of the most preferred incisions, especially in combination with total laryngectomy and neck dissection. An advantage of this flap is that it protects the descending arterial recovery and carotid artery. But the ascending arterial and venous recovery is impaired by this approach. Furthermore, the bottom corner may develop venous congestion and oedema. Even though the success rate of the apron flap is high, surgical revision is rarely needed due to circulatory failure. The majority of failures, typically occurring within the first 3 days, are caused by venous (53-57%) and arterial thrombosis (20-43%)[1-3].

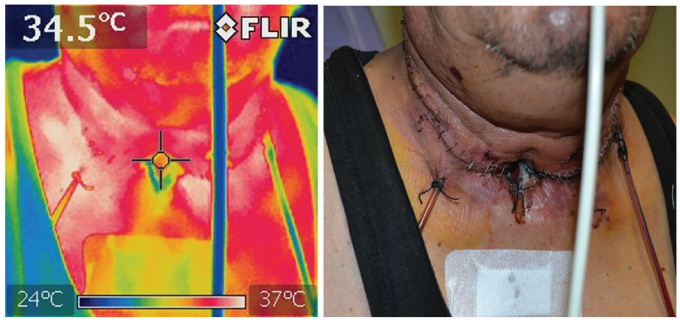

Figure 1. Clinical signs of venous congestion (figure right side). Compared to both the reference point and the mean temperature of the healthy flaps, this finding was associated with the overall lower temperature of this flap, as shown in (figure left side) a drop in temperature difference from 0.5 °C to-1.5 °C was revealed by thermal data

By measuring capillary refilling, turgor, swelling, flap color and/or pinprick examination, monitoring of free flaps can be achieved mainly by clinical observation. The analysis of these findings, however, is highly reliant on the medical staff's clinical expertise. In recent years, more technologically advanced techniques have been performed, such as implantable Doppler ultrasonography, minimally invasive tissue oxygen tension or non-invasive oxygen saturation via near-infrared spectroscopy. Since both advantages and disadvantages are provided by each of these procedures, there is a possibility that someone or something will improve. Therefore, during the first critical 72 h after flap shift, there is a constant search for improved monitoring systems[3,5].

One of the oldest techniques of postoperative monitoring is surface temperature analysis. This may be done either by putting a sensor directly on the skin or by using a contactless system to measure temperature. The purpose of our study was to determine the feasibility and potential of using a contactless method to monitor vascular failure detection in postoperative apron flap surveillance. Thermal imaging is an advanced scanning diagnostic device which measures the temperature by detecting infrared radiation from an object. Given that vascularization affects skin temperature, infrared thermography can also be used as reflection of the flow of cutaneous blood. The lack of radiation or intravenous contrast agents, readily accessible, relatively cheap, and also the fact that it is simple and easy to use, may be considered major advantages. It is even used as a mobile phone application today. It can also be used as an early warning sign of infection to evaluate subclinical inflammation[6,7].

As a method for monitoring postoperative flaps used for elderly advanced laryngeal cancer patients, we have successfully used Thermal imaging. Venous blocking lead to blood congestion, which can lead to a temporary temperature increase[8]. If the pressure increases and the congestion persists, the flow of blood will decrease and remain static gradually. This led to tissue deoxygenation, hydrostatic pressure increase, and fluid leakage into the interstitium. Increased interstitial pressure, namely, oedema will suppress arterial inflow, causing steady temperature decreases[7-11].

In our study, we took as reference healthy tissue around the flap at a stable room temperature of 25 °C. The majority of literature studies have indicated relating the mean flap temperature as a reference temperature to the adjacent skin. This will minimize the effects of environmental conditions that influence the temperature of the flaps, such as air flow or blanket coverage[9-13].

Study Limitations

The main limitation of this study that can be addressed and overcome in future research is the relatively limited sample size.

Conclusion

Infrared thermography could be a modern, feasible, and non-invasive method of monitoring flap subcutaneous vascularization. In particular, it appeared to be useful in identifying failed flaps from healthy flaps by comparing the measured flap temperature difference to an adjacent reference position. Combination with other modalities, may play an additional role in the non-invasive early detection of flap failure.

Ethics

Ethics Committee Approval: The study was performed in accordance with the ethical standards of the Institutional and National Research Committee and was approved by the Ethics Committee of University of Health Sciences Turkey, Antalya Training and Research Hospital (17th July 2020-protocol number 14/1).

Informed Consent: For this type of study informed consent is not required.

Authorship Contributions

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

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CASE REPORT / OLGU SUNUMU

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Concurrent Percutaneous Intervention for Simultaneous Acute Myocardial Infarction and Acute Bifurcated Graft Thrombosis of Lower Extremities

Akut Bacak İskemisi ve Akut Miyokard Enfarktüsü için Eş Zamanlı Perkütan Girişim

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Abstract

Acute limb ischemia (ALI) is a medical emergency associated with high morbidity, significant disability, and life-threatening complications. Acute myocardial infarction (AMI) with concurrent ALI is a challenging clinical condition associated with adverse events including mortality and requires immediate simultaneous reperfusion. We present the case of a patient with a history of bifurcated graft operation due to abdominal aortic aneurysm six years ago who presented with inferior ST-elevation AMI and acute bifurcated graft thrombosis of the lower extremities causing ALI. The patient was successfully treated with simultaneous percutaneous coronary and peripheral revascularization. We emphasize that AMI and ALI may occur simultaneously, and concurrent percutaneous revascularization can be a safe and feasible treatment strategy in such patients.

Keywords: Acute limb ischemia, acute myocardial infarction, percutaneous revascularization

Öz

Akut bacak iskemisi (ALI), yüksek morbidite, önemli sakatlık ve yaşamı tehdit eden komplikasyonlarla ilişkili tıbbi bir acil durumdur. Akut miyokard enfarktüsüne (AMI) eşlik eden eş zamanlı ALI ise yüksek morbidite ve ölüm ile ilişkili olan ve en kısa sürede eş zamanlı reperfüzyon gerektiren zorlu bir klinik durumdur. Biz bu olguda abdominal aort anevrizması nedeniyle bifürkasyon greft operasyonu öyküsü olan ve alt duvar AMI'ye eşlik eden ALI kliniği ile başvuran bir hastayı sunmayı amaçladık. Hasta eş zamanlı olarak perkütan koroner ve periferik revaskülarizasyon ile başarılı bir şekilde tedavi edildi. AMI ve ALI aynı anda ortaya çıkabilir ve bu gibi durumlarda eş zamanlı perkütan revaskülarizasyon güvenli ve uygulanabilir bir tedavi yöntemidir.

Anahtar Kelimeler: Akut bacak iskemisi, akut miyokard enfarktüsü, perkütan revaskülarizasyon

Introduction

Acute limb ischemia (ALI) is an emergent condition that threatens the viability and functionality of the extremities[1]. To improve ischemia and associated morbidity and mortality, prompt diagnosis and an early approach to this clinical entity is essential. ALI most commonly originates from an acute thrombotic occlusion or thromboembolism related to atrial fibrillation, left ventricle, heart valves, etc.[2]. Therapeutic options include endovascular or surgical interventions

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such as local thrombolysis, percutaneous thrombectomy, stenting, angioplasty, or bypass. ALI with concomitant acute myocardial infarction (AMI) is an uncommon presentation and rarely reported in the literature[3,4]. Herein, we present the case of a patient who presented with inferior ST-elevation AMI and acute split graft thrombosis of the lower extremities causing ALI that was successfully treated with simultaneous percutaneous coronary and peripheral revascularization.

Case Report

A 56-year-old male patient complaining of retrosternal chest pain that started 3 h ago, followed by sudden onset of pain, numbness, and coldness in the lower extremities, was admitted to the emergency department (ED). His anamnesis revealed a smoking history and bifurcated graft operation because of an abdominal aortic aneurysm six years ago. Initial evaluation of vital signs demonstrated a blood pressure of 80/50 mmHg and a heart rate of 96 beats per minute. Auscultation of the cardiovascular system demonstrated 2/6 systolic murmur at the apex. There were no arterial pulses in his right lower extremity, and the left lower extremity arterial pulses were diminished. Neurological evaluation of the lower extremities was consistent with bilateral sensory and motor loss and an accompanying dropped foot in the right lower extremity. The electrocardiogram obtained in the ED showed elevation of the ST segment in inferior leads and ST segment depression in reciprocal lateral leads. Bedside transthoracic echocardiography revealed inferior wall hypokinesis with no thrombus in the heart chambers. Creatinine kinase-MB and troponin T peaked at 312 U/L and >10.000 ng/mL, respectively. The patient was preloaded with acetylsalicylic acid and ticagrelor, and heparin was intravenously administered. The patient was then transferred to the catheterization laboratory for primary percutaneous coronary intervention (PCI) through the left radial route. Conventional peripheral angiography was also planned for evaluating ALI. Coronary angiography demonstrated subtotal thrombotic occlusion of the left circumflex (LCx) artery and plaque in the proximal left anterior descending artery (Figure 1A). An angiogram of the right coronary artery also noted a critical lesion in the proximal segment. Aortoiliac angiography demonstrated total occlusion of the right common iliac artery (CIA) and subtotal thrombotic occlusion of the left CIA (Figure 2A). Thus, consecutive intervention for LCx artery and bifurcated graft thrombosis was planned. Initially, a 3.0 18-mm Xience PRIME™ stent (Everolimus drug-eluting stent, Abbott, USA) was successfully deployed into LCx (Figure 1B). Percutaneous transluminal angioplasty (PTA) was planned for both CIA. A guidewire was advanced across the lesions in an antegrade manner, and balloon angioplasty of the right CIA was performed with a 6x200 mm balloon (EverCross™ 0.035 OTW PTA dilatation catheter, Medtronic, USA) (Figure 2B). Then, balloon angioplasty of the left CIA was performed with an 8.0x40 mm balloon (EverCross™ 0.035" OTW PTA dilatation catheter, Medtronic, USA) (Figure 2C). Control arteriography demonstrated reperfusion of both arteries (Figure 2D). Abciximab therapy was administered, and the patient tolerated the procedures well without any complications. The leg pain of the patient improved, and peripheral arterial pulses became palpable immediately after the procedure. During the intensive care unit follow-up, the patient maintained a stable hemodynamic state and remained asymptomatic. Five days after admission, he was discharged home with an ambulatory status. Ultrasonographic examination performed during the outpatient follow-up did not reveal any thrombus images in the aortic and iliac arteries. Furthermore, the hematological examination did not reveal any pathology. At the end of two years, he did not experience any vascular or coronary events. Written informed consent was obtained from the patient.

Discussion

There have been tremendous improvements in the interventional cardiology era in recent decades, and percutaneous interventions have been the mainstay of treatment in acute thrombotic occlusions. Thanks to these improvements, even complex cases can be successfully managed with percutaneous approaches in both coronary

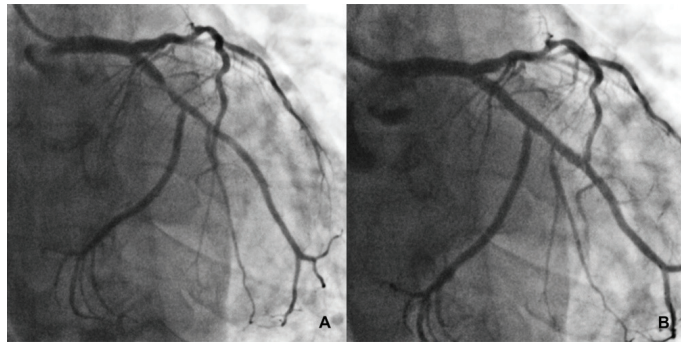

Figure 1. A. Coronary angiography of the patient demonstrating subtotal thrombotic occlusion of the left circumflex artery. **B.** Successful deployment of 3.0x18 mm Xience PRIME™ stent (Everolimus drug-eluting stent, Abbott, USA) resulting in TIMI-3 flow in the left circumflex artery

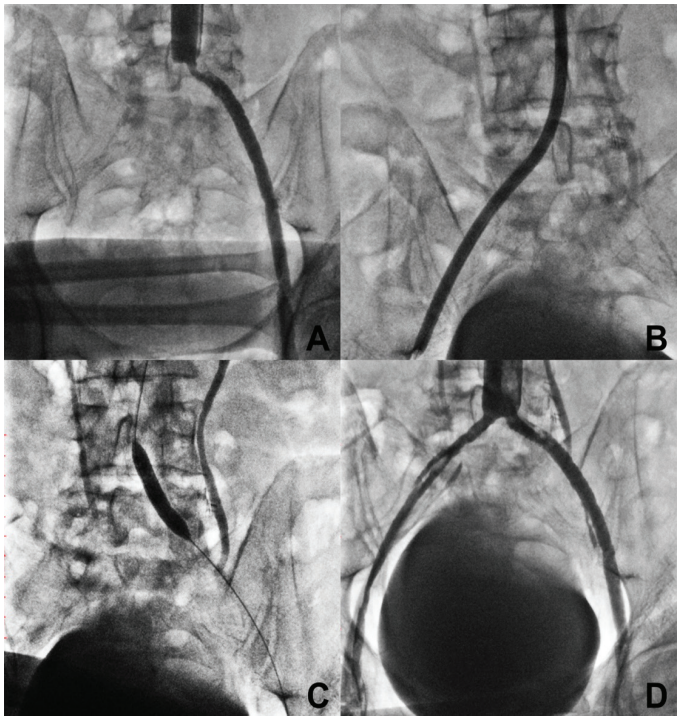

Figure 2. A. Aortoiliac angiography of the patient demonstrating occlusion of the proximal right common iliac artery (CIA) and subtotal thrombotic occlusion of the proximal left CIA. **B.** Balloon angioplasty of the occluded right CIA with a 6x200 mm balloon (EverCross™ 0.035" OTW PTA dilatation catheter, Medtronic, USA). **C.** Balloon angioplasty of the left CIA with an 8.0x40 mm balloon (EverCross™ 0.035" OTW PTA dilatation catheter, Medtronic, USA). **D.** Aortoiliac angiography after percutaneous angioplasty of the right and left CIAs

and peripheral arteries. To the best of our knowledge, this is the first case report in the literature presenting with simultaneous acute bifurcated graft thrombosis of the lower extremities and AMI successfully treated with percutaneous intervention in the same session.

ALI is a severe condition associated with high morbidity, significant disability, and life-threatening complications[1,5]. Thrombotic obstructions and emboli are the most common causes of ALI. Atrial fibrillation, ventricular thrombus after MI, and valvular heart disease are the most common causes of embolism. Thrombotic obstructions related to atherosclerotic progression and thrombosis *in situ* arising from hypotension, hypovolemia, hyperviscosity, acute plaque rupture, or malignancy are other causes of acute occlusion[2]. In contrast, simultaneous occurrence of AMI and ALI is an extremely rare and challenging clinical situation that may be associated with adverse events, including mortality[3,4,6]. In this case, the mechanism of bifurcated graft thrombosis of the lower extremities that causes ALI could be thrombosis *in situ* that could arise from hypotension following AMI. The patient initially described chest pain and then complained of sudden onset of pain in the bilateral lower extremities. In addition, his blood pressure was 80/50 mmHg at admission. Therefore, we hypothesized that the factor predisposing the patient to acute thrombosis in the bifurcated graft may be hypotension following AMI.

AMI with concurrent ALI is a challenging clinical condition that can be associated with high morbidity and mortality and requires simultaneous reperfusion as soon as possible. Although there are many therapeutic alternatives, such as hybrid surgery after PCI or local thrombolysis, we decided to treat the patient with simultaneous percutaneous revascularization by stenting LCx and subsequent angioplasty of the iliac arteries. It should be acknowledged that advances in interventional cardiology have led operators to consider percutaneous revascularization as the first-line therapeutic strategy when compared with other treatment approaches, even in complex and challenging cases such as ours.

In conclusion, AMI and acute bifurcated graft thrombosis of the lower extremities causing ALI might occur simultaneously, and concurrent percutaneous revascularization can be a safe and feasible treatment strategy in such patients.

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Ethics

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

Authorship Contributions

Surgical and Medical Practices: İ.E.Ç., S.Ö., M.D., S.N.M., Concept: İ.E.Ç., S.Ö., M.D., S.N.M., Design: İ.E.Ç., S.Ö., M.Y., M.D., S.N.M., Data Collection or Processing: İ.E.Ç., S.Ö., M.Y., M.D., S.N.M., Analysis or Interpretation: İ.E.Ç., S.Ö., M.Y., M.D., S.N.M., Literature Search: İ.E.Ç., S.Ö., M.Y., S.N.M., Writing: İ.E.Ç., S.Ö., M.Y., S.N.M.

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

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

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CASE REPORT / OLGU SUNUMU

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Siblings with Severe Neonatal ARDS: Immune Deficiency Versus COVID-19

Neonatal ARDS'li İki Kardeş: COVID-19 ve Şiddetli Kombine İmmün Yetmezlik

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Abstract

Neonatal acute respiratory distress syndrome (ARDS) is a relatively new diagnosis. Specific treatment, beyond managing the underlying disease, generally relies on lung protective ventilation strategies. Viral infections such as coronavirus-2 are associated with severe ARDS. Dysfunctions in innate immunity contribute to the loss of control over viral replication and inflammatory processes, inevitably leading to a more severe clinical presentation and poor outcomes. In this case report, we present the cases of two siblings diagnosed and managed as N-ARDS with severe combined immune deficiency related to adenosine deaminase deficiency. These cases highlight the challenges of managing neonatal ARDS and the severity of viral infections in patients with immune system disorders, underlining the impact of these conditions on clinical outcomes.

Keywords: Neonatal ARDS, COVID-19, ADA deficiency, SCID

Öz

Neonatal akut solunum sıkıntısı sendromu (ARDS), nispeten yeni bir tanıdır. Altta yatan hastalığın tedavisinden başka, özgül tedavi genellikle akciğer koruyucu ventilasyon stratejilerine dayanır. Şiddetli akut solunum sendromu koronavirüsü-2 gibi viral enfeksiyonlar, şiddetli ARDS ile ilişkilidir. Bağışıklık sisteminin etkilendiği durumlarda, viral replikasyon ve enflamatuvar süreçlerin kontrolü bozulur ve bu durum, kaçınılmaz olarak kötü sonuçlara yol açar. Bu çalışmada, adenosin deaminaz eksikliği ile ilişkili şiddetli kombin immün yetmezliği olan ve farklı viral enfeksiyonlar sebebi ile N-ARDS tanısı alan ve yönetilen iki kardeş olgusu sunulmuştur. Bu olgularda, neonatal ARDS'nin yönetimindeki zorlukları ve özellikle bağışıklık sistemi bozuklukları olan hastalarda viral enfeksiyonların şiddetini ve bu durumun klinik sonuçları üzerindeki etkilerini vurgulamaktadır.

Keywords: Yenidoğan ARDS, COVID-19, ADA eksikliği, SCID

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Introduction

Acute respiratory distress syndrome (ARDS) was first defined in 1967[1]. After 48 years, the pediatric acute lung injury consensus conference established the first specific definition for pediatric patients[2]. Neonatal ARDS (NARDS), which was first described by de Luca et al.[3], is a relatively new diagnosis compared with other types. Although different drugs and ventilation modalities for the treatment of ARDS have been tried over the years, there is no specific treatment other than the treatment of the underlying disease, and the treatment mostly relies on lung protective ventilation strategies and therapeutic agents to improve gas exchange. Various factors can trigger NARDS, such as pneumonia, sepsis, aspiration, and asphyxia. Viral infections such as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) are associated with severe ARDS. Innate immunity plays a key role in antiviral responses. Thus, dysfunction of innate immunity may also contribute to the loss of control of viral replication and hence the severity of viral infections[4]. Here we describe 2 siblings diagnosed and managed with NARDS. Further examination for underlying disease revealed adenosine deaminase (ADA) deficiency.

Case Reports

Case 1

A 24-day-old infant was referred to our emergency department with fever for 2 days and cough for a week. This 3150-gram female infant was born at 39 weeks of gestation to a 21-year-old gravida 4, para 2, and abortus 2 mother. The pregnancy was complicated by imminent abortus, and the mother had been using low-molecular-weight heparin (LMWH) since 20 weeks of gestation. Her initial examination revealed no respiratory distress, lymphopenia, slightly elevated C-reactive protein (CRP), and suspected right pericardial pneumonic infiltration on chest X-ray (Figure 1A). Her laboratory findings are summarized in Table 1. The patient was hospitalized and started antibiotic treatment. Her quick nasal swap RSV antigen test was negative. Polymerase chain reaction (PCR) of nasal swap was positive for human parainfluenza type 3 (HPIV-3). Because of the gradual increase in oxygen demand in the first week of her hospitalization and her inability to tolerate oxygen with a simple mask, she was taken to the intensive care unit and non-invasive mechanical ventilation (NIV) was applied. After being followed up on NIV for 1.5 days, the patient was

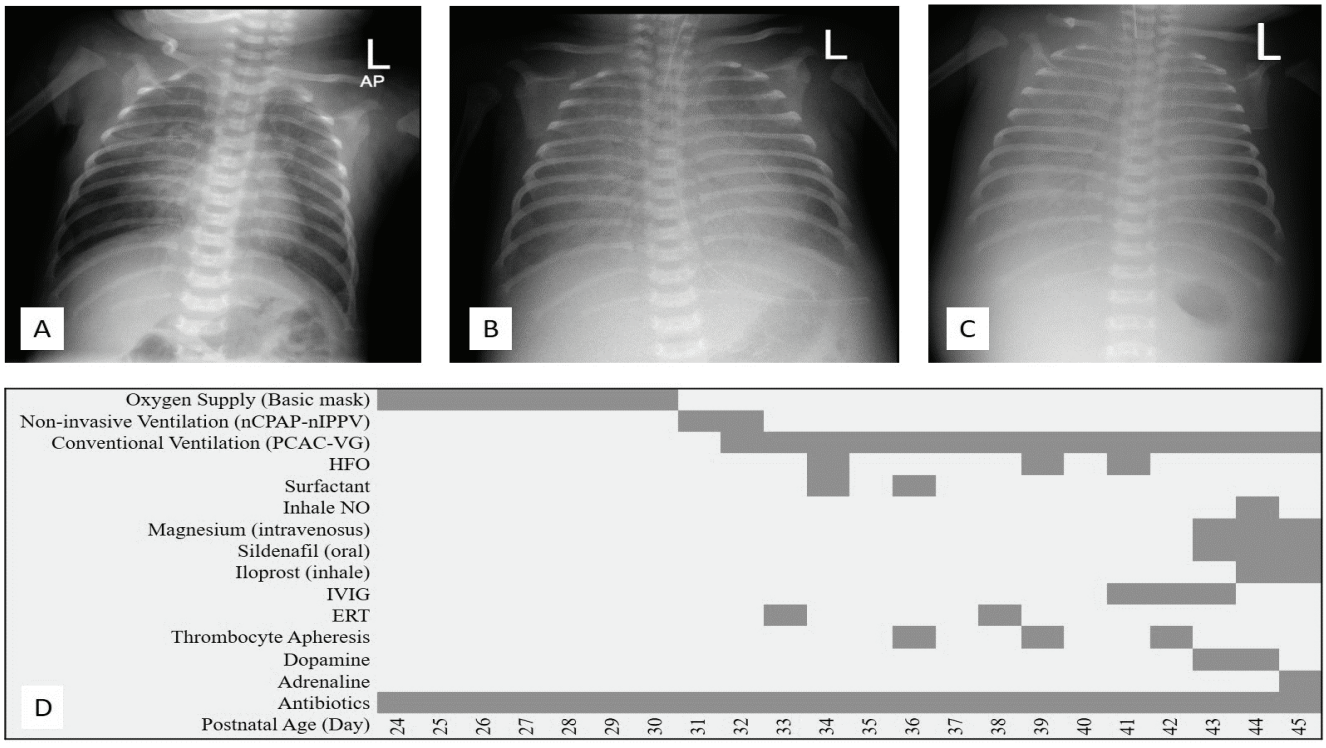

Figure 1. A: Initial chest X-ray of Case 1 (stars: cupping of costochondral junctions); **B:** Chest X-ray of case 1 at the time of NARDS diagnosis; C: Chest X-ray of case 1 on follow-up (arrow: squaring of the inferior scapular angle) **D:** Treatment regimen of case 1

Table 1. Laboratory results of cases 1 and 2

	Case 1			Case 2		
	Initial	At the time of ARDS diagnosis	Follow-up	Initial	At the time of ARDS diagnosis	Follow-up
WBC (10^3/uL)	3400	8800	6100	6300	7800	48900
LYM (10^3/uL)	400	400	100	3000	4500	800
Hb (g/dL)	13	11.3	11.2	13.5	12.1	12.7
PLT (10^3/uL)	258000	52.000	28.000	347.000	52.000	16.000
CRP (mg/L)	13.7	49	98.5	31.4	87.2	59
Cre (mg/dL)	0.18	0.07	0.33	0.17	0.22	1.05
ALT (U/L)	60	49	23	56	41	830
INR	1.1	1.3	1.18	1.2	1.23	3.64
pH/pCO_2/HCO_3 (--mm/Hg- mmol/L)	7.45/44/29	7.30/64/25.7	7.30/69/29	7.44/30.5/22	7.11/110/23.7	7.44/71.8/42.6
Oxygenation index	-	10	24	-	15	28
IgA/IgM/IgG (mg/dL)	32.9/20/328.1			<10/20/1357		
Respiratory tract PCR	Human parainfluenza type 3			SARS-CoV-2		

ARDS: Acute respiratory distress syndrome, WBC: White blood cell, CRP: C-reactive protein, PLT: Platelet count, PCR: Polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, Hb: Hemoglobin, ALT: Alanine transaminase, LYM: Lymphocytes, Cre: Creatinine, INR: International normalized ratio

intubated and followed for another 2 weeks. In this process, the patient, who was mostly followed on the pressure control-assist control-volume guarantee (PCAC-VG) mode, was also intermittently tried for high-frequency oscillatory ventilation (HFOV). On the 10th day of her stay (2nd day of intubation), she was diagnosed with ARDS based on clinical and laboratory findings (Figure 2B, C). Her echocardiography revealed only a secundum-type atrial septal defect. Bone marrow aspiration was applied to the patient because of lymphopenia at admission, hepatosplenomegaly, and thrombocytopenia that developed at the time of ARDS. While no hemophagocytic lymphohistiocytosis was observed in bone marrow examination, an increase in myeloid series and a marked decrease in lymphoid precursors were detected. Intravenous immunoglobulin (IVIG) treatment for two days, multiple surfactant treatment, inhaled nitric oxide (iNO), magnesium, sildenafil, inotropes, and iloprost were tried for the management of ARDS and clinical pulmonary hypertension (Figure 2D). During her hospitalization, various cultures obtained from the cerebrospinal fluid, blood, urine, and respiratory tract was negative. Extracorporeal membrane oxygenation (ECMO) was considered, but unfortunately the patient died 22nd day of hospitalization. Due to the declaration of autopsy and further evaluation by the family, the patient's diagnoses were not fulfilled.

Case 2

A 20-day-old infant (sibling of case 1) was referred to our emergency department because of apnea. This 3110-gram female infant was born at 38 weeks of gestation to a 28-year-old gravida 6, para 5, and abortus 2 mother. The patient, whose initial tests for apnea were performed during her observation in the emergency department, was followed up in the intensive care unit because she had recurrent apnea. Other than apnea, her physical examination was normal. Her complete blood count and biochemistry values were in the normal range except for lightly elevated CRP and transaminases (Table 1). Transfontanelle ultrasound and chest X-ray were normal (Figure 2A). Hence, at the time of hospitalization, the Coronavirus disease-2019 (COVID-19) pandemic was started and her nasal swap test was positive. On the 4th day, she needed NIV. Later that day, she developed acute worsening of oxygenation and was intubated, followed by HFOV plus volume guarantee (HFOV-VG). Chest X-ray revealed bilateral irregular diffuse opacity (Figure 2B, C). Echocardiography was normal. The patient met the criteria for neonatal ARDS related to COVID-19, including acute onset hypoxemic respiratory failure, diffuse bilateral lung opacification, absence of pulmonary edema due to cardiogenic disease, and an oxygenation index (OI) exceeding four. According to national/international COVID treatment

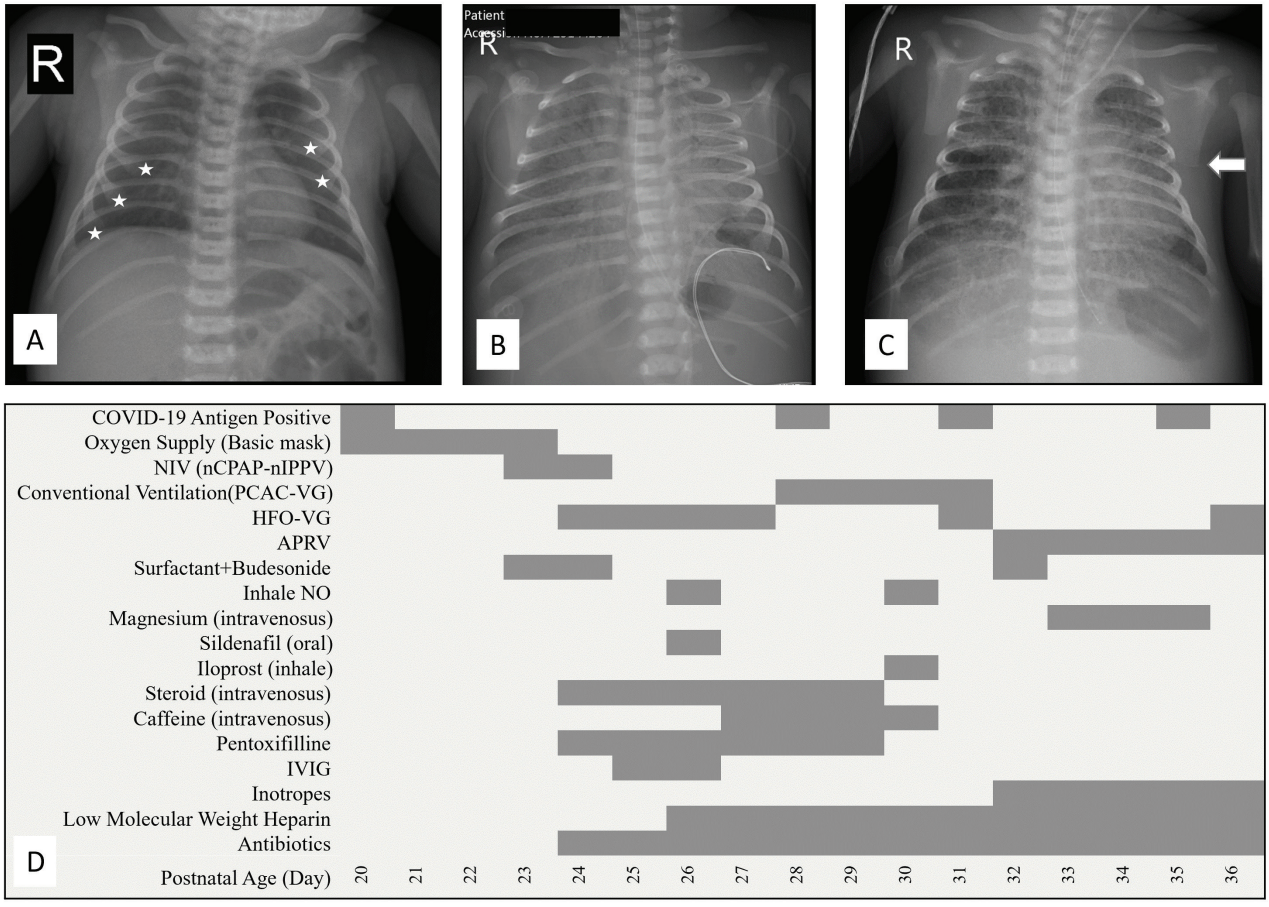

Figure 2. A: Initial chest X-ray of Case 2 (stars: cupping of costochondral junctions); B: Chest X-ray of case 2 at the time of NARDS diagnosis; C: Chest X-ray of case 2 on follow-up (arrow: squaring of the inferior scapular angle); D: Treatment regimen of case 2

COVID-19: Coronavirus disease-2019, IVIG: Intravenous immunoglobulin

regimens and case reports, steroids, low-molecular-weight heparin, antibiotics, budesonide+surfactant combination, caffeine, and pentoxifylline were administered (Figure 2D). With this exacerbation, the family history was questioned in more detail, and we learned that the case had a sibling who had experienced similar things (Case 1). Although lymphopenia was not detected in the complete blood count, the patient's lymphocyte panel could not be studied because of insufficient lymphocytes. The patient was referred to the immunology and hematology departments with a preliminary diagnosis of severe combined immunodeficiency (SCID) considering current information. While the tissue group analyses were sent from the relatives of the patient for bone marrow transplantation, genetic analysis was conducted in terms of immune deficiency from the patient. iNO, sildenafil, and iloprost treatments were tried because oxygenation got worse in HFOV-VG or PCAC-VG between 6th and 12th day. In her last 5 days, she was ventilated on airway pressure-release ventilation (APRV) mode, and blood gas analysis was normalized. After the preparations for ECMO treatment, she developed disseminated intravascular coagulation and multiple organ dysfunction syndrome (MODS) despite all supplementary treatment, and she died on 36th day of life. Her genetic analysis revealed a homozygous "c.956_960delAAGAG (p. E319Gfs*3) mutation in the *ADA* gene that consisted of ADA-deficient SCID.

Discussion

NARDS was first defined by de Luca et al.[3]. According to Montreux standards, five diagnostic criteria must be fulfilled: 1) acute onset of exacerbation; 2) dyspnea (r/o respiratory distress syndrome, transient tachypnea of the newborn, congenital malformations); 3) diffuse, bilateral, and irregular opacities or complete opacification of the lungs; 4) absence

of congenital heart disease explaining the edema; and 5) OI ≥4[3]. In the multicenter cohort study, which evaluated 239 newborns diagnosed with NARDS from 15 different neonatal intensive care units following this study, the prevalence was found to be 1.5%, while the most common etiology was sepsis, aspiration, and pneumonia[5].

In both our cases, all these criteria were met. The first case was diagnosed on the 10th day (50th day of life), and the second was diagnosed on 7th day (26th day of life) of hospitalization. In the first case, the agent that started the process was HPIV-3, whereas in the second case it was SARS-CoV-2. Both cases were previously healthy. Although parainfluenza virus is a much older and known virus than SARS-CoV-2, it usually manifests itself with self-limiting bronchiolitis in young children, but severe infections occur in immune compromised patients[6]. In a study by Roberts et al.[7], viral etiology was detected in 212 of 544 pediatric ARDS patients, and the most frequently detected viruses wererespiratory syncytial virus (RSV), human metapneumovirus (HMPV), adenovirus, and influenza. In a meta-analysis by Lukšić et al.[8] evaluating 56091 severe lower respiratory tract infections under 5 years of age, at least 1 virus was detected in 50.2% of patients aged 0-4 years, while the most common viruses were similar to those found in the study of Roberts et al.[7], parainfluenza was detected in only 2.4% of patients. There are a few cases of parainfluenza-related ARDS, but only two cases have been reported of HPIV-3-related ARDS; one of them is a healthy adult and the other is a 1-year-old patient with transient hypogammaglobulinemia[9,10]. On the other hand, since the beginning of the pandemic, SARS-CoV-2 has caused significant mortality and morbidity because of ARDS all over the world, especially in adults. While severe disease has been observed at very low rates in the childhood age group, in a study of 66 newborns, only 5% of the patients needed mechanical ventilation[11]. Similarly, in the review of Raschetti et al.[12], 176 SARS-CoV-2-positive newborn cases were evaluated, and 70% of them were found to be infected in the postpartum period. ARDS was not detected in any case, although respiratory findings were prominent in 52% of the cases[12]. After these publications, ARDS was reported in 5 neonatal cases, and only one of the patients died[13-17].

The first patient was hospitalized for follow-up with upper respiratory tract symptoms and remained quite stable in the first few days of hospitalization. She was diagnosed with moderate ARDS on the 10th day of hospitalization because of rapid deterioration and inability to provide ventilation and oxygenation despite intubation, high FiO_2 requirement, and an OI of 10. On chest X-ray, there were diffuse opacities and no condition to explain this in the echocardiography (Figure 1B, C). However, her sister, the second case, was diagnosed with moderate-to-severe ARDS on the 6th and 7th day of hospitalization with a more rapid worsening and a more severe clinic, with an OI of 15. Earlier worsening of the patient was considered consistent with the mean clinical worsening time in COVID-19-positive adult and pediatric cases[18,19].

Currently, there is no clear approach for medications and ventilation methods in the management of NARDS. Surfactant therapy is a common treatment for preterm newborns or neonates with secondary surfactant deficiency. Furthermore, the benefits of surfactant administration have been demonstrated even in adults, where SARS-CoV-2 has been shown to reduce surfactant production by damaging type 2 pneumocytes[20,21]. On the other hand, ARDS itself, with its inflammatory cascades, reduces the surfactant. Although recurrent surfactant applications were made with the diagnosis of NARDS in both of our cases, only short-term clinical benefit was achieved, as reported in other studies[13,14]. In our second case, surfactant was administered along with budesonide because cases of N-ARDS had previously benefited from this treatment[22]. Although no signs of pulmonary hypertension were detected in the echocardiographic examination of the patients, iNO treatment was tried once in the first case and twice in the second case as a rescue treatment to correct the ventilation perfusion imbalance; however, the treatment was not continued because of the lack of clinical response similar to other SARS-CoV-2 positive NARDS cases[13,14]. Similarly, magnesium, sildenafil, and iloprost treatments, which were thought to be beneficial, did not provide clinical improvement in patients. With regard to ventilation strategies, lower tidal volumes and higher positive end-expiratory pressure (PEEP) levels have been considered appropriate in ARDS management. In the first case in 2014, HFOV was only used three times for recruitment maneuver, she was mainly followed on PCAC-VG mode, and day after day her PEEP was getting higher starting from 6 to 15 cmH_2O. The second case was followed on HFOV mode; on the 3rd-4th day her PCO_2 levels were getting higher and she needed to be transferred into conventional ventilation (PCAC-VG). While in the HFOV-VG mode, oxygenation was better, ventilation deteriorated, and in the PCAC-VG mode, the opposite was the case. Although intermittent recruitment maneuvers were performed in both modes, there was only temporary well-being. Although the APRV mode has been a frequently preferred mode in

the acute lung injury of adult patients, especially with the COVID-19 pandemic, there are not enough studies on its use in the pediatric age group, especially in newborns[23]. In some animal experiments, neonatal case reports and case series, and pediatric randomized controlled trials, it has been shown that it can be used as a rescue mode for open lung strategy in patients[24-27]. Our patient was followed in the APRV mode for the last 5 days because she could not provide the appropriate conditions for ECMO and ventilation and oxygenation balance could not be achieved despite all other supportive treatments, together with the other two modes. In this process, the patient's blood gasses were observed at more normalized values compared with the other two modes.

Similar to the treatment of ARDS, there are no definite and clear recommendations for the treatment of SARS-CoV-2-infected children. For newborns, recommendations are based on case reports and adult studies. In a systematic review study of patients under the age of 1 with a diagnosis of COVID-19, conducted by Raba et al.[18], approximately half of the patients were treated with interferon, one-third with antibiotics, and only a few with steroids and immunoglobulin. Although the World Health Organization recommends steroid treatment for all COVID-19-infected patients, there is still no definite recommendation for children. Considering various guidelines and treatment protocols, the patient was treated with steroids, LMWH, and IVIG[27-29].

In a study by Peyneau et al.[4], COVID-19-positive patients had adaptive innate immune deficiency, which is associated with disease severity and prognosis because of the loss of control of viral replication. In the second case, lymphopenia was not detected in the first five hemograms of the patient. At the same time, although the patient's peripheral blood smear showed several normoblasts, lymphocytes were considered present. Upon the sudden deterioration in the general condition of the patient, a more detailed anamnesis was performed on the relatives of the patient, and the findings of her deceased sibling were examined in detail. Lymphocyte panel analysis was requested, and lymphopenia was found in the patient. The patient's previous normal lymphocyte values were attributed to the counter counting normoblasts as lymphocytes. The repeated COVID-19 polymerase chain reaction test results were positive in the samples taken intermittently during hospitalization. When the chest radiographs of the patient were evaluated retrospectively, it was seen that there was no thymus shadow and the presence of squaring of the inferior scapular angle and cupping of costochondral junctions (Figure 1 and 2: Arrows and stars) also supported ADA-SCID[30]. Early diagnosis of ADA-SCID and initiation of treatment is essential; otherwise, it is a fatal condition. Therefore, in many countries, unfortunately in our country, SCID is slowly being integrated into the neonatal screening program. ADA-deficient SCID is characterized by severe lymphocytopenia affecting T-and B-lymphocytes and NK cells; however, because of the ubiquitous nature of the enzyme, non-immunological manifestations are also observed, including neurodevelopmental deficits, sensorineural deafness, and skeletal abnormalities[31]. due to severe deterioration of cellular and humoral immunity, ADA deficiency typically manifests early in life with severe infections and failure to thrive, and affected individuals normally die in the first or second year of life without treatment. Early definitive therapy with hematopoietic stem cell transplantation results in a good overall outcome[31].

Conclusion

Neonatal ARDS is a fairly new diagnosis; regardless of the cause, its management is very difficult and there are no definitive guidelines. However, in case of severe clinical manifestation with atypical organisms or unexpected clinical manifestations with known organisms, detailed re-evaluation of the patient and his/her history are of vital importance, especially in countries where immune deficiencies are not screened in the newborn screening program.

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Ethics

Informed Consent: Informed consent was obtained from the parents of the infants included in this report.

Authorship Contributions

Surgical and Medical Practices: C.A., T.Ü.E., Ca.A., F.E., N.D., Design: C.A., Data Collection or Processing: C.A., T.Ü.E., Ca.A., Analysis or Interpretation: C.A., T.Ü.E., Ca.A., F.E., N.D., Literature Search: C.A., S.A., Su.A., H.Ö., Writing: C.A., F.E., N.D., H.Ö.

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CASE REPORT / OLGU SUNUMU

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Cor Triatriatum Sinister Associated with Partial Anomalous Pulmonary Venous Return Mimicking Total Anomalous Pulmonary Venous Connection

Total Anormal Pulmoner Venöz Dönüş Anomalisini Taklit Eden Parsiyel Anormal Pulmoner Venöz Dönüş ve Cor Triatriatum Sinister

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Abstract

One year old patient was referred to our clinic with the diagnosis of total anomalous venous connection. Despite tachycardia and pulmonary plethora, the patient was acyanotic and the transthoracic echocardiography detected pulmonary venous baffle or vertical vein. Considering these doubtful findings, computed tomography angiography was performed and revealed that right pulmonary veins was draining towards an enlarged vena cava superior while right pulmonary veins into the left atrium. Furthermore, a fibrotic tissue that encurtains the mitral orifice was observed. Consequently, the patient underwent surgery with the diagnoses of cor triatriatum sinistrum and partial anomalous pulmonary connection. The exact diagnosis was confirmed after a profound surgical inspection; afterwards, then the whole process was accomplished smoothly and the patient discharged in good condition.

Keywords: Cor triatriatum sinistrum, partial anomalous pulmonary venous return, total anomalous pulmonary venous connection

Öz

Bir yaşındaki hasta total anormal venöz dönüş ön tanısıyla kliniğimize yönlendirildi. Taşikardi ve pulmoner konjesyona rağmen hasta asiyanotikti ve transtorasik ekokardiyografide pulmoner venöz kese veya vertikal ven saptanmadı. Bu şüpheli bulgular göz önünde bulundurularak yapılan bilgisayarlı tomografi anjiyografide sağ pulmoner venlerin genişlemiş vena kava superiora, sol pulmoner venlerin ise sol atriyuma boşaldığı görüldü. Ayrıca mitral kapağı çevreleyen fibrotik zar da gözlendi. Bunun üzerine hasta kor triatriatum sinister ve parsiyel anormal pulmoner dönüş tanılarıyla ameliyata alındı. Kesin tanı, kapsamlı bir cerrahi incelemenin ardından doğrulandı; sonrasında tüm süreç sorunsuz bir şekilde tamamlandı ve hasta sağlıklı bir şekilde taburcu edildi.

Anahtar Kelimeler: Cor triatriatum sinistrum, parsiyel anormal pulmoner venöz dönüş, total anormal pulmoner venöz dönüş

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Introduction

Cor triatriatum sinister (CTS) is identified as an anatomical division of the left atrium by a fibromuscular membrane that separates the pulmonary venous drainage from the mitral valve orifice. Various theories have been assessed to determine the reason for CTS such as fault in mal-septation, mal-incorporation, or entrapment during cardiac development so far. Nevertheless, the underlying embryological mechanism is yet unclear and remains controversial. A similar mechanism also cause pulmonary venous connection anomalies if pulmonary venous drainage is interrupted at earlier gestational age in reference to CTS[1]. Consequently, a combination of CTS and partial anomalous pulmonary venous return (PAPVR) or total anomalous pulmonary venous connection (TAPVC) are not exceptional. On the other hand, manifestations and severity of symptoms among patients considerably vary, thus often lead to misdiagnosis. Such patients, therefore, require further examination to conclude the optimal surgery type and operative timing.

Herein, we present a patient who was referred to our clinic as late-diagnosed TAPVC and subsequently got definitive diagnosis as CTS and PAPVR peroperatively.

Case Report

One year old boy weighing 8.8 kg's was referred to our clinic with the diagnosis of TAPVC. Dyspnea and tachycardia were determined in the physical examination, however, there was no cyanosis ($SATO_2$ 98%). The heartbeat was 132 bpm and the rhythm was sinus. The chest graphy was not significant except for pulmonary plethora. The transthoracic echocardiography (TTE) performed in our center revealed doubtful findings. No pulmonary venous baffle and atrial septal defect (ASD) were detected. Enlarged right atrium, vena cava superior (VCS), and an apparent azygous vein were observed; and increased pulmonary venous blood pressure was measured. Considering the suspicious diagnosis and questionable TTE examinations, computed tomography (CT) angiography was performed to define the precise anatomy.

CT angiography demonstrated that the right pulmonary veins drains towards the enlarged VCS whilst the left pulmonary veins towards the left atrium. Moreover, a cavernous obstructive fibrous tissue was observed in the left atrium that hindering the pulmonary venous flow towards the mitral orifice (Figure 1A, B). However, there was no apparent vertical vein in CT as well as in the TTE images.

Consequently, the certain diagnosis was established as CTS, PAPVR with intact interatrial septum. Then, considering the current hemodynamic situation, the patient underwent urgent surgery. The mediastinal access was achieved thru midline sternotomy. Following bi-caval cannulation, the cardiopulmonary bypass was initated. The diameter of VCS was significantly enlarged and a right upper pulmonary vein adjacent to VCS was observed, however, no pulmonary

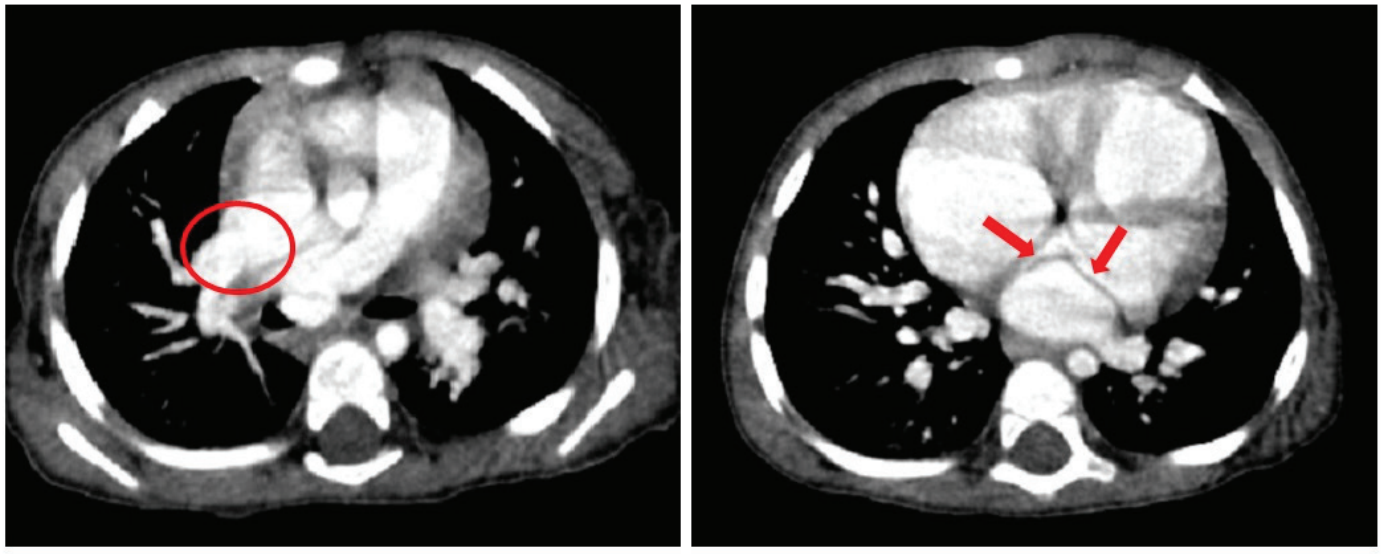

Figure 1. A, B. In the red circle right upper pulmonary vein and the superior vena cava connection is being shown. Red arrows marking the C shaped image of the fibrous membrane separating the pulmonary veins from the rest of the left atrium

venous baffle detected when the apex was removed. After cardioplegia administration and right atriotomy incision, the cardiac anatomy was precisely identified. CTS and right PAPVD and small secundum ASD were diagnosed by profound inspection (Figure 2). After septectomy, an occlusive fibrous membrane that encurtains the mitral valve was observed then resected. Afterwards the septectomy was closed via ePTFE graft with continuous stitches so as to reroute the right upper pulmonary venous flow into the left atrium. The whole surgical process was accomplished smoothly.

Afterward, the patient was transferred to the intensive care unit with negligible inotrope support and readily extubated at the sixth postoperative hour. However, pulmonary arterial hypertension led to prolonged non-invasive mechanical support and sildenafil 1 mg/kg/day was initiated. After the recovery period, the patient was transferred to ward on the POD 7 and then discharged on POD 13 in good condition with the daily medication of acetylsalicylic acid (5 mg/kg) and sildenafil (1 mg/kg).

The control TTE examination on the first month of follow-up was uneventful. The sildenafil treatment was gradually rarefied, then terminated in the control examinations.

Discussion

The development of the CTS begins with the appearance of the primitive pulmonary vein as an outpouching from the left atrium, subsequently connects with the primitive pulmonary venous plexus. Then, the common pulmonary baffle is incorporated into the posterior left atrium, and the connection between the pulmonary venous plexus and other venous systems gradually peters out. In the lack of complete partitioning CTS occurs.

Depending on the gestational age at the interruption in the usual embryogenesis, various connections between the atrial chamber and the cardinal venous system may develop. For instance, early atresia in the common pulmonary vein results in TAPVC by canalizing the drainage through either the umbilicovitelline or cardinal venous system[2]. Although both CTS and PAPVR or TAPVC share the same hypothetical mechanism simultaneous cases are virtually rare.

The majority of CTS cases remain asymptomatic, however coexisting cardiac defects lead to various clinical manifestations and may be cloud certain diagnoses.

In occasional cases, CTS and TAPVC can be diagnosed by saline contrast echocardiography[3]. However, CT angiography mostly aids to determine certain diagnoses. However, challenging cases may require cardiac catheterization for confirmation[3].

Although no vertical vein and ASD was observed and the patient was acyanotic; in the misguidance of TTE, our case was suspected of TAPVC. Hence, absolute exclusion of the CTS and associated intracardiac TAPVC was not possible. In a similar case, Kwak et al.[4] highlight the importance and guidance of preoperative evaluation of the CT images.

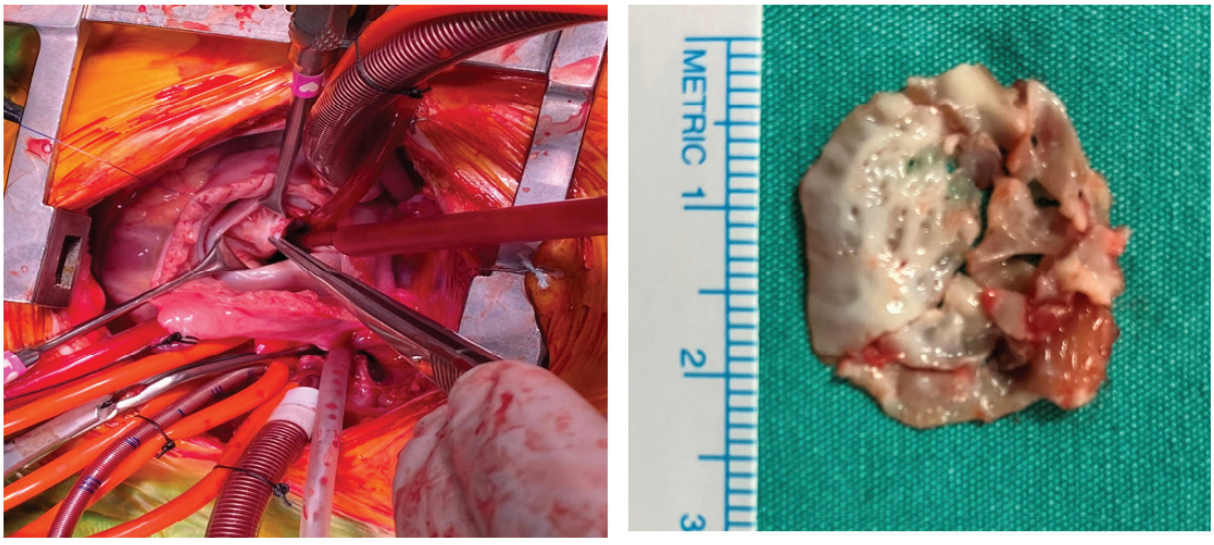

Figure 2. The surgical view through left atrial incision. The fibrous obstructive tissue in front of the mitral valve is visualized

Beyond that, CTS and PAPVD may develop rapid cardiogenic shock, especially in the presence of restrictive ASD. Such patients warrant immediate treatment. For instance, Schiller et al.[5] prefer staged surgery in cardiogenic shock in infancy. Firstly, they maintained the ECMO support to establish hemodynamic stabilization. During this delay, catheterization was performed to confirm the diagnosis. Similarly, Moscoso et al.[6] highlight that even the detailed anatomy and the exact diagnosis are highly required prior to the operation; nevertheless, in case of urgency, the confirmation of the diagnosis awaits the perioperative findings. For these reasons, the authors recommend a profound inspection and a careful anatomical analysis during surgery.

In conclusion, we state that CTS and PAPVD cases often manifest with severe symptoms and may easily be misdiagnosed with TAPVC. However, in experienced hands, CT angiography provides useful findings as becomes as sufficient as TTE images. Nevertheless, if urgent surgery is required in the lack of adequate sufficient time to determine the exact diagnosis, precautions must be taken and current anatomy should be inspected profoundly during surgery.

Ethics

Informed Consent: A written informed consent was obtained from both parents of the patient.

Authorship Contributions

Surgical and Medical Practices: G.A., M.Ç., M.A., O.I., Concept: G.A., Design: G.A., O.I., Data Collection or Processing: G.A., Analysis or Interpretation: M.A., O.I., Literature Search: M.Ç., M.A., Writing: G.A., O.I.

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CASE REPORT / OLGU SUNUMU

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Prostate Cancer Metastasis to the Occipital Bone Detected on Prostate-specific Membrane Antigen Imaging: A Case Report

Prostat Spesifik Membran Antijen Görüntülemede Tespit Edilen Prostat Kanserinin Oksipital Kemiğe Metastazı: Bir Olgu Sunumu

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Abstract

Prostate cancer metastasizes most commonly to the pelvic lymph nodes and to the axial skeleton. Metastatic spread of prostate adenocarcinoma to the occipital bone is very rare. ^{68}Ga-labelled prostate-specific membrane antigen position emission tomography/computed tomography (PSMA PET/CT) scanning has been shown to be more sensitive than conventional imaging techniques in patients with prostate cancer. ^{68}Ga-PSMA PET/CT scans detect previously unsuspected disease and may influence planned clinical management in a high proportion of patients with prostate cancer. Our intention is to emphasize the role of the ^{68}Ga-PSMA PET/CT where prostate cancer metastasis cannot be demonstrated by conventional imaging methods and thus contributes to the treatment choice.

Keywords: Prostate cancer, PSMA PET, occipital bone, metastasis, diagnosis

Öz

Prostat kanseri en yaygın olarak pelvik lenf nodlarına ve aksiyal iskelete metastaz yapar. Prostat adenokarsinomunun oksipital kemiğe metastatik yayılımı çok nadirdir. ^{68}Ga işaretli prostat spesifik membran antijen pozisyonu emisyon tomografisi/bilgisayarlı tomografi (PSMA PET/BT) taramasının, prostat kanserli hastalarda konvansiyonel görüntüleme tekniklerinden daha duyarlı olduğu gösterilmiştir. ^{68}Ga-PSMA PET/BT taramaları önceden şüphelenilmeyen hastalıkları saptar ve prostat kanserli hastaların büyük bir kısmında planlanan klinik yönetimi etkileyebilir. Amacımız, prostat kanseri metastazının konvansiyonel görüntüleme yöntemleriyle gösterilemediği durumlarda ^{68}Ga-PSMA PET/BT'nin rolünü vurgulamak ve böylece tedavi seçimine katkıda bulunmaktır.

Anahtar Kelimeler: Prostat kanseri, PSMA PET, oksipital kemik, metastaz, tanı

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Introduction

Prostate cancers (PCa) possess the property to metastasize to the bone frequently and these metastases appear particularly in the axial skeletal system[1]. Although rarely, these metastases may be seen in unusual bones such as the extracranial skull[2]. Skull metastases most commonly originate from PCa in males and PCas constitute 12-18% of these metastases[3].

^{68}Ga-labelled prostate-specific membrane antigen position emission tomography/computed tomography (PSMA PET/CT) has been a commonly used imaging method in the recent years for determining primary PCa stage and scanning for metastasis in cases of recurrence following definitive treatment of PCa. It is a more sensitive method that is particularly advantageous for individuals under high risk of metastasis when lymphadenopathy (LAP) and bone metastasis associated with PCa cannot be demonstrated by conventional imaging methods[4,5]. This case report aims to present a case who successively underwent Transrectal ultrasound guided biopsy (TRUSG-Bx) due to high serum prostate specific antigen (PSA) levels, received a diagnosis of PCa, presented no metastasis in conventional imaging methods during staging, but in the ^{68}Ga-PSMA PET/CT scan, manifested metastasis in the occipital bone without involvement of the axial skeletal system.

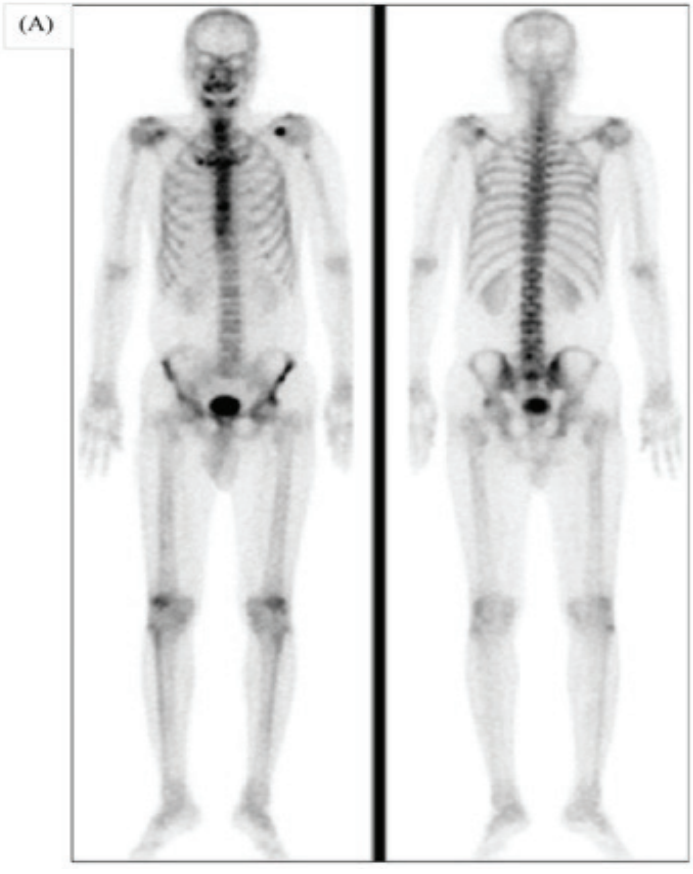

Figure 1. ^{99mTc}-Bone scan findings at diagnosis (A) no findings of bone metastasis

Case Report

Seventy-five-year-old male patient presented to our polyclinic due to symptoms associated with the lower urinary system that had persisted for approximately a year. The patient had a serum PSA level of 98 µg/L, a creatinine level of 4.2 mg/dL and a glomerular filtration ratio (GFR) of 32 mg/dL. His prostate gland was found to be irregularly large and fixed to the surrounding tissue in the rectal examination. The patient underwent 10-quadrant TRUSG-Bx. Biopsy result indicated a prostatic adenocarcinoma, ISUP grade group 5, in situ ductal carcinoma, and a Gleason score 5+4=9. A multiparametric magnetic resonance imaging scan had been planned for the purpose of staging but an abdominopelvic CT was performed instead due to low GFR value. The abdominopelvic CT scan presented bilateral grade 3-4 hydroureteronephrosis, conglomerate LAP in the right obturator region and a prostate gland indenting the bladder. ^{99mTc}-Bone scan presented no findings of bone metastasis (Figure 1). While the ^{68}Ga-PSMA PET/CT scan of the patient showed no metastasis in the axial skeletal system, a 20x10 mm extracranial metastasis was identified on the right side of the occipital bone (SUV_{max}: 21.1), right obturator, left supraclavicular and left axillary areas demonstrated LAP, consistent with metastasis (Figure 2 A-D). In addition, right obturator, left supraclavicular, and left axillary areas demonstrated LAP, consistent with metastasis. The patient sustained no pain due to occipital bone metastasis and presented no neurological findings as metastasis was extracranial. Bilateral nephrostomy was performed and following nephrostomy, the serum creatinine level of the patient regressed to 1.2 mg/dL.

The patient was diagnosed with oligometastatic hormone-sensitive PCa. The patient was treated with subcutaneous luteinizing hormone releasing hormone (LHRH) agonist goserelin and 6 cycles of chemotherapy with docetaxel in addition to LHRH. No toxicity was observed. At 6 months follow-up, his PSA and testosterone were found to have decreased to 0.46 µg/L and 8.3 ng/dL (normal reference 175-781 ng/dL), respectively.

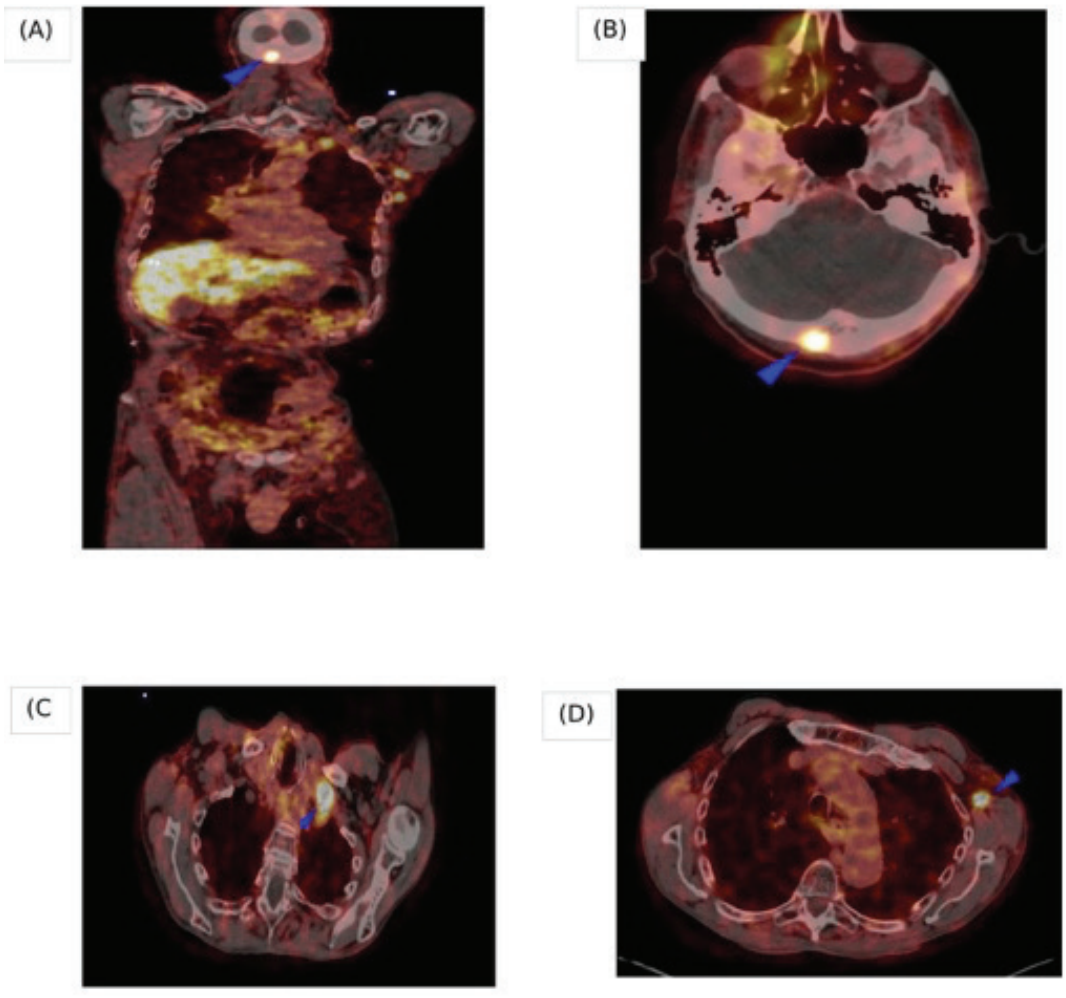

Figure 2. (A) Coronal fusion ^{68}Ga-PSMA PET/CT and (B) transaxial fusion PET/CT showed increased metabolic activity (SUV_{max}: 21.1) on the right side of the occipital bone (arrows), (C) on the left supraclavicular and (D) left axillary areas (arrows) (SUV_{max}: 13)

PSMA PET/CT: Prostate-specific membrane antigen position emission tomography/computed tomography

Discussion

This case report has presented a case diagnosed with PCa who did not present any bone metastasis in conventional imaging methods but, for the first time in the literature, manifested extracranial metastasis in the occipital bone without involvement of the axial skeletal system in a ^{68}Ga-PSMA PET/CT scan. According to the literature, extracranial skull metastases most commonly originate from breast and lung cancers, whereas in males, they most commonly originate from PCa[1]. These metastases may be extra or intracranial. While intracranial metastases may be symptomatic due to the involvement of dural sinus and cranial nerves, extracranial skull metastases are usually asymptomatic as observed in our case[6].

^{68}Ga-PSMA PET/CT is an important method for the diagnosis of lymph node metastasis in PCa. With this method, the mean LAP size that allows a diagnosis of PCa metastasis is 13.1±7.7 mm[7]. Also, a multi-center prospective study conducted with ^{68}Ga-PSMA PET/CT determined some patients who had manifested no metastasis in conventional methods during PCa staging to have oligometastatic PCa. Moreover, the study detected more wide spread polymetastatic diseases in 20% of metastatic PCa patients[4]. Similarly, abdominopelvic CT and ^{99mTc}-Bone scans failed to detect metastasis in our

patient in spite of high PSA levels and a high Gleason score in TRUSG-Bx. Consequently, a ^{68}Ga-PSMA PET/CT was performed and this imaging method demonstrated high SUV in the obturator, supraclavicular, axillary regions and the occipital bone of the patient. The patient was diagnosed with oligometastatic PCa instead of non metastatic PCa and the treatment choice was therefore changed.

Occipital bone is a rare site for prostate cancer metastasis. ^{68}Ga-PSMA PET/CT is a useful method for detecting metastasis in cases where PCa metastasis cannot be demonstrated by conventional imaging methods and thus contributes to the treatment choice. This demonstrates the potential clinical value of ^{68}Ga-PSMA PET/CT in the management of prostate cancer.

Ethics

Informed Consent: Written informed consent form was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: M.Y.Y., E.K., Concept: E.K., Y.Ö.İ., Design: C.Y., Data Collection or Processing: U.M., Analysis or Interpretation: M.Y.Y., C.Y., Literature Search: M.Y.Y., E.K., Writing: M.Y.Y., E.K.

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