Ahi Evran Medical Journal

Ahi Evran Tıp Dergisi

Year/Yıl:2025 Volume/Cilt: 9 Issue/Sayı:1

Ahi Evran Medical Journal

Year: 2025 Volume: 9 Issue: 1
e-ISSN: : 2619-9203

Ahi Evran Medical journal is indexed in ULAKBIM, TRdizin, DOAJ, Index Copernicus Master List, EBSCO, Türk Medline, Türkiye Atıf Dizini (Turkiye Citation Index)

AHİ EVRAN MEDİCAL JOURNAL 2025;9(1)

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AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Could Parental Vaccine Hesitancy in Childhood Immunization Programs Increase After COVID-19 Vaccines?

COVID-19 Aşılarından Sonra Çocukluk Çağı Bağışıklama Programlarında Ebeveynlerin Aşı Tereddütleri Artabilir mi?

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Received: 18.08.2024; Accepted: 09.09.2024

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How to cite: Demirtaş MD. Could parental vaccine hesitancy in childhood immunization programs increase after COVID-19 vaccines? Ahi Evran Med J. 2025;9(1):1-2. DOI: 10.46332/aemj.1535229

Dear Editor,

This article evaluates the vaccine hesitancy among parents, which was also highlighted in the article titled "Covid-19 Vaccine Acceptance Among Parents: Are They Willing to Vaccinate Their Children?", which was published in your journal and was our starting point.[1] Vaccine hesitancy, defined as the postponement or refusal of vaccination despite the possibility of vaccination, differs from vaccine refusal, which is not vaccination at all. Vaccine hesitancy has become a focus of increasing concern due to its potential to lead to delays in vaccination, vaccine refusals and to jeopardize the public health outcomes of vaccine-preventable disease outbreaks.[2,3] Vaccine hesitancy is an important issue affecting public health that can be influenced by many factors such as confidence, social media interaction and convenience. Given that vaccine hesitancy is often specific to certain subgroups and not generalized across populations, it is important to understand which groups are hesitant to vaccinate, what their concerns are, which of a variety of possible reasons may be contributing to their hesitancy, and where the people who are hesitant are located, i.e. the geographical, sociocultural or political microenvironment that may lead to hesitancy.[1,2] The anti-vaccination movement and the vaccine hesitancy that is being spread throughout society started almost as soon as vaccination itself. While these movements can have a beneficial effect on developing and publicizing the safety of vaccines, they can also have a negative impact on parents.[4]

The emergence of the COVID-19 pandemic has affected vaccine undecideds, especially the discussions on mRNA vaccines and vaccines developed rapidly due to the emergency situation. These debates and inaccurate information have increased the ambivalence of parents towards the childhood immunisation program, and this seems to be a situation that will interrupt the childhood vaccination program. With the decrease in childhood immunizations, diseases such as measles, tetanus and polio will appear and spread. Therefore, necessary precautions need to be taken. In this context physicians, especially pediatricians, have an important role to play in ensuring that parents understand the importance of vaccination and vaccine-preventable diseases. In addition to being the most important determinant of vaccine acceptance, the advice given by physicians to families also plays a role in eliminating vaccine hesitancy.[3,5,6]

Health professionals in the field of child health should promote immunization, and to do this effectively, they should devote sufficient time to each family and provide infor-

mation based on scientific data on questions and hesitations about vaccination. This information should be presented in a way that recognizes that the main concern of families is the health and safety of the child. Vaccine hesitancy should be taken seriously, not only by pediatricians and other health professionals, but also by governments and health policy makers. Governments, relevant public institutions and NGOs need to take an active role in informing the public about childhood immunization, and in setting/implementing policies to reduce and prevent risks associated with vaccine hesitancy. Removing false and inaccurate information about vaccination from social media and the internet can be achieved through collaboration between governments, the technology sector, health professionals and civil society organizations.[4,7]

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Changes in Polarity and Regeneration-Related Gene Expression in In Vitro Bone Marrow Mesenchymal Stem Cells in a Rheumatoid Arthritis Injury Model and Pharmacological Modulation

Romatoid Artrit Yaralanma Modelinde In Vitro Kemik İliği Mezenkimal Kök Hücrelerinde Polarite ve Rejenerasyonla İlişkili Gen İfadesindeki Değişiklikler ve Farmakolojik Modülasyonu

Muhammet OCAK[1]

ÖZ

Amaç: Bu çalışmanın hedefi patogenez basamakları iyi anlaşılmış kronik, inflamasyon sebebiyle dokusal erozyonun sonucunda oluşan Romatoid Artirit (RA) hastalığının farmakolojik modülasyon ile gen-protein düzeyinde polarite ve rejenerasyondaki değişimleri incelenmiştir.
Araçlar ve Yöntem: Hastalığın patogenez basamaklarının hücre içi polarite ve rejenerasyona verdiği zararı araştırabilmek için Il-1β ve IL-6 ile hasar taklidi yapılmış kemik iliği mezenkimal kök hücrelerinde IL-1β antagonist antikoru canakinumab ve IL-6 antagonist antikoru tocilizumab kombinasyon halinde uygulanmasının hücre canlılığı, sitotoksisite ve hücre içi polarite ve rejenerasyon ile ilgili genlerin ifadesi incelenmiştir.
Bulgular: Analizler sonucunda IL-1β ve IL-6 beklendiği üzere RA hasar taklidi yapılan insan kemik iliği kök hücrelerinde canlılığının azalmasına sitotoksisitenin aynı oranda artmasına sebep olmuştur. Bunun yanında gen ifade analizlerinde polarite yolaklarında görevli genlerin ifadelenmesinde düşük oranda anlamlı değişiklik görülmüş ancak rejenerasyon ile ilgili genlerin ifadelenmelerinde anlamlı değişikliklere rastlanmıştır. Bunun yanında antagonist ajanların uygulanması bu durumu tersine çevirmiş sınırlı seviyede normalleşme hatta hücrelerin canlılık testlerinde canlılığı artıran değişimler gözlemlenmiştir.
Sonuç: Bu durumda hasar taklidi sonrası elde edilen RA benzeri patogenez modelinde hastalığın gelişim basamaklarında gerçekleşen inflamasyonun etkisiyle kök hücrelerin adherasyon, yön bulma, gibi özelliklerini kaybetmeleri, korudukları rejenerasyon özellik verimliliğini etkilemekte olduğu düşünülmüştür.

Anahtar Kelimeler: artrit; ınterlökin; kemik iliği mezenkimal kök hücresi; monoklonal antikor

ABSTRACT

Purpose: The aim of this study was to investigate the changes in polarity and regeneration at the gene-protein level with pharmacological modulation of rheumatoid arthritis (RA) disease, which occurs as a result of chronic, inflammation-induced tissue erosion whose pathogenesis steps are well understood.
Materials and Methods: To investigate the damage caused by the pathogenetic steps of the disease to intracellular polarity and regeneration, bone marrow mesenchymal stem cells subjected to injury mimicry using IL-1β and IL-6 were treated with a combination of the IL-1β antagonist antibody canakinumab and the IL-6 antagonist antibody tocilizumab. The effects on cell viability, cytotoxicity, and the expression of genes related to intracellular polarity and regeneration were examined.
Results: As a result of the analyses, as expected, IL-1β and IL-6 caused a reduction in viability and an acceleration in cytotoxicity in human bone marrow stem cells imitating RA damage. In addition, in gene expression analyses, low significant changes were observed in the expression of genes consisted in polarity pathways, but significant changes were found in the expression of genes take place in regeneration mechanisms. In addition, the application of antagonist agents reversed this situation and limited normalization and even changes that increased the viability of the cells in viability tests were observed.
Conclusion: In this case, in the RA-like pathogenesis model obtained after injury mimicry, it is thought that the inflammation occurring during the disease's developmental stages causes stem cells to lose their properties such as adhesion and navigation, thereby affecting the efficiency of the regenerative properties they maintain.

Keywords: arthritis; bone marrow mesenchymal stem cell; ınterleukin; monoclonal antibody

Received: 31.05.2024; Accepted: 18.07.2024

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How to cite: Ocak M. Alterations in polarity and regeneration-related gene expression in bone marrow mesenchymal stem cells in vitro in rheumatoid arthritis injury model and pharmacological modulation. Ahi Evran Med J. 2025;9(1):3-11. DOI: 10.46332/aemj.1493279

INTRODUCTION

Rheumatoid Arthritis (RA) is a persistent, inflammatory disease that occurs in childhood and consists of clinical pictures rather than a single disease.[1,2] Recent scientific studies have shed light on the pathogenesis of RA.[3] Classically, white blood cells such as neutrophils and monocytes in the cell-conjugated phase of inflammation migrate to the damaged tissue area and secrete the early inflammatory factors S100A8, S100A9 and neutrophil-based S100A12 in the extracellular matrix of the area.[4] These alarmins, part of the S100 protein family, play a crucial role in triggering and maintaining the inflammatory response.[5] Their increased levels are frequently associated with disease activity and can act as biomarkers for tracking disease progression.[6] Additionally, these proteins can enhance the local inflammatory response by promoting the synthesis of more chemokines and pro-inflammatory cytokines.[7] These cells, predominantly found in the synovial fluid and synovium membrane of the interacted area in RA pathogenesis, are activated by neutrophils and their metabolites IL-1 and IL-6, leading to the secretion of degradation proteases.[8] IL-1 and IL-6 are crucial pro-inflammatory cytokines that not only assemble an excess of immune cells to the site but also amplify the inflammatory response.[9] These cytokines play a significant role in the feedback loop that sustains the chronic inflammation characteristic of RA.[10] Following these mechanisms, the appearance of blood vessels in the synovial fluid becomes more frequent.[11] This formation of new blood vessels is crucial for maintaining chronic inflammation, as it allows more immune cells to access the joint space.[12] The rise in blood vessel formation is driven by VEGF (vascular endothelial growth factor) is one of the growth factors, which is elevated in the inflamed synovium.[13] This facilitates increased inflammation by enabling the migration of inflammatory cells.[10] CD28 T cells migrating into the synovial fluid produce significant amounts of IL-6 when CD80/86 antigen-presenting cells present antigen in the synovial epithelium. This epithelium acts as a barrier to the synovial liquid in beholds by membrane and defines the boundaries of the joint.[11] Because of their essential role in the adaptive immune response, these T cells contribute to the chronic nature of RA by consistently producing pro-inflammatory cytokines.[12] The persistent activation of these T cells and their interaction with antigen-presenting cells perpetuates the inflammatory cycle.[13] Destructive proteases break down the intercellular desmosomes and tonofilaments in the synovial epithelium and cause the membrane lining the synovial fluid to disappear, initiating an erosion into the synovial fluid.[14] Joint injury and function loss result from the breakdown of these structural proteins, which also undermine the integrity of the synovial membrane.[15] Synovial fibroblasts, stimulated by the inflammatory environment, further contribute to the destruction by releasing MMPs, or matrix metalloproteinases, disintegrate extracellular matrix constituents.[16] The inflammatory state is maintained by these fibroblasts' additional role in the synthesis of pro-inflammatory cytokines.[17] Monoclonal antibody treatment can be used to inactivate and reduce the impact of inflammatory chemicals in the early stages of inflammation.[18] These therapies target specific cytokines such as IL-6 and IL-1β, aiming to reduce inflammation and prevent joint damage.[19] Antagonist antibody agents such as canakinumab, infliximab, and tocilizumab have demonstrated effectiveness in controlling symptoms and enhancing the quality of life for patients with RA.[20] Additionally, newer antagonist antibody targeting IL-6, such as tocilizumab, have been developed and are being used to treat RA.[21] To improve disease control, these therapies are frequently used with traditional disease-modifying antirheumatic medications (DMARDs), such as methotrexate.[22] Recent advances in understanding the genetic and environmental factors such as polarity instability and regeneration capacity decline contributing to RA have also opened up new avenues for potential therapeutic targets in managing this complex disease.[23] For this purpose, we inspected some of the targeted genes that has crucial role in cell polarity and regeneration. Pard3, a gene involved in cell polarity, has been found to play a role in the development and progression of rheumatoid arthritis (RA) through its regulation of synovial fibroblast behavior and inflammatory responses.[24,25] Mapk8 is crucial in RA pathogenesis by mediating pro-inflammatory cytokine production and joint destruction.[26,27] Dmp1, which is related to bone matrix protein, influences bone metabolism and osteoclast differentiation, thereby contributing to the bone erosions seen in RA.[24,25] Yap1, a key regulator of cell proliferation and apoptosis, is implicated in RA by promoting synovial hyperplasia and joint inflammation.[26,27] Junb, a transcription

factor, modulates inflammatory responses in RA by regulating the expression of pro-inflammatory genes and cytokines.[24,25] Mepe impacts bone mineralization and has been linked to altered bone homeostasis in RA.[26,27] Mmp13, a matrix metalloproteinase, contributes to the degradation of cartilage and extracellular matrix in RA, exacerbating joint damage.[24,25] Similarly, Mmp2, another matrix metalloproteinase, is involved in tissue remodeling and synovial inflammation, playing a significant role in RA progression.[26,27] In this study, we aimed to elucidate the cellular mecha-nisms contributing to the pathogenesis of RA and especial-ly the roles of genes associated with cell polarity and tissue regeneration capacity. In this context, the functions of genes such as Pard3, Mapk8, Dmp1, Yap1, Junb, Mepe, Mmp13 and Mmp2 in inflammation and joint destruction were evaluated.

MATERIALS and METHODS

Reagents and Chemicals

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), Lactate Dehydrogenase Colorimetric Activity Kit, TRIzol Reagents and dimethyl sulfoxide (DMSO) were purchased from Invitrogen (Waltham, Massachusetts, USA). High-Capacity cDNA Reverse Transcription Kit and TaqMan™ Master Mix for qPCR were purchased from Applied Biosystems (Waltham, Massachusetts, USA). IL-1β and IL-6 obtained from Gibco (Gibco, Waltham, Massachusetts, USA). Canakinumab was obtained as ACZ885-Ilaris from Novartis (Novartis, Basel, Switzerland) and Tocilizumab was obtained as Actemra from Roche (Roche, Basel, Switzerland). Canakinumab and Tocilizumab concentration were adjusted by dissolving in PBS. All other reagents, unless noted otherwise, were obtained from Invitrogen in their highest available purity.

Cell Culture

Human Mesenchymal Bone Marrow Derived Adult Stem Cells are a type of cell line commonly used in cartilage formation research, particularly in the study of Arthritis. Human Mesenchymal Bone Marrow Derived Adult Stem Cells were obtained from Celprogen (SKU: 36094-22, Celprogen; Benelux, Netherlands). The cells were cultured in Human Bone Marrow Derived Mesenchymal Stem Cell Complete Media with Serum (SKU: 36094-21S, Celprogen; Benelux, Netherlands) in a humidified atmosphere (95% humidity) at 37 °C with 5% CO_2. The cells in passages 2–6 were used for testing. Experiments were conducted using cells in the exponential growth phase. Both agents were dissolved in H_2O to create stock solutions, which were subsequently diluted to the required concentrations for analysis. Since this was an in vitro study, ethics committee approval was not required.

Cell Viability Assay

The proliferation of cells treated with different concentrations of IL-1β, IL-6, Canakinumab, and Tocilizumab was assessed using the 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, which measures mitochondrial dehydrogenase activity in living cells.[28] An MTT assay was conducted to determine the viability of Human Mesenchymal Bone Marrow Derived Adult Stem Cells after treatment with cytokine and antagonist antibody agents, and their combination, and the IC_{50} was defined as the concentration of the agent required to block 50% cell viability. For this purpose, an equal number of hBMMSC cells (1 x 10^5 cells/well) were cultured in 96-well plates and allowed to attach overnight. Since the stem cells are adult, too much cell division is not desired. When the cell confluence was almost %80, the cells were then treated as different groups as Group I: 5 ng/mL IL-1β + 50 ng/mL IL-6 (Cyt I), Group II: 10 ng/mL IL-1β + 100 ng/mL IL-6 (Cyt II), Group III: 1 µg/mL Canakinumab + 1 µg/mL Tocilizumab (Mab), Group IV: 5 ng/mL IL-1β + 50 ng/mL IL-6 + 1 µg/mL Canakinumab + 1 µg/mL Tocilizumab (Comb I), Group V: 10 ng/mL IL-1β + 100 ng/mL IL-6 + 1 µg/mL Canakinumab + 1 µg/mL Tocilizumab (Comb II) and incubated at 37°C for 48h and 72h. At the end of the time, 10 µL of 5 mg/mL MTT was added to each well and incubated at 37°C for 4 h. Subsequently, the cell culture medium was removed, and 100 µl DMSO was added to dissolve formazan crystals and the absorbance of each well was measured at 570 nm using a Multiskan SkyHigh Microplate Reader (Thermo Fisher, Waltham, Massachusetts, USA). The percentage of cell growth inhibition was calculated as follows: cell inhibition percentage (%): (mean absorbance in test wells/mean absorbance in control wells) x100. All experiments were repeated six

times for each concentration and independently replicated for a minimum of three times.

Cytotoxicity Assay

Cytotoxicity was evaluated by lactate dehydrogenase (LDH) release assay using Lactate Dehydrogenase Colorimetric Activity Kit (Invitrogen Cat No. EEA013) assay.[28] The Cytotoxicity kit used to determine whether cytokines or antagonist antibodies have any cytotoxic effect on hBMMSC lines. Briefly, hBMMSC were cultured in a 96-well plate at $1x10^5$ cells/well for 24 h. Since the stem cells are adult, too much cell division is not desired. When the cell confluence was almost %80, the cells were then treated as different groups as Group I: 5 ng/mL IL-1β + 50 ng/mL IL-6 (CytI), Group II: 10 ng/mL IL-1β + 100 ng/mL IL-6 (Cyt II), Group III: 1 µg/mL Canakinumab + 1 µg/mL Tocilizumab (Mab), Group IV: 5 ng/mL IL-1β + 50 ng/mL IL-6 + 1 µg/mL Canakinumab + 1 µg/mL Tocilizumab (Comb I), Group V: 10 ng/mL IL-1β + 100 ng/mL IL-6 + 1 µg/mL Canakinumab + 1 µg/mL Tocilizumab (Comb II) for an additional 48h. This assay was performed according to the manufacturer's protocol. The optical density was measured at 490 nm with a Multiskan SkyHigh Microplate Reader (Thermo Fisher, Waltham, Massachusetts, USA). The percentage of LDH release was calculated according to the formula provided in the manufacturer's protocol. All experiments were performed in three replicates in three independent experiments.

RNA Isolation and Quantitative Real-Time PCR Analysis

Cells were treated with agents and antagonist antibodies for polarity and regeneration genes expression study. Treatment groups are Group I: 5 ng/mL IL-1β + 50 ng/mL IL-6 (Cyt I), Group II: 10 ng/mL IL-1β + 100 ng/mL IL-6 (Cyt II), Group III: 1 µg/mL Canakinumab + 1 µg/mL Tocilizumab (Mab), Group IV: 5 ng/mL IL-1β + 50 ng/mL IL-6 + 1 µg/mL Canakinumab + 1 µg/mL Tocilizumab (Comb I), Group V: 10 ng/mL IL-1β + 100 ng/mL IL-6 + 1 µg/mL Canakinumab + 1 µg/mL Tocilizumab (Comb II) for 48h. TRIzol Reagent was used to extract total RNA from excised cell culture with several concentrations of agent combinations (~100 mg) per the manufacturer's instructions. Total RNA concentration was then quantified at 260 nm and 280 nm using Nano-Drop 1000 spectrophotometer (Thermo Fisher Scientific). cDNA synthesis was performed from 1 µg of total RNA with a High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, USA), following the manufacturer's protocols. The cDNA samples were stored at -80 °C until use. qPCR reactions were then performed using the Applied Biosystems 7300 Real-Time PCR System with a TaqMan™ Master Mix for qPCR according to the manufacturers' instructions. The qPCR primers for Pard3, Mapk8, Dmp1, Yap1, Junb, Mepe, Mmp13, Mmp2 genes were designed using the Neoformit database program. Table 1 shows the gene-specific primer sequences (in the 5'-3'direction) for each gene used for the qPCR reaction. The mRNA level of Actin β (Beta-actin, housekeeping gene) was used to normalize the levels of the target genes. Thermal cycling conditions were as follows: denaturation at 95 °C for 10 min, 45 cycles of amplification: 95 °C for 10 sec, 60 °C for 20 sec and cooling at 40 °C for 30 sec. Expression levels of target genes were determined employing the $2^{-\Delta\Delta CT}$ method.[29,30] Samples from each experiment were used in triplicate.

Table 1. Gene-specific primer sequences used in qPCR.

Gene	Forward primer (5'- 3')	Reverse primer (5'- 3')
Pard3	TCAGCTCCTACCTATCCCGG	CTCAACTCCCAAGTCAGGCC
Mapk8	AATGGCGTGATCTTGGCTCA	GGGAGGCTGAGGTAGGAGAA
Dmp1	CTTCTCAGAGGAAAGCCCGG	GAGCTGCTGTGAGACTGGAG
Yap1	CCTCTCCAGCTTCTCTGCAG	TGGGCCAGAGACTACTCCAG
Junb	TGGCCTCTCTCTACACGACT	CTTTGAGACTCCGGTAGGGG
Mepe	TGCAACAAGGGTGTGCAGTA	ATGGGGTCTCGCAAATGTGT
Mmp13	CACCATGATGTAGGAGCCCC	GGCTGATCTGCTGATGGACA
Mmp2	TGAAGCACAGCAGGTCTCAG	TCAAACCAGGCACCTCCATC
Actb	AGACCTGTACGCCAACACAG	TTCTGCATCCTGTCGGCAAT

UPL: Universal Probe Library; qPCR: Quantitative Real Time Polymerase Chain Reaction

Statistical Analysis

Statistical analyses were performed with the help of SPSS 16.0 (IBM, USA). GraphPad Prism 6 software (GraphPad Software Inc., San Diego, CA, USA) was utilized to ascertain the concentration at which 50% cytotoxicity (IC50) was achieved.[31] Viability assay and LDH release assay (with Bonferroni post hoc test) results were analyzed using student t-test, qPCR analysis was analyzed using analysis of variance (ANOVA) test. Combination Index curves and Dose-effect curves calculated and visualized using Compusyn (BioSoft, Cambridge UK).[32] The Relative Expression Software Tool (REST® 2009 v2.013) was used to assess the mRNA levels of EMT-related genes, and the GeneGlobe Data Analysis Center (Qiagen) verified the results.[29,30] Every single statistic was displayed as Mean ± Standard Deviation (SD), with *P<0.05* deemed statistically significant. The reporting of this study conforms to STROBE guidelines.[33]

RESULTS

Effects of IL-1, IL-6, Canakinumab and Tocilizumab on Cell Viability

The hBMMSC cell viability was determined by the MTT assay (Figure 1). hBMMSC cells were treated with IL-1β, IL-6, Canakinumab, Tocilizumab for 48 and 72 h. The administration of Mab group for 48, and 72 h did not alter the viability of the cells at the concentrations (P>0.05). Administration of Cyt I group (5 ng/mL IL-1β + 50 ng/mL IL-6) to hBMMSC culture resulted in a slightly diminished cell viability, (P<0.05), but it significantly decreased at higher concentrations when the Cyt II (10 ng/mL IL-1β + 100 ng/mL IL-6) administered (P<0.05). The effects of cytokines and antagonist antibodies combined treatments on cell viability are shown in Comb I and Comb II. After 48 h treatment, the lowest cell viability (37.41%) was observed in the Cyt II group. It was determined that high dosage of cytokine treatments significantly decreased cell viability below 50% in both 48 and 72 h (Figure 1). But the combined treatments led to a normalization in cell viability compared to individual use of the agents. According to the results obtained from the combination index analysis and dose-effect curve, Canakinumab and Tocilizumab showed antagonism against IL-1β and IL-6 in the treatment of RA model of hBMMSC even if there is not immunity cell to effect (Figure 2).

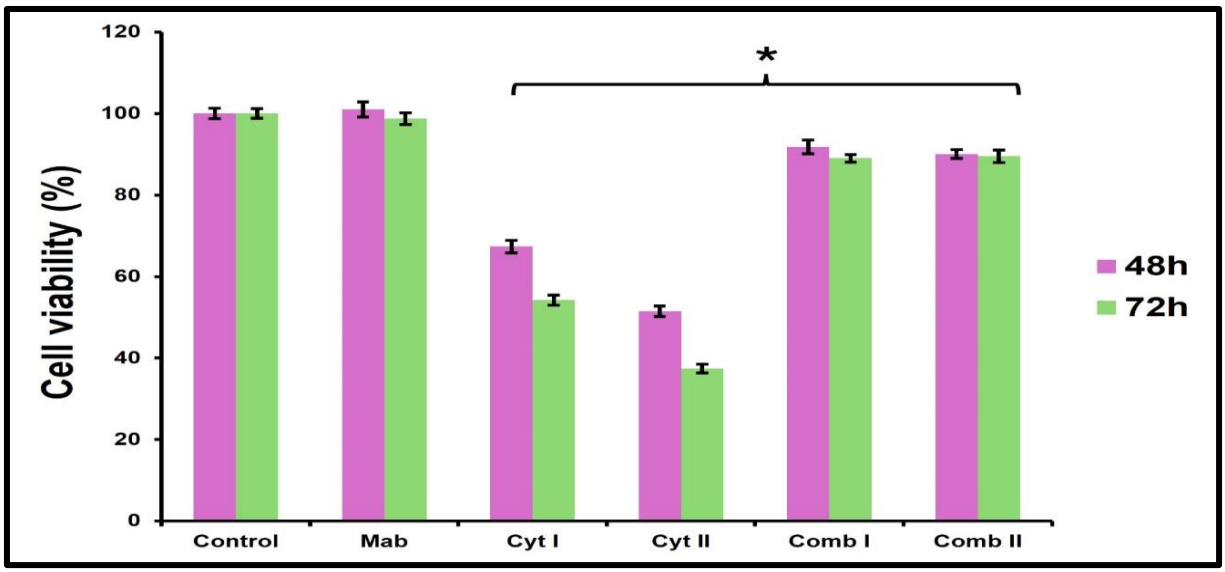

Figure 1. Demonstration of cell viability of groups consist of different combinations of con-centration of IL-1β, IL-6, Canakinumab, Tocilizumab applied to hBMMSC at 48h and 72h. The results shown are representative of the 3 independent experiments. Data were expressed as mean ± standard deviation. *P<0.05 according to the student's t-test.

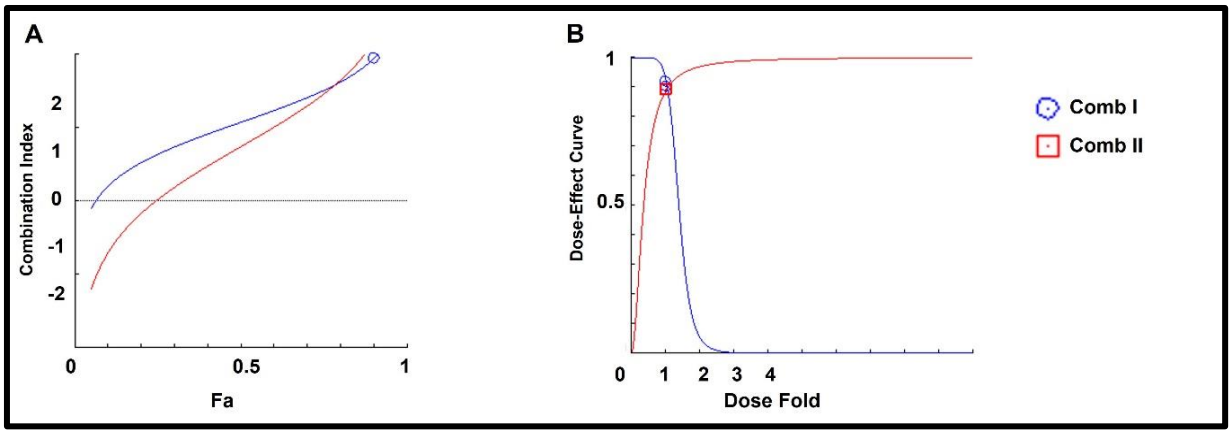

Figure 2. Combination Index Drug Synergy Analysis (CI) of the IL-1β, IL-6, Canakinumab and Tocilizumab synergetic affiliation (A), Dose-Effect Curve demonstration of the combina-tion groups (B). Linear regression was used to render the CI values. Trendlines demonstrate CI values for any expected effect (Fa, fraction affected, 0 to 1; 0-%100 inhibition), and CI values <1, =1, >1 indicate synergy, additivity, or antagonism, respectively.

Effects of IL-1, IL-6, Canakinumab and Tocilizumab on Cytotoxicity

The cytotoxic effects of IL-1β, IL-6, Canakinumab and Tocilizumab on hBMMSC were evaluated by LDH release assay. The individual administration of IL-1β and IL-6 as Cyt I and Cyt II group induced cytotoxicity in the RA model of hBMMSC treated for 48 h. Cytotoxicity was very low and similar in hBMMSC exposed to a selected con-centration of Canakinumab and Tocilizumab as Mab group (1 µg/ml for each) at 48 h. The percentages of LDH release at Cyt I and Cyt II were as follows: 34.05% and 55.47% (P<0.05), respectively. The treatment of hBMMSC with monoclonal antibodies decreased cytokine caused a dose-dependent release of LDH (5 ng/ml IL-1β + 50 ng/ml IL-6) (P<0.05). Results show that combined treatment of cy-tokines and monoclonal antibodies markedly decreased the cytotoxic effects of cytokines alone in hBMMSC (Figure 3).

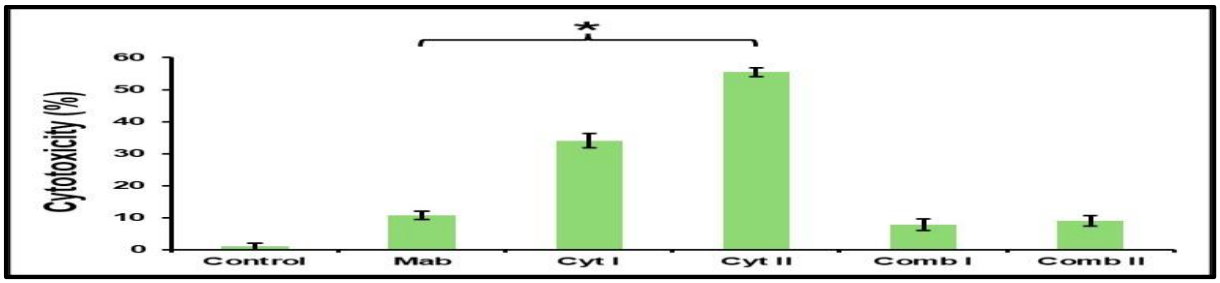

Figure 3. Demonstration of Effect of IL-1β, IL-6, Canakinumab and Tocilizumab on cytotox-icity determined by LDH release in hBMMSC. The results shown are representative of the 3 independent experiments. Data were expressed as mean ± standard deviation. *P<0.05 ac-cording to the student's t-test.

Effects of IL-1, IL-6, Canakinumab, Tocilizumab on mRNA Levels of Polarity and Regeneration-Related Genes In Vitro

The mRNA levels of Pard3, Mapk8, Dmp1, Yap1, Junb, Mepe, Mmp13, Mmp2 genes were evaluated by qPCR. The levels of Pard3 and Dmp1 mRNA significantly de-creased in the Cyt I and Cyt II groups. The mRNA levels of Mapk8, Yap1, Junb, Mepe, Mmp13, Mmp2 genes in Cyt I and Cyt II groups were significantly higher than com-bination groups Comb I and Comb II (P<0.05). Moreover, the mRNA expression levels of Mapk8, Yap1, Junb, Mepe, Mmp13, and Mmp2 were observed to be lower in the com-bination groups, particularly in Comb I, compared to the Cyt I and Cyt II groups, approaching closer to the normal-ization threshold. *(*P<0.05) (Figure 4).

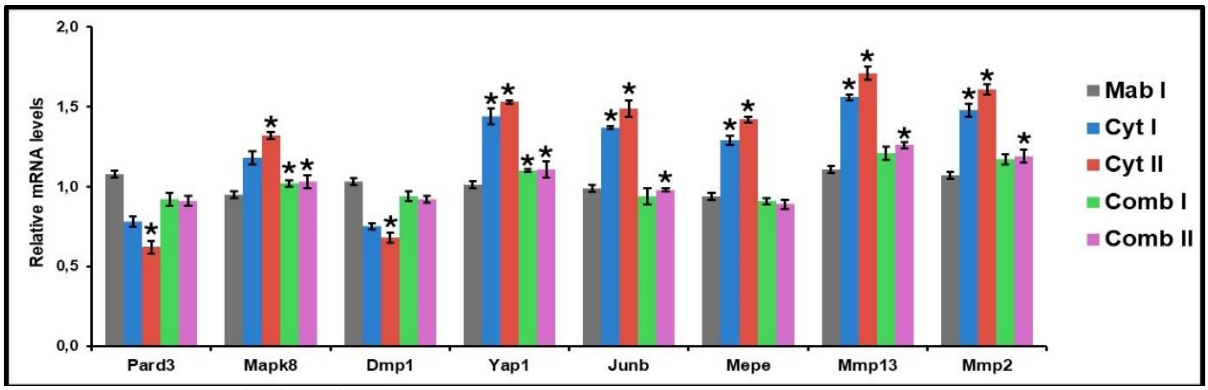

Figure 4. Demonstration of Effects of IL-1β, IL-6, Canakinumab and Tocilizumab on Polarity and Regeneration-related mRNA levels in hBMMSC culture. Data were expressed as mean ± standard deviation. The results shown are representative of the 3 independent experi-ments. *P<0.05 according to the ANOVA test.

DISCUSSION

The effects of IL-1β and IL-6 on human bone marrow mesenchymal stem cells (hBMMSCs) are highlighted in this work, along with the possible therapeutic advantages of combining IL-1β antagonist canakinumab with IL-6 antagonist tocilizumab. The results provide fresh insights into the regulation of inflammatory responses in RA models and are consistent with other studies on the etiology of rheumatoid arthritis (RA).

The observed decrease in cell viability and increase in cytotoxicity in hBMMSCs treated with IL-1β and IL-6 highlight the destructive nature of these cytokines in RA. Even in the recent studies IL-1β and IL-6 are shown to play crucial roles in the inflammatory processes of RA by promoting the recruitment and activation of inflammatory cells, leading to joint damage and erosion.[9,10] It has also been observed that these cytokines stimulate the formation of matrix metalloproteinases (MMPs), which break down components of the extracellular matrix and aid in tissue death.[19]

The combination therapy with canakinumab and tocilizumab demonstrated a significant protective effect on hBMMSCs, reducing cytotoxicity and improving cell viability. This synergistic effect can be attributed to the complementary mechanisms of action of these antagonists. Canakinumab specifically targets IL-1β, a key mediator of acute inflammation, while tocilizumab inhibits IL-6 signaling, which is proven from former studies, involved in chronic inflammation and the promotion of autoimmunity.[24] The combination of these antagonists can effectively reduce the inflammatory burden in RA, offering a potential therapeutic strategy for managing the disease.

In our study, we deliberately selected key genes associated with polarity and regeneration to elucidate the molecular mechanisms influenced by inflammatory events in bone marrow stem cells. Significant alterations in the expression of polarity and regeneration-related genes were seen in hBMMSCs treated with cytokines and antagonists, according to gene expression analysis. The downregulation of polarity-related genes (Pard3, Dmp1) in response to cytokines IL-6 and IL-1β indicates disruption of cellular orientation and structure, which are demonstrated to pivotal for maintaining tissue integrity.[34] As it was already in the literature, the upregulation of regeneration-related genes (Mapk8, Yap1, Junb, Mepe, Mmp13, Mmp2) suggests an attempt by the cells to repair and regenerate damaged tissues in the presence of inflammation.[35]

The application of canakinumab and tocilizumab reversed these gene expression changes, promoting normalization and enhancing the regenerative capacity of hBMMSCs. This finding supports the recent studies about notion that targeting specific inflammatory pathways can restore cellular functions and improve tissue repair processes in RA.[26] The results align with previous studies demonstrating the benefits of cytokine inhibitors in reducing inflammation and promoting tissue regeneration in RA models.[18,22]

The significant reduction in cytotoxicity observed in the combined treatment groups further emphasizes the potential of combination therapy in RA management. By concurrently targeting multiple cytokines, it is possible to

achieve a more comprehensive suppression of inflammatory pathways, leading to better clinical outcomes as previous research claims.[11] This approach is particularly relevant in RA, where multiple cytokines and signaling pathways contribute to disease progression and chronic inflammation.[18]

In addition to the observed cellular and molecular effects, the study also highlights the importance of early interruption in RA. The application of cytokine antagonists in the early stages of inflammation can prevent irreversible tissue damage and preserve joint function. Previous studies have demonstrated that early treatment with such medicines improves outcomes over time in individuals with RA by lowering disease activity and preventing structural damage.[6,19]

The findings of this study have important implications for the development of treatment strategies in RA. Through the identification of distinct cytokine profiles and molecular markers related to the advancement of the disease, guided medicines can be developed, resulting in increased therapeutic effectiveness and reduced side effects.[21] Guided medicine approaches in RA are gaining increasing attention, with ongoing research focused on identifying biomarkers and developing targeted therapies.[11,19]

Future studies should aim to explore and define the detailed molecular mechanisms underlying the synergistic effects of cytokine antagonists in RA models. Researching the connections between various cytokines and the signaling pathways they interact with will shed light on the pathophysiology of RA and help create more potent treatment plans.[25] Furthermore, to confirm the results of this investigation and evaluate the security and effectiveness of combination treatments in RA patients, clinical trials are required.[22,25]

In conclusion, this study demonstrates the potential benefits of combining IL-1β and IL-6 antagonists in an in vitro RA model. The findings support the use of combination therapy to enhance treatment efficacy and improve patient outcomes in RA. The study also underscores the importance of early intervention and guided medicine approaches in managing this complex disease. It is necessary to do additional study to investigate the molecular mechanisms and therapeutic implications of these discoveries.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Acknowledgments

I would like to express my sincere gratitude to Prof. Dr. Afig BERDELİ for his invaluable contributions and unwavering support throughout this study. I am also deeply thankful to Prof. Dr. Rüştü HATİPOĞLU for his expert guidance, mentorship, and compassionate approach.

Ethics Committee Permission

Since this was an in vitro study, ethics committee approval was not required.

Authors' Contributions

Concept/Design: MO. Data Collection and/or Processing: MO. Data analysis and interpretation: MO. Literature Search: MO. Drafting manuscript: MO. Critical revision of manuscript: MO.

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Assessment of cfDNA Levels in Saliva Samples of Stressed Young Adults: Preliminary Study

Stres Altındaki Genç Yetişkinlerin Tükürük Örneklerinde cfDNA Düzeylerinin Değerlendirilmesi: Ön Çalışma

Ekin ÇELİK[1] Miraç Berkay KÖKSAL[2] Hacı Mehmet AKBULUT[2] Selahattin Ata AYDIN[2]

Yiğit Emre KURT[2] Can OKAN[2] Simay ÇETİNKAYA[2]

ÖZ

Amaç: Bu pilot çalışmada, ikinci sınıf tıp öğrencilerinin sınav öncesi ve sonrasında tükürük örneklerindeki hücre dışı DNA (hdDNA, cfDNA) düzeylerinin incelenmesi amaçlanmıştır.
Araçlar ve Yöntem: Stres profilleri DASS-21 ölçeği ile değerlendirilen 20 öğrencinin sınav öncesi ve sonrası tükürük örnekleri alınarak hücre dışı DNA izole edilmiştir. İzole edilen DNA'lar spektrofotometre ve otomatik elektroforez sistemi ile ölçülmüştür.
Bulgular: Spektrofotometre analizleri, sınav sonrası öğrencilerden alınan cfDNA miktarlarında anlamlı bir azalma göstermiştir ($p \leq 0.05$). Bu fark otomatik elektroforez sistemi ile doğrulanmış ve özellikle 40-200 bp aralığındaki cfDNA miktarlarının stresin azalmasıyla birlikte azaldığı tespit edilmiştir ($p \leq 0.05$).
Sonuç: Psikososyal stres hdDNA salınımını etkilemektedir. Bu çalışmada, tükürük örneklerinde bulunan hdDNA miktarlarının stresle ilişkili olarak anlamlı değişiklikler gösterdiği raporlanmıştır. Bu ön çalışma, tükürük numunelerindeki hdDNA'nın sağlıklı bireylerde stresin potansiyel biyolojik bir belirteci olarak değerlendirilebileceğini ortaya koymuştur.

Anahtar Kelimeler: biyobelirteç; hdDNA; plazma

ABSTARCT

Purpose: The aim of this pilot study was to examine the levels of cell-free DNA (cfDNA) in the saliva samples of second-year medical students before and after a stress-inducing event, exams.
Materials and Methods: Saliva samples were collected from 20 students, whose stress profiles were assessed using the DASS-21 scale, both before and after the exams. Cell-free DNA was isolated from these samples, and measured using spectrophotometry and automated electrophoresis system.
Results: Spectrophotometric analysis revealed a significant decrease in cfDNA levels in the saliva samples collected after the exams ($p \leq 0.05$). This difference was confirmed by the automated electrophoresis system, particularly showing a reduction in cfDNA amounts in the 40-200 bp range with the reduction of stress ($p \leq 0.05$).
Conclusion: Psychosocial stress affects the release of cell-free DNA. This study reports that the amount of cfDNA found in saliva samples significantly changes in relation to stress. This preliminary study suggests that cfDNA in saliva samples could potentially serve as a biological marker for stress in healthy individuals.

Keywords: biomarker; cfDNA; plasma

Received: 29.07.2024; Accepted: 19.08.2024

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How to cite: Çelik E, Köksal MB, Akbulut HM, Aydın SA, Kurt YE, Okan C, Çetinkaya S. Assessment of cfDNA levels in saliva samples of stressed young adults: preliminary study. Ahi Evran Med J. 2025;9(1):12-16. DOI: 10.46332/aemj.1524197

INTRODUCTION

DNA that is present in blood plasma, serum, cerebrospinal fluid, saliva, and urine without being associated with cells is known as cell-free DNA (cfDNA) or extracellular DNA (ecDNA).[1,2] The exact biological sources of cell-free DNA are still not fully understood; it is suggested that they may originate from mechanisms like active secretion, apoptosis, necrosis, or netosis.[3,4]

Elevated amounts of cell-free DNA (cfDNA) in the blood, whether originating from the genome or mitochondria, are distinctive indicators of both acute systemic inflammatory reactions and long-term inflammation.[5] Such heightened levels have been observed following events like trauma, sepsis, stroke, ischemia/reperfusion injury, and myocardial infarction, as well as in individuals with cancer, autoimmune diseases, cardiovascular conditions, and metabolic disorders.[6] In these situations, cfDNA has been firmly established as a dependable and consistent biomarker. Measuring cfDNA levels holds promise as a valuable clinical tool for assessing risk and monitoring therapy effectiveness across various inflammatory contexts.[7]

Stress is a common psychophysiological reaction produced by the body in response to adverse, challenging, and difficult situations or stressors.[8] It impacts the immune system and triggers peripheral inflammatory pathways, resulting in the secretion of certain biomolecules like hormones, and as recently revealed, cfDNA.[9]

The effect of psychosocial stress on plasma cell-free DNA (cfDNA) levels has become a focal point in recent years.[6-12] Czamanski-Cohen et al, studied the relationship between elevated cortisol levels and cfDNA amounts in plasma and showed a positive correlation.[10] Another study indicated that stress reduction might promote changes that result in lowered plasma cfDNA levels.[11] Shan and his colleagues conducted a case-control study in 2024, which showed increased stress levels resulted in elevated cfDNA levels in plasma.[12]

MATERIALS and METHODS

Study Design

This pilot study, conducted at the Kırşehir Ahi Evran University Faculty of Medicine from October 2023 to May 2024, included a sample of 20 participants. The DASS-21 scale, a tool designed to evaluate symptoms of depression, anxiety, and stress, was utilized to identify 20 medical students experiencing stress.[13] Stress levels were evaluated using both self-reported assessments and the validated DASS-21 scale.[14] Participants completed a questionnaire addressing perceived stress and stress-related symptoms before exam. Individuals with pre-existing medical conditions, obesity, ongoing dental treatment and elderly participants were excluded from the study. This study was approved by Kırşehir Ahi Evran University Faculty of Medicine, Health Sciences Scientific Research Ethics Committee (dated 30.04.2024 and numbered 2024-09/69).

Sample Collection

The students with a mean age of 22 years (range, 20–24 years) participated in the study were chosen using a convenience sampling method. Participants abstained from consuming any food or beverages, except for water, for one hour prior to the collection. Saliva samples (3ml) were collected both before and after the first semester examinations from same individuals and delivered to the laboratory within one hour and subjected to two-step centrifugation. Samples were first centrifuged at 2000g for 15 min to remove any cellular debris, then centrifuged at 2000g for 10 min. Samples were stored at −80°C until cfDNA isolation.[15]

cfDNA Isolation

cfDNA was isolated with magnetic beads, using ZipPrime SafeCAP Cell-Free DNA Extraction and Capturing Kit (ZipPrime, Turkey) according to the manufacturer's protocol. Isolated cfDNA were stored at −80°C until quantification.

Quantification of cfDNA

Isolated cfDNA was first quantified via Jenway Genova Nano Micro-Volume Life Science Spectrophotometer (Cole-Parmer, US). Samples were briefly vortexed and centrifuged before quantification using 2 µL of DNA. Fragment size of cfDNA was assessed using the Agilent 2100 Bioanalyzer (Agilent Technologies, US) with the High Sensitivity DNA kit (Agilent Technologies, US), following the manufacturer's instructions. The predominant fragment size was identified as the peak with the highest molar concentration in the bioanalyzer output.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 10 software (US). Data were presented as means ± standard deviations and significance of differences were analysed using the t test for spectrophotometry results and the nonparametric Mann-Whitney test for Bioanalyzer data.[16] The value of $p \leq 0.05$ was considered statistically significant. Error bars represent technical replicates.

RESULTS

In this study, twenty saliva samples were collected both before and after the first semester examinations from same individuals identified as stressed based on the DASS-21 questionnaire. After cfDNA isolations, amounts were quantified using spectrophotometry initially. Data showed cfDNA levels were significantly elevated in 80% of the participants before examinations ($p \leq 0.05$) (Figure 1).

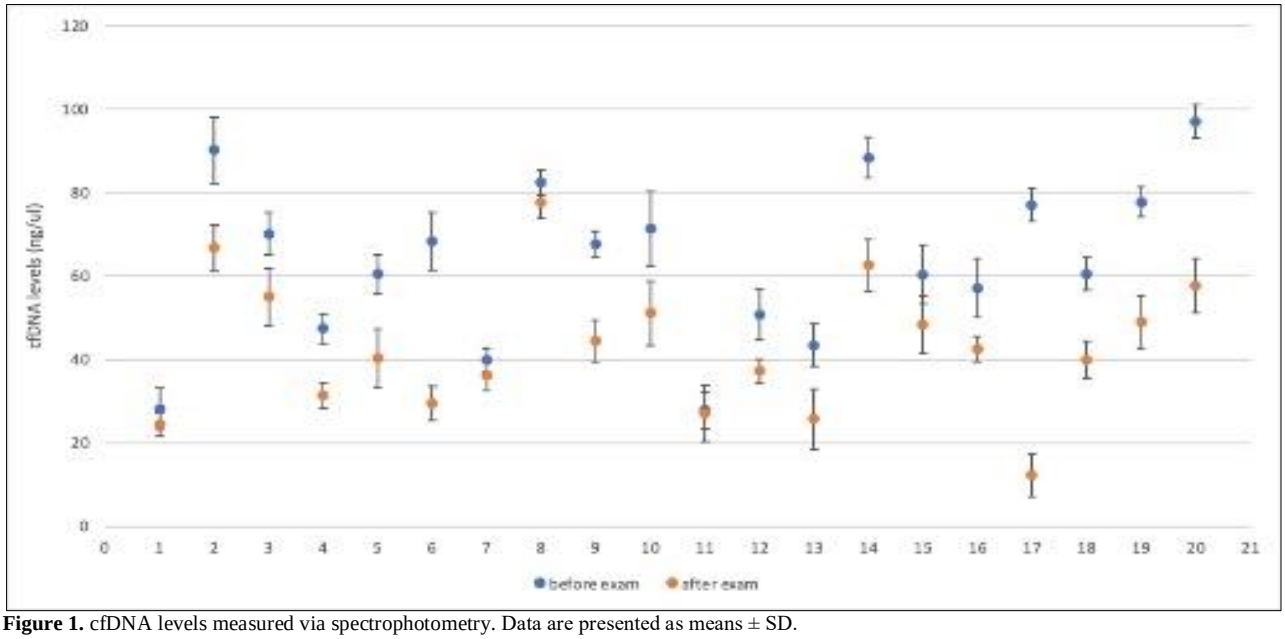

Figure 1. cfDNA levels measured via spectrophotometry. Data are presented as means ± SD.

Since spectrophotometric analysis cannot determine the lengths of cfDNAs, all isolated cfDNAs were quantified collectively after isolation for each sample. Although these results offer a general basis for comparison, they are insufficient for making definitive conclusions. To accurately measure cfDNAs based on their length, we conducted an analysis using automated electrophoresis.[17] In the second phase of the experiment, samples were subjected to Bioanalyzer analysis. Bioanalyzer results showed a significant decrease in all samples correlated with stress elimination ($p \leq 0.05$). cfDNAs range between 40-200 bp were taken into consideration. Data revealed a more than twofold decrease in all samples after examinations, results are shown in Figure 2. A representative Bioanalyzer graph is also added as Figure 3.

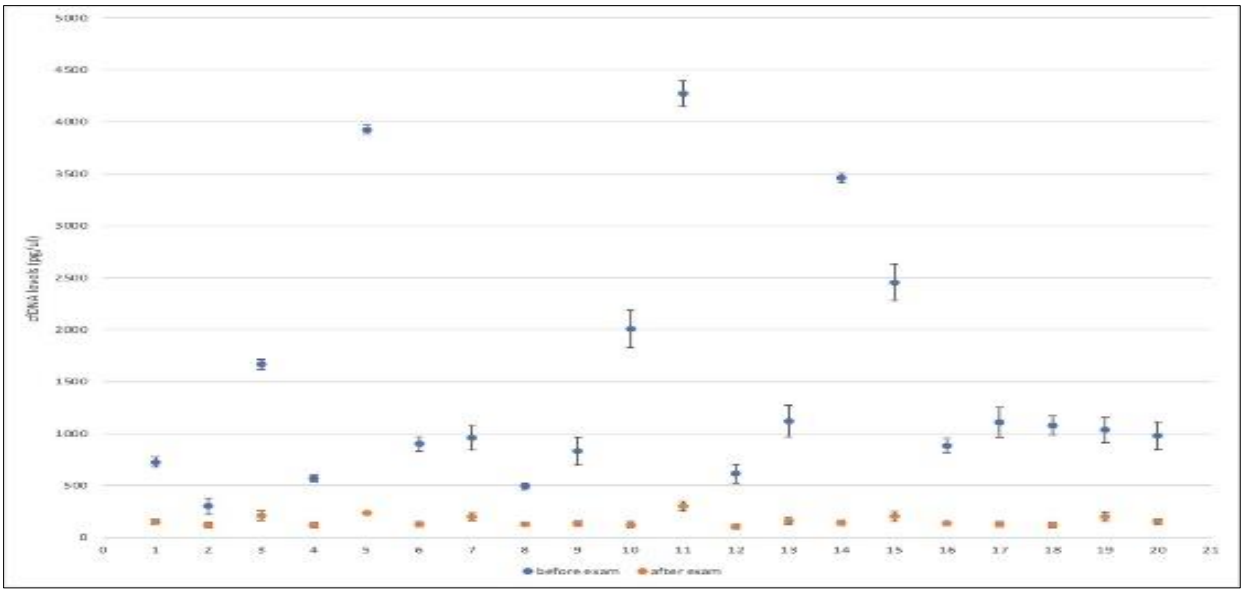

Figure 2. cfDNA levels measured via Bioanalyzer. Data are presented as means ± SD.

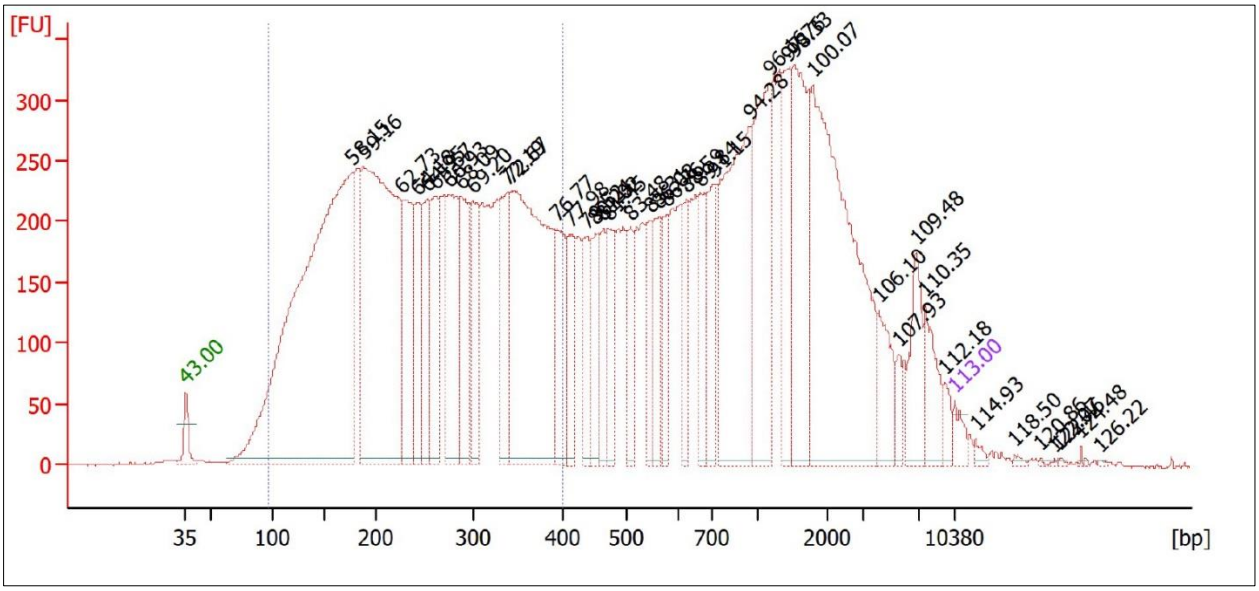

Figure 3. Representative bioanalyzer graph.

DISCUSSION

The purpose of this preliminary study was to investigate the relationship between cell-free DNA (cfDNA) levels and stress. The study included 20 medical students identified as stressed according to DASS-21 scale, whose saliva samples were analyzed for cfDNA levels both before and after the stress-inducing event, which were exams. Data quantified with spectrophotometric analysis (Jenway Genova Nano Micro-Volume Life Science Spectrophotometer) and assessed via automated electrophoresis (Agilent 2100 Bioanalyzer). The results showed elevated cfDNA levels in saliva samples before the exams, cfDNAs whose length between 40-200 bp were taken into consideration ($p \leq 0.05$). Our findings were consistent with the literature.[12]

In addition, our data also showed that participants had longer cfDNAs within the ranges of 500-10.380 bp and 35-10.380 bp (data not shown). These cfDNAs were excluded from the quantification data due to the possibility that they may have originated from the oral microbiome.[18]

Moreover, additional analysis is necessary to ascertain the source of the isolates within the specified range. Although this preparatory study needs additional analysis to draw definitive conclusions, it indicates that stress may impact cfDNA levels in saliva, suggesting the potential use of cfDNA as a biomarker for stress.

Conflict of Interest

The authors declare that there is not any conflict of inter-est regarding the publication of this manuscript.

Ethics Committee Permission

This study was approved by Kırşehir Ahi Evran University Faculty of Medicine, Health Sciences Scientific Research Ethics Committee (dated 30.04.2024 and numbered 2024-09/69).

Authors' Contributions

Concept/Design: EÇ, MBK, HMA, SAA, YEK, CO, SÇ. Data Collection and/or Processing: MBK, KMA, SAA, YEK, CO. Data analysis and interpretation: AÇ, SÇ. Literature Search: EÇ, HMA, SÇ. Drafting manuscript: EÇ. Critical revision of manuscript: EÇ, MBK, HMA, SAA, YEK, CO, SÇ. Supervisor: EÇ.

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

D-Dimer/Fibrinogen Ratio as a Prominent Predictor of Mortality in COVID-19 Patients Admitted To the Intensive Care Unit

Yoğun Bakım Ünitesinde Yatan COVID-19 Hastalarında Mortalitenin Belirgin Bir Belirleyicisi Olarak D-Dimer/Fibrinojen Oranı

Avşar ZERMAN[1] Cihan AYDIN[2] Nermin ZERMAN[1]

ÖZ

Amaç: Bu retrospektif kohort çalışmada komorbidite varlığı üzerinden herhangi bir kısıtlama olmaksızın D-dimer/fibrinojen oranının COVID-19'da bir belirleyici olarak değerlendirilmesi amaçlandı.
Araçlar ve Yöntem: Yoğun bakım ünitesine kabul edilen hastalarla retrospektif kohort çalışması yapıldı. Demografik veriler (cinsiyet, yaş, vücut kitle indeksi, komorbiditeler), prognostik klinik skorlar, sıralı organ yetmezliği değerlendirme (SOFA) skoru ve Glasgow Koma Skalası (GKS) skorları, Yoğun bakımda yatan hastaların laboratuvar sonuçları ve invazif mekanik ventilasyon (İMV) ihtiyacı ve süresi kaydedildi.
Bulgular: Kronik böbrek hastalıkları, akut böbrek yetmezliği, kalp hastalıkları ve şiddetli sepsis, çıkış grubunda anlamlı olarak daha yüksekti. Daha düşük lenfosit seviyelerinin artan ölüm oranıyla ilişkili olduğu bulunmuştur. Ayrıca nötrofil/lenfosit oranı (NLR) ve nötrofiller artan mortaliteyle ilişkiliydi. Daha yüksek D-dimer/fibrinojen oranı (DDFR) mortalite için bir risk faktörüydü, ancak yoğun bakım ünitesinde yatış süresi için bir risk faktörü değildi.
Sonuç: DDFR'nin, COVID-19'da hastane içi mortaliteyi öngörmede potansiyel bir etkisi vardır.

Anahtar Kelimeler: COVID-19; doğuştan gelen inflamatuar yanıt; kan pıhtılaşması; ölüm oranı

ABSTRACT

Purpose: In this retrospective cohort study, evaluating the role of the D-dimer/fibrinogen ratio in predicting the in-hospital mortality rate of COVID-19 regardless of the presence of comorbidities was aimed.
Materials and Methods: This retrospective cohort study included patients admitted to the intensive care unit. The demographic data of the patients (sex, age, body mass index, comorbidities), their prognostic clinical scores, laboratory results, and need for and duration of invasive mechanical ventilation (IMV) were recorded.
Results: The rates of chronic renal diseases, acute renal failure, cardiac diseases, and severe sepsis were significantly higher in the exitus group. It was found that lower levels of lymphocytes were associated with increased mortality. Furthermore, neutrophil counts and the neutrophil to lymphocyte ratio (NLR) were associated with increased mortality. A higher D-dimer/fibrinogen ratio (DDFR) was a predictor of mortality but not a predictor of the duration of hospitalization in the ICU.
Conclusion: DDFR has a potential impact in anticipating mortality rates in COVID-19 patients.

Keywords: COVID-19; blood coagulation; innate inflammatory response; mortality rate

Received: 30.08.2023; Accepted: 07.10.2024

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How to cite: Zerman A, Aydın C, Zerman N. D-Dimer/fibrinogen ratio as a prominent predictor of mortality in COVID-19 patients admitted to the intensive care unit. Ahi Evran Med J. 2025;9(1):17-23. DOI: 10.46332/aemj.1352549

INTRODUCTION

COVID-19 has spread all over the world since December 2019. COVID-19 infection has been shown to have a considerable potential for high mortality and morbidity.[1]

In the early phase of the COVID-19 pandemic, several studies were conducted to determine risk factors for poor prognosis.[2,3] These studies found comorbidities such as diabetes mellitus (DM), ischemic heart diseases, and heart failure which include the pathological inflammation and coagulation processes in the cellular background as risk factors.[4,5] COVID-19 infection may cause a fatal course via the dysregulation of coagulation and inflammation responses.[1,3-5]

The interrelations between coagulation and inflammation in COVID-19 infections led researchers and clinicians to evaluate COVID-19 as a thrombo-inflammatory syndrome.[6,7] Widespread endothelial dysfunction, severe coagulopathy, and thromboembolism occur in severe COVID-19 infection cases.[8] Anticoagulants and proteases activated in the coagulation process regulate inflammation through specific cell receptors, whereas proinflammatory cytokines and chemokines affect procoagulant and anticoagulant processes.

D-dimer forms after fibrin decomposition during fibrinolysis.[9] D-dimer and fibrinogen are both products in the coagulation cascade, and their high levels have been found as predictors of poor outcomes in COVID-19 cases.[1,3,10-12]

In previous studies, the D-dimer/fibrinogen ratio (DDFR) was shown to be a predictor of poor outcomes of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and heart failure.[9,13]

Elevated DDFR was found to have a worsening impact on outcomes of COVID-19 with concomitant heart failure.[14]

In this retrospective cohort study, we aimed to research the predictive role of DDFR in COVID-19 without regard to the presence of comorbidities and to contribute to the current literature considering the limited number of studies investigating this parameter in this context.

MATERIALS and METHODS

Patients

This study was approved by the Clinical Research Ethics Committee of Kırşehir Ahi Evran University (dated 09.08.2022 and numbered 2022-15/137). Patients hospitalized with COVID-19 infection in the intensive care unit (ICU) between April 2020 and September 2022 were included. Patients with pregnancy and life-threatening conditions such as severe heart failure, renal failure, malignancy, and acute coronary syndrome were not included in the sample.

Methods

The demographic data of the patients (sex, age, body mass index, comorbidities), their prognostic clinical scores, their laboratory results, and their need for and duration of inva-sive mechanical ventilation (IMV) were recorded.

APACHE II

APACHE II is a clinical parameter used to predict the chances of mortality in patients hospitalized in the ICU.[15] Age, body temperature, mean arterial pressure, arterial blood gas pH results, heart rate, respiratory rate, laboratory test results (sodium, potassium, creatinine, acute renal failure, white blood cell count, and hematocrit), Glasgow Coma Scale (GCS) scores, and the fraction of inspired oxygen (FiO_2) are all included in the clinical score. The concentration of oxygen in room air is approximately 21%. The APACHE II score represents the probability of mortality as a percentage (%).

SOFA

SOFA is a sepsis-related organ failure assessment score that includes the partial pressure of oxygen, FiO_2, need for mechanical ventilation, platelets, bilirubin, creatinine, GCS, and mean arterial pressure or need for vasopressor medication. The SOFA score refers to the probability of mortality as a percentage.[16,17]

Glasgow Coma Scale

The GCS is used to systematically assess the degree of compromised consciousness and includes three aspects of responsiveness: eye-opening, motor responses, and verbal responses. GCS scores vary in the range of 3-15.[18]

Statistical Analysis

The rate of in-hospital mortality was the primary outcome measure, while the length of hospital stay in the ICU and the requirement of invasive mechanical ventilation were the secondary outcome measures. The Statistical Package for the Social Sciences version 28.0 software for Windows (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp., USA) was used to conduct the statistical analyses. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality assumptions of the quantitative variables. Depending on the type of variable and the normality of distributions, the Chi-Squared test, Fisher-Freeman-Halton test, and the Mann Whitney-U test were employed for the univariate analysis of the variables. The relationship between ICU hospitalization duration and DDFR was analyzed using Spearman correlation test. The descriptive statistics of the variables are presented as mean±standard deviation, frequencies (n), and percentages (%). Bivariate logistic regression analysis was performed to determine the effective risk factors in determining the mortality rates of the patients. Forward: The conditional logistic regression analysis method was used to determine the most accurate logistic model.

RESULTS

We included 267 patients in this study. Among these patients, 55.8% (n:149) died due to COVID-19 infection. The results of the group of patients who died from COVID-19 were compared with those of the group who survived (Supplement Table 1). The differences between the sex (p=0.937) and BMI (p=0.254) distributions of the two groups were not statistically significant. A significant mortality risk factor was older age (p=0.000). A 1-unit increase in age corresponded to a 0.077-unit increase in the probability of mortality (OR: 1.077, 95% CI: 1.046-1.109, p=0.000). A 1-unit increase in ferritin levels was found to increase the probability of mortality by 0.001 units (OR: 1.001, 95% CI: 1.000-1.002, p=0.022) (Table 1).

Following the univariate analysis conducted to evaluate the differences in mortality status among patients based on the included parameters, bivariate logistic regression analysis was performed to determine whether these parameters were significant risk factors for mortality. The forward conditional logistic regression analysis method was used to determine the most accurate logistic model, and the percentage correct value was 85.7%. The model's correct estimation value was also appropriate according to the Hosmer-Lemeshow test score (χ^2=5.857, P=0.663). The coefficients found as a result of the bivariate logistic regression analysis are shown in Table 1.

Table 1. Bivariate logistic regression analysis results.

Variables	B	S.E.	Sig.	OR	95% CI for Exp(B) Lower-Upper
Age	0.074	0.015	0.000	1.077	1.046-1.109
Serum albumin	1.392	0.447	0.002	4.022	1.674-9.663
Ferritin	0.001	0.002	0.022	1.001	1.000-1.002
LDH	0.002	0.001	0.007	1.002	1.001-1.004
IMV	3.827	0.573	0.000	45.903	14.928-141.150
Hospitalization duration	0.085	0.024	0.000	1.089	1.039-1.142

LDH: Lactate dehydrogenase, IMV: invasive mechanical ventilation

Clinical Scores

The clinical scores of the exitus group, including their APACHE-II (p=0.000), SOFA (p=0.000), and GCS (p=0.000) scores, were significantly higher than those of the non-exitus group.

Comorbidities

Chronic renal diseases (p=0.028), acute renal failure (p=0.014), cardiac diseases (p=0.014), and severe sepsis (p=0.000) were associated with mortality.

Hemogram Parameters

Lower lymphocyte counts (p=0.006), higher neutrophil to lymphocyte ratios (NLR) (p=0.000), and higher neutrophil counts (p=0.044) were risk factors for an increased risk of mortality.

Biochemical Parameters

Lower plasma serum albumin levels (p=0.000) were a predictor of increased mortality. Furthermore, higher levels of procalcitonin, C-reactive protein (CRP) (p=0.034), neutrophils (p=0.044), ferritin (p=0.002), lactate dehydrogenase (LDH) (p=0.003), uric acid (p=0.001), troponin (p=0.000), CK-MB (p=0.005), lactate (p=0.013), and aspartate aminotransferase (AST) (p=0.005) were related to increased mortality rates.

A 1-unit decrease in serum albumin values corresponded to a 3.022-unit increase in mortality rates (OR: 4.022, 95% CI: 1.674-9.663, p=0.002). A 1-unit increase in ferritin values corresponded to a 0.001-unit increase in mortality rates (OR: 1.001, 95% CI: 1.000-1.002, p=0.022). A 1-unit increase in LDH 1 values corresponded to a 0.002-unit increase in mortality rates (OR: 1.002, 95% CI: 1.001-1.004, p=0.007).

Other Clinical Parameters

The requirement of invasive mechanical ventilation was related to mortality (55.7% vs 6.0%, p-value: 0.000). A 1-unit increase in the requirement of invasive mechanical ventilation corresponded to a 44.903-unit increase in mortality rates (OR: 1.089, 95% CI: 14.928-141.150, p=0.000).

D-Dimer/Fibrinogen Ratio

A higher DDFR was a predictor of mortality (p=0.000), but it was not a predictor of the duration of hospitalization in the ICU (p=0.313). Spearman's Rho coefficients showing the relationship between ICU hospitalization durations and DDFR values are shown in Supplement table Table 1. There was no statistically significant relationship between DDFR values and ICU hospitalization durations (ρ=-0.062, p=0.313) (Table 2).

Table 2. The relationship between the D-dimer/Fibrinogen ratio and ICU hospitalization durations.

Spearman's rho	ICU hospitalization duration	DDFR
ICU hospitalization duration	Rho	-0.062
	1.000	
	p	0.313
DDFR	Rho	
	p	1000

ICU: Intensive care unit, DDFR: D-dimer/Fibrinogen ratio.

DISCUSSION

We found that the D-dimer/Fibrinogen ratio (DDFR) was a potential predictor of the mortality of COVID-19 in the ICU. The exitus group had significantly higher DDFR values than the non-exitus group (p<0.005). The elevation of this biomarker is caused by the dysregulation of inflammation and thrombosis. The comparison of the laboratory results of the two groups also supported this implication. Lower plasma serum albumin and higher values of procalcitonin, CRP, neutrophils, ferritin, and LDH were associated with increased mortality. The results of this study were consistent with the current literature. Previously, older age, chronic renal diseases, acute renal failure, cardiac diseases, and severe sepsis have been identified as predictors of poor prognosis.[19-22] Considering our laboratory results and those reported in previous studies, it can be concluded that higher levels of troponin, NLR, LDH, AST, CRP, procalcitonin, and ferritin, in addition to lower levels of serum albumin and lymphocytes, are predictors of mortality in COVID-19 cases.[21-25]

An important aspect to emphasize is the limited number of studies that have evaluated the worsening impact of higher DDFR values in COVID-19 cases. Most previous studies have revealed that D-dimer and fibrinogen are independent predictors of poor outcomes.[26-29]

In the review article by Bivona et al., the potential of laboratory parameters to affect COVID-19 severity was analyzed comprehensively.[30] An evaluation was carried out separately for each laboratory parameter with qualified

studies. Similar to our results, higher levels of troponin, NLR, LDH, AST, CRP, procalcitonin, and ferritin, in addition to lower levels of serum albumin and lymphocytes, were identified as predictors of severe infection. These results considered along with our results demonstrate the need for more research about new biomarkers in this context.

In the meta-analysis study conducted by Zhan et al., 33 studies were included. Elevated D-dimer values were found as a risk factor for thromboembolism, infection severity, and mortality in COVID-19 cases.[26] These findings were also strongly linked to the underlying mechanism of death. The interaction between inflammation and coagulation, as well as dysregulated inflammation, lead to severe COVID-19 infection. Thrombotic processes can also cause fatal outcomes via thromboembolism.[26]

Fibrinogen was also found to be an important product in the coagulation cascade and identified as a critical laboratory parameter in the study conducted by D'Ardes et al.[28] The underlying mechanism of the prognostic role of fibrinogen was explained by altered polymerization kinetics, partly accounted for by an increase in sialic acid on the cellular level.[29] These findings also indicated the crucial role of coagulation, inflammation, and endothelial damage in these processes. Anticoagulants and proteases activated during coagulation regulate inflammation through specific cell receptors, whereas proinflammatory cytokines and chemokines affect procoagulant and anticoagulant processes.

The expression of tissue factor in endothelial surfaces is increased by IL-6, TNF-, IL-1, and CRP, and the presentation of tissue factor is the first step in the coagulation cascade.[31]

Aydin et al. found that DDFR was a predictor in AECOPD, which is characterized also by respiratory failure similar to the case in patients with COVID-19 infection.[9]

Murat et al. conducted a retrospectively designed two-center study with 232 COVID-19 patients with concomitant heart failure (HF) hospitalized in the ICU.[14] The tertiles 1-3 of patients with HF and COVID-19 were categorized. DDFR values below 0.37, between 0.38 and 1.13, and above 1.13 were included in the first tertile, second tertile, and third tertile, respectively. The optimal cutoff value of serum DDFR was calculated to be 0.61. DDFR was related to in-hospital mortality. Our findings were consistent with these results, and we analyzed this marker in a sample formed without a restriction based on the presence of comorbidities. Patients with severe heart failure were probably included in their study, as far as understood from the inclusion and exclusion criteria. Besides, to make clear conclusions, we excluded patients with life-threatening conditions such as severe heart failure, renal failure, malignancy, and acute coronary syndrome.

A fatal course via the dysregulation of the thrombotic and inflammatory processes occurs at on cellular level.[1] The interrelations between thrombosis and inflammation led researchers and clinicians to evaluate COVID-19 as a thrombo-inflammatory syndrome.[6,7]

D-dimer forms after fibrin decomposition during fibrinolysis.[9] Both D-dimer and fibrinogen have functions in the coagulation cascade and have been reported to be markers of poor prognosis in COVID-19 cases.[1,3,10-12]

It was determined that elevated levels of D-dimer and fibrinogen were brought on by pulmonary inflammation led by COVID-19, along with localized platelet activation, blood coagulation, and relative hypofibrinolysis.[7] Hyperinflammation is triggered by COVID-19 through the impairment of innate and adaptive antiviral defense mechanisms. The renin-angiotensin-aldosterone system (RAAS) activates pathological hypercoagulability and immunothrombosis. At this point, it should also be emphasized that the COVID-19 infection process in the human body is facilitated through the ACE-2 receptors on the cell surface.

This study, with an optimal design, has the potential to contribute to the current literature considering the low number of previous studies on the topic in this context and the suboptimal designs in these studies. DDFR has a potential role in the anticipation of mortality in COVID-19. Besides, physicians can contribute to the current literature by researching new biomarkers.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

This study was approved by the Clinical Research Ethics Committee of Kırşehir Ahi Evran University (dated 09.08.2022 and numbered 2022-15/137).

Authors' Contributions

Concept/Design: AZ, CA. Data Collection and/or Processing: AZ, NZ. Data analysis and interpretation: AZ, CA. Literature Search: NZ, CA. Drafting manuscript: CA, NZ. Critical revision of manuscript: AZ.

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Evaluation of the Relationship Between Systemic Immune-Inflammatory Index and Morning Blood Pressure Surge in Newly Diagnosed Essential Hypertension Patients

Yeni Tanı Almış Esansiyel Hipertansiyon Hastalarında Sistemik İmmün İnflamatuar İndeksi ve Sabah Kan Basıncı Dalgalanması Arasındaki İlişkinin Değerlendirilmesi

***Muhammet Salih ATEŞ*[1] *Fikret KELEŞ*[1]**

ÖZ

Amaç: Bu çalışma, yeni tanı konmuş esansiyel hipertansiyon hastalarında Sistemik İmmün-İnflamatuar İndeks (Sİİ) ile Sabah Kan Basıncı Yükselmesi (SKBY) arasındaki ilişkiyi araştırmayı amaçlamaktadır.
Araçlar ve Yöntem: Nisan ve Haziran 2024 tarihleri arasında, kardiyoloji polikliniğinden 217 kontrol ve 188 hipertansif hastadan oluşan 405 katılımcıyı içeren kesitsel bir çalışma yapılmıştır. Katılımcıların kan basıncı, Ayaktan Kan Basıncı İzleme (AKBİ) kullanılarak izlenmiş ve Sİİ dahil inflamatuar belirteçler değerlendirilmiştir. Sİİ, platelet sayısının nötrofil sayısıyla çarpılması ve lenfosit sayısına bölünmesiyle hesaplanmıştır. İstatistiksel analizler, SKBY'yi öngörmede Sİİ'nin değerini değerlendirmek için ROC eğrisi analizini içermektedir.
Bulgular: Hipertansif hastalar, kontrol grubuna kıyasla 24 saatlik, gündüz ve gece sistolik ve diyastolik kan basıncı değerlerinin anlamlı derecede yüksek olduğunu göstermiştir (hepsi $p<0.001$). SKBY ve Sİİ de hipertansif grupta anlamlı derecede yükselmiştir (her ikisi de $p=0.003$). ROC analizi, Sİİ'nin 27.3 mmHg'nin üzerinde SKBY 'yi öngörmede 577.38 kesim değeri ile %56.4 duyarlılık ve %67 özgüllükle 0.645 ($p=0.001$) AUC'ye sahip olduğunu göstermiştir. Yüksek nötrofil ve platelet sayıları, daha yüksek kan basıncı seviyeleri ve kardiyovasküler risk ile ilişkilendirilmiştir.
Sonuç: Çalışma, hipertansif hastalarda Sİİ ve SKBY arasında anlamlı bir ilişki olduğunu belirlemiş, bu da sistemik inflamasyonun kan basıncının düzenlenmesinde ve hipertansiyonun patogenezinde rol oynayabileceğini önermektedir. Sİİ, SKBY ve ilgili kardiyovasküler riskleri öngörmede değerli bir biyomarker olarak kullanılabilir ve daha erken ve daha hedeflenmiş müdahaleleri kolaylaştırabilir.

Anahtar Kelimeler: enflamatuar belirteçler; kan basıncı değişkenliği; kardiyovasküler hastalık; kardiyovasküler risk

ABSTRACT

Purpose: This study aims to explore the relationship between the Systemic Immune-Inflammatory Index (SII) and Morning Blood Pressure Surge (MBPS) in patients with newly diagnosed essential hypertension.
Materials and Methods: A cross-sectional study was conducted between April and June 2024, involving 405 participants, 217 controls, and 188 hypertensive patients, recruited from a cardiology outpatient clinic. Participants' blood pressure was monitored using Ambulatory Blood Pressure Monitoring (ABPM), and inflammatory markers, including SII, were assessed. SII was calculated by multiplying platelet count by neutrophil count and dividing by lymphocyte count. Statistical analysis included ROC curve analysis to evaluate SII's predictive value for MBPS.
Results: Hypertensive patients exhibited significantly higher 24-hour, daytime, and nighttime systolic and diastolic blood pressure values compared to controls (all $p<0.001$). MBPS and SII were also significantly elevated in the hypertensive group (both $p=0.003$). ROC analysis demonstrated that SII had an AUC of 0.645 ($p=0.001$) with a sensitivity of 56.4% and specificity of 67% at a cut-off value of 577.38 for predicting MBPS greater than 27.3 mmHg. Elevated neutrophil and platelet counts were associated with higher blood pressure levels and cardiovascular risk.
Conclusion: The study identified a significant association between SII and MBPS in hypertensive patients, suggesting that systemic inflammation may play a role in the regulation of blood pressure and the pathogenesis of hypertension. SII could serve as a valuable biomarker for predicting MBPS and associated cardiovascular risks, facilitating earlier and more targeted interventions.

Keywords: blood pressure variability; cardiovascular disease; cardiovascular risk; inflammatory markers

Received: 30.07.2024; Accepted: 04.11.2024

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How to cite: Ateş MS, Keleş F. Evaluation of the relationship between systemic immune-inflammatory index and morning blood pressure surge in newly diagnosed essential hypertension patients. Ahi Evran Med J. 2025;9(1):24-29. DOI: 10.46332/aemj.1525095

INTRODUCTION

Hypertension remains a pervasive cardiovascular risk factor, significantly contributing to the global burden of heart disease, cerebrovascular accidents, and renal dysfunction.[1] Among the various forms of hypertension, essential hypertension is particularly prevalent, affecting a large segment of the adult population.[2] This condition is characterized by elevated blood pressure levels in the absence of a discernible secondary cause, making its management a primary focus of clinical practice and public health initiatives. The pathophysiology of essential hypertension is multifaceted, involving a complex interplay of genetic, environmental, and lifestyle factors that culminate in sustained hypertension and end-organ damage.[3]

Recently, there has been increasing recognition of the role systemic immune and inflammatory mechanisms play in the etiology and progression of essential hypertension.[4,5] Chronic low-grade inflammation and immune system dysregulation have been implicated in vascular remodeling, endothelial dysfunction, and heightened vascular resistance-all key features of hypertension. The identification of reliable biomarkers that can capture the extent of immune and inflammatory activity is crucial for advancing our understanding of hypertension and improving prognostic assessments.

The Systemic Immune-Inflammatory Index (SII) is an innovative biomarker that encapsulates the systemic inflammatory status by integrating three readily available hematological parameters: platelet count, neutrophil count, and lymphocyte count. This composite index has garnered attention for its prognostic value across a spectrum of diseases, including oncological, infectious, and cardiovascular conditions.[6,7] In the context of hypertension, elevated SII levels may reflect an ongoing inflammatory process that exacerbates vascular dysfunction and contributes to poor clinical outcomes. Understanding the relationship between SII and hypertension could offer novel insights into the disease's pathophysiology and potential therapeutic targets.

Adding to the complexity of hypertension management is the phenomenon of the morning blood pressure surge (MBPS), a transient but significant rise in blood pressure occurring during the early morning hours. This surge has been associated with an increased risk of cardiovascular events; stroke and myocardial infarction, underscoring the need for effective monitoring and intervention strategies.[8,9] The pathogenesis of MBPS is thought to involve a combination of neurohormonal fluctuations, autonomic nervous system activity, and vascular reactivity. Investigating the interplay between SII and MBPS may reveal critical links between inflammation, circadian rhythms, and cardiovascular risk in hypertensive patients.

This study aims to investigate the relationship between SII and MBPS in patients with newly diagnosed essential hypertension. By examining these associations, we hope to delineate the potential role of systemic inflammation in the initial stages of hypertension and its impact on circadian blood pressure patterns.

MATERIALS and METHODS

Study Design and Participants

This cross-sectional study was conducted between June and July 2024, involving patients who were newly diagnosed with essential hypertension. Participants were recruited from the cardiology outpatient clinic. Inclusion criteria encompassed adults aged 18-75 years with newly diagnosed essential hypertension, while exclusion criteria involved patients with secondary hypertension, malignancies, hyperthyroidism, chronic renal disease, rheumatologic conditions, inflammatory diseases, active infections, those on antiplatelet or antibiotic therapy, and those on antihypertensive medication. A power analysis using G*Power (version 3.1.9.4) with an effect size of 0.50 determined a required sample size of 88 participants per group, totaling 176 participants. This study was approved by the Scientific Ethics Committee of Kırşehir Ahi Evran University Faculty of Medicine, Health Sciences (dated 11.06.2024 and numbered 2024-12/98).

Ambulatory Blood Pressure Monitoring (ABPM)

ABPM was utilized to obtain accurate blood pressure measurements over a 24-hour period. An appropriately sized cuff was placed on the non-dominant arm of each participant. ABPM devices were calibrated every six

months to ensure accuracy and reliability of the measurements. Blood pressure was measured every half hour at night and every 15 minutes during the day. Participants were instructed to adhere to their usual daily routines and remain still during measurements. The recorded data was transferred to a computer for analysis.

Measurement of Blood Pressure and Calculation of MBPS

The data collected encompassed systolic blood pressure (SBP) and diastolic blood pressure (DBP) values over 24 hours, as well as during daytime and nighttime periods. Hypertension was classified based on a 24-hour average SBP exceeding 130 mmHg and/or DBP exceeding 80 mmHg. Additionally, an average daytime SBP over 135 mmHg and/or DBP over 85 mmHg, and an average nighttime SBP above 120 mmHg and/or DBP above 70 mmHg were also indicative of hypertension.[10] MBPS was determined by subtracting the mean SBP one hour before waking from the mean SBP two hours after waking.[11]

Inflammatory Markers

Blood samples were obtained the following morning after an overnight fast to assess inflammatory markers. SII was calculated by multiplying the platelet count by the neutrophil count and then dividing this product by the lymphocyte count.[12] Other markers were also assessed, including the platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR).

Statistical Analysis

The statistical analyses were performed using IBM SPSS version 29.0 for Windows (Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. Descriptive statistics were presented as median (25th-75th percentiles) and frequencies (n %). In the study, the comparisons between two groups for continuous quantitative variables, where the assumption of normality was not met, were conducted using the Mann-Whitney U test. Categorical variables were analyzed using chi-square. A receiver operating characteristic (ROC) curve analysis was conducted, with particular emphasis on establishing a diagnostic threshold for a MBPS greater than 27.3 mmHg.

RESULTS

A total of 405 participants were enrolled in the study, comprising 217 individuals in the control group and 188 in the hypertensive group. Age differences between the control and hypertensive groups were not statistically significant (p=0.099). The gender distribution was similar across both groups, with males representing 46.1% of the control group and 50% of the hypertensive group (p=0.431).

Lipid profiles, hematological parameters, and lymphocyte counts showed no significant differences between the control and hypertensive groups, though neutrophil counts were marginally higher in the hypertensive group (Table 1).

Blood pressure measurements indicated significantly higher values in the hypertensive group across all periods, including 24-hour, daytime, and nighttime SBP and DBP (all p<0.001). The MBPS and the SII were also significantly elevated in the hypertensive group (p=0.003 for both). Additionally, the PLR and NLR were higher in the hypertensive group (p=0.034 and p=0.023, respectively). For comprehensive data, refer to Table 1.

Hypertensive patients were divided into two groups based on the median MBPS value of 27.3, with the median serving as the cutoff point. Age and gender distribution were similar between hypertensive patients with MBPS below and above 27.3 mmHg. However, platelet counts were significantly higher in the group with MBPS above 27.3 mmHg (p=0.002). Neutrophil counts were significantly elevated in the group with higher MBPS (p<0.001).

The SII was notably higher in hypertensive patients with MBPS above 27.3 mmHg compared to those with MBPS below this threshold (p=0.001). In contrast, the PLR and NLR did not show significant differences between these two groups, with p-values of 0.147 and 0.216, respectively (Table 2).

ROC curve analysis evaluated the predictive value of SII, NLR, and PLR for MBPS above 27.3 mmHg in hypertensive patients. The SII had an AUC of 0.645 (p=0.001), a

cut-off of 577.38, 56.4% sensitivity, and 67% specificity. PLR showed an AUC of 0.561 (p=0.147), with a cut-off of 115.39, 55.3% sensitivity, and 59.6% specificity. NLR had an AUC of 0.552 (p=0.217), a cut-off of 2.05, 51.1% sensitivity, and 61.7% specificity. (Figure 1).

Table 1. Comparison of demographic and laboratory characteristics of Controls and Hypertensive groups.

Variable	Control Group (n=217)	Hypertensive (n=188)	p-value
Age, year	54 (45.5-64)	57 (47-65)	p=0.099
Gender (male), n (%)	100 (46.1)	94 (50)	p=0.431
LDL, mg/dl	110 (89-134)	116.5 (93-142)	p=0.215
HDL, mg/dl	46 (39-56)	46 (39-55)	p=0.940
Triglyceride, mg/dl	142 (96-214)	160 (104.5-233)	p=0.098
Hgb, g/dl	14.3 (13.2-15.5)	14.3 (13.1-15.6)	p=0.778
White Blood Cell, 103/µl	7.60 (6.53-8.99)	7.74 (6.45-9.69)	p=0.194
Platelet, 103/µl	264 (225-302)	270 (225-304)	p=0.595
Neutrophil, 103/µl	4.46 (3.65-5.19)	4.84 (3.75-5.90)	p=0.055
Lymphocyte, 103/µl	2.43 (1.97-2.88)	2.34 (1.86-2.84)	p=0.296
Glucose, mg/dl	101 (91-110)	104 (90-142)	p=0.145
Creatinine, mg/dl	0.80 (0.67-0.91)	0.82 (0.69-0.98)	p=0.073
24-h SBP, mmHg	111 (106-116)	130 (123-137)	p<0.001
24-h DBP, mmHg	63 (59-68)	76.5 (70.25-82)	p<0.001
Daytime SBP, mmHg	113 (108-120)	132 (124-140)	p<0.001
Daytime DBP, mmHg	66 (61-71)	78 (71-85)	p<0.001
Nighttime SBP, mmHg	104 (99-112)	126 (120-134)	p<0.001
Nighttime DBP, mmHg	59 (54-63.5)	73 (67-79)	p<0.001
MBPS, mmHg	25 (16.46-32.35)	27.30 (21.1-36.45)	p=0.003
SII	494.5 (379.5-593.5)	545.7 (381.5-697.9)	p=0.003
PLR	110.9 (87.7-130.4)	113.5 (89.6-144.4)	p=0.034
NLR	1.85 (1.48-2.23)	1.96 (1.51-2.61)	p=0.023

Values are n (%),median (25th and 75th percentiles). LDL: Low-density lipoprotein, HDL: High-density lipoprotein, Hgb: Hemoglobin, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBPS: Morning Blood Pressure Surge, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune-inflammation index.

Table 2. Comparison of demographic and laboratory characteristics according to the median value of MBPS in hypertensive patients

Variables	MBPS<27.30 (n=94)	MBPS>27.30 (n=94)	p-value
Age, year	57.5 (47-66)	57 (45.75-65)	p=0.775
Gender (male), n (%)	48 (51.1)	46 (48.9)	p=0.770
Platelet, 103/µl	254 (212-286)	275.5 (234.5-343.2)	p=0.002
Neutrophil, 103/µl	4.25 (3.59-5.15)	5.22 (4.02-6.86)	p<0.001
Lymphocyte, 103/µl	2.31 (1.74-2.70)	2.37 (2.01-3.02)	p=0.082
SII	508.9 (350.5-610.8)	614.54 (403.6-888.2)	p=0.001
PLR	110.9 (89.9-137.2)	118.4(89.4-148.3)	p=0.147
NLR	1.96 (1.58-2.35)	2.07 (1.50-2.91)	p=0.216

Values are n (%), median (25th and 75th percentiles). MBPS: Morning Blood Pressure Surge, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune-inflammation index.

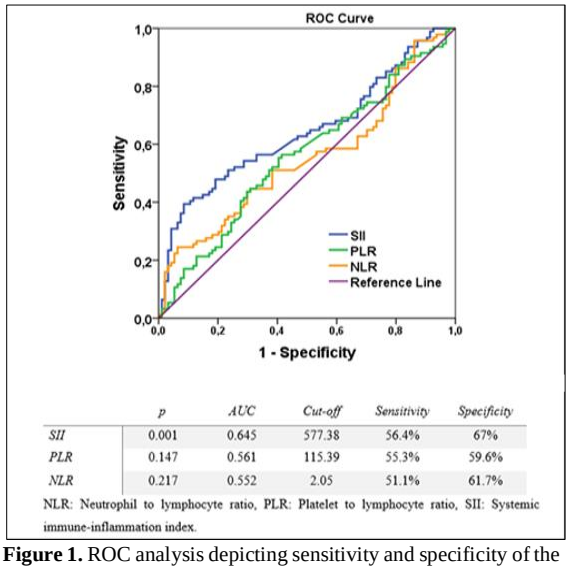

Figure 1. ROC analysis depicting sensitivity and specificity of the Systemic Immune-Inflammation Index (SII), Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to Lymphocyte Ratio (PLR) for predicting a mean Blood Pressure Surge (MBPS) exceeding 27.3 in hypertensive patients.

DISCUSSION

In this study, we observed that hypertensive patients exhibited significantly higher 24-hour systolic and diastolic blood pressure values compared to controls, alongside an elevated MBPS. Our findings suggest a significant association between the SII and MBPS, indicating that higher SII values are linked with greater MBPS. These results highlight the potential role of systemic inflammation in the regulation of blood pressure and the pathogenesis of hypertension.

Earlier research has shown a connection between inflammation and elevated blood pressure. For instance, Saylik et al. reported that higher SII levels were independently associated with exaggerated morning surge in newly diagnosed, treatment-naive hypertensive patients.[13] Our study

corroborates these findings, showing a significant correlation between SII and MBPS, and further extends the understanding of how systemic inflammation might contribute to blood pressure variability.

In our study, the significant differences in neutrophil and platelet counts observed between the hypertensive and control groups support the association between systemic inflammation and BP variability. Elevated neutrophil counts have been implicated in the pathogenesis of hypertension through mechanisms involving oxidative stress and endothelial dysfunction.[14] Similarly, increased platelet counts, and activity have been associated with higher blood pressure levels and cardiovascular risk.[15] These findings underscore the importance of inflammatory pathways in the development and progression of hypertension.

Besides SII, we assessed other inflammatory markers like NLR and PLR. Both NLR and PLR were significantly elevated in hypertensive patients compared to controls, consistent with previous research identifying these ratios as predictors of hypertension and cardiovascular events.[16,17] The inclusion of these markers alongside SII provides a comprehensive assessment of the inflammatory status in hypertensive patients and their potential impact on blood pressure regulation.

Given the strong association between SII and MBPS, SII could serve as a valuable biomarker for identifying hypertensive patients at higher risk for cardiovascular events. The ability to predict MBPS through a simple blood test could facilitate earlier intervention and more personalized treatment strategies, improving patient outcomes. Furthermore, targeting systemic inflammation through lifestyle modifications and pharmacological interventions may offer a novel approach to managing hypertension and reducing cardiovascular risk.

Despite the strengths of our study, including a large sample size and the use of ABPM for accurate blood pressure measurement, there are limitations that must be acknowledged. The exclusion of patients on antihypertensive treatment limits the generalizability of our findings to all hypertensive patients. Additionally, the reliance on self-reported waking and sleeping times for calculating MBPS may introduce variability. Future studies should incorporate objective measures such as actigraphy to validate these periods and provide more accurate assessments.

Another limitation is the cross-sectional design of our study, which precludes conclusions about causality between systemic inflammation and MBPS. Longitudinal studies are required to establish the temporal relationship between these factors and to determine whether anti-inflammatory interventions can effectively reduce MBPS and related cardiovascular events. Moreover, our study did not evaluate other potential contributors to blood pressure variability, such as genetic factors, stress, and lifestyle habits, including diet and physical activity, which should be considered in future research.

The clinical importance of our study lies in the identification of SII as a potential biomarker for predicting exaggerated MBPS. Given that MBPS has been associated with increased cardiovascular events, our findings suggest that SII could be used as a simple, cost-effective marker to identify high-risk hypertensive patients. This could facilitate earlier and more targeted interventions to mitigate cardiovascular risk. Moreover, the use of SII in clinical practice could enhance risk stratification and personalized treatment approaches for hypertensive patients.

Conclusion

Our study demonstrates that hypertensive patients have significantly higher SII and MBPS compared to controls. The strong association between SII and MBPS highlights the potential role of systemic inflammation in the pathogenesis of hypertension and suggests that SII could serve as a valuable biomarker for predicting MBPS and associated cardiovascular risks. These findings underscore the importance of integrating inflammatory markers into the management of hypertension to improve patient outcomes and reduce the burden of cardiovascular disease.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

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Ethics Committee Permission

This study was approved by the Scientific Ethics Committee of Kırşehir Ahi Evran University Faculty of Medicine, Health Sciences (dated 11.06.2024 and numbered 2024-12/98).

Authors' Contributions

Concept/Design: MSA. Data Collection and/or Processing: MSA, FK. Data analysis and interpretation: MSA. Literature Search: MSA, FK. Drafting manuscript: MSA, FK. Critical revision of manuscript: MSA, FK.

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

The Role of Disease Activity as a Determinant of Central Sensitivity and Body Awareness in Fibromyalgia Patients: A Cross-Sectional Study

Fibromiyalji Hastalarında Merkezi Duyarlılık ve Vücut Farkındalığının Belirleyicisi Olarak Hastalık Aktivitesinin Rolü: Kesitsel Bir Çalışma

***Yasemin MİRZA*[1] *Adem KÜÇÜK*[1]**

ÖZ

Amaç: Bu çalışmanın amacı fibromiyalji sendromu (FMS) hastalarında hastalık aktivitesinin santral sensitizasyon ve vücut farkındalığı üzerine etkisini belirlemektir.
Araçlar ve Yöntem: Bu kesitsel çalışmaya FMS'li 45 hasta (ortalama yaş: 45.9 (6.9) yıl, ortanca hastalık süresi: 3 (2-6) yıl) katıldı. Hastalık aktivitesi, Fibromiyalji Etki Anketi (FEA) kullanılarak değerlendirildi ve daha yüksek puan yüksek hastalık aktivitesi olarak kabul edildi. Santral sensitizasyonu değerlendirmek için Santral Sensitizasyon Ölçeği (SSÖ) uygulandı. Vücut farkındalığı seviyeleri Vücut Farkındalığı Anketi (VFA) ile değerlendirildi. Ağrı şiddetini belirlemek için Görsel Analog Skala (GAS) kullanıldı. Hastalık aktivitesini hangi bağımsız değişkenin açıklayabileceğini araştırmak için basit doğrusal regresyon analizleri kullanıldı.
Bulgular: Ortalama FEA ve VFA puanları sırasıyla 53.4 ve 90 dı. Ortanca GAS ve SSÖ puanları sırasıyla 8 ve 52 idi. Tüm hastaların %82.2'sinde santral sensitizasyon pozitifti. FEA, GAS skoruyla orta düzeyde ilişkiliydi (r=0.445, R2=0.198, p=0.002) ve SSÖ ile yüksek düzeyde ilişkiliydi (r=0.539, R2=0.291, p<0.001). FEA ve VFA arasında ise anlamlı bir korelasyon saptanmadı (p=0.791). Basit doğrusal regresyon analizinin sonuçları, GAS'ın hastalık aktivitesinin %19.8'ini açıkladığını gösterdi. FEA (r=0.445, p=0.002) ağrı şiddetini anlamlı şekilde tahmin etti. Ayrıca SSÖ hastalık aktivitesinin %29.1'ini açıklarken, FEA (r=0.539, p<0.001) santral sensitizasyonu anlamlı şekilde öngörüldü.
Sonuç: Yüksek hastalık aktivitesi FMS'li hastalarda santral sensitizasyon ve vücut farkındalığını olumsuz bir şekilde etkilemektedir. Klinisyenler yüksek hastalık aktivitesi olan hastaların yönetiminde rutin tedavilere ek olarak multimodal biyopsikososyal bakış açısını da göz önünde bulundurmalıdır.

Anahtar Kelimeler: beden farkındalığı; fibromiyalji sendromu; hastalık aktivitesi; santral sensitizasyon

ABSTRACT

Purpose: The present study aimed to identify the influence of disease activity on central sensitization (CS) and body awareness in fibromyalgia syndrome (FMS) patients.
Materials and Methods: Forty-five patients with FMS (mean age: 45.9 (6.9) years, median disease duration: 3 (2-6) years) were participated this cross-sectional study. Disease activity was assessed using the Fibromyalgia Impact Questionnaire (FIQ) and higher score was considered high disease activity. The Central Sensitization Inventory (CSI) was performed for central sensitivity. Body awareness levels were evaluated with the Body Awareness Questionnaire (BAQ). Visual Analogue Scale (VAS) was used to identify pain severity. Simple linear regression analyses were used to determine which independent variables could explain disease activity.
Results: The mean FIQ and BAQ were 53.4 and 90 points, respectively. The median VAS and CSI were 8 cm and 52 point, respectively. The CS is positive in 82.2% of all patients. FIQ was moderately correlated with the VAS score (r=0.445, R2=0.198, p=0.002) and is highly correlated with CSI (r=0.539, R2=0.291, p<0.001). There was no significant correlation between FIQ and BAQ (p=0.791). The results of the simple linear regression analysis presented that VAS explained 19.8% of the the disease activity. FIQ (r=0.445, p=0.002) significantly predicted pain severity. Additionally, The CSI explained 29.1% of the disease activity and FIQ (r=0.539, p<0.001) significantly predicted CS.
Conclusion: High disease activity negatively impacts CS and body awareness in FMS patients. Clinicians should consider a multimodal biopsychosocial perspective in addition to routine treatments in the management of patients with high disease activity.

Keywords: body awareness; central sensitization; fibromyalgia syndrome, disease activity

Received: 14.08.2024; Accepted: 06.11.2024

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How to cite: Mirza Y, Küçük A. The role of dısease actıvıty as a determınant of central sensıtıvıty and body awareness in fibromyalgıa patıents: A cross-sectıonal study. Ahi Evran Med J. 2025;9(1):30-36. DOI: 10.46332/aemj.1533118

INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic disease characterized by widespread pain and tender points, accompanied by many symptoms such as sleep disturbance, morning stiffness, fatigue and psychiatric disorders.[1] The prevalence of FMS in the European population is 4.7%, with a higher prevalence in women than in men.[2] Currently, the most commonly used patient-based outcome measure to evaluate disease activity in FMS patients is the Fibromyalgia Impact Questionnaire (FIQ). FIQ evaluates factors such as pain, fatigue, stiffness, physical impairment, number of days feeling good, ability to do work, anxiety and depressive symptoms.[3] Evaluation of disease activity in FMS patients is very important in the management of the disease, follow-up of patients and prediction of prognosis.

Although the etiopathogenesis of FMS is unclear, central sensitization (CS) causing changes in pain modulation may explain widespread musculoskeletal pain.[4] CS is defined as increased response of nociceptive neurons in the central nervous system to various peripheral stimuli such as temperature, light, pressure and medication.[5] This central hyperactivity induces allodynia, hyperalgesia, and chronic widespread pain.[6] Through previous studies, CS has been shown to occur in a number of specific chronic pain populations, including FMS.[6-8] Furthermore, previous researches have demonstrated chronic musculoskeletal pain, emotional status and cognitive impairment associated with body awareness.[9,10] However, there is little knowledge about body awareness and CS in patients with FMS and its association with disease activity.

Body movements are key concepts for rehabilitation and the evaluation of body movements and awereness are crucial.[11] Body awareness is defined as focusing on internal body sensations, being aware of them, and perceiving movement responses with environmental and relational conditions.[12] Body awareness occurs through the integration of many sensory inputs such as interoceptive, exteroceptive, proprioceptive and vestibular and includes biopsychosocial mechanisms.[13] These complex cortical connections help the perception of body position, the relationship between body parts, and the ability to recognize one's own body.[14] Body awareness is thought to be related to body structure/functions and pain within the scope of the biopsychosocial mechanism.[15] Earlier studies have showed that there is a relationship between pain, depression level, functional status and body awareness in FMS patients.[16,17] In addition, preliminary evidences suggest that body awareness therapy may provide significant benefits in reducing pain and improving health-related quality of life in patients with FMS.[18,19]

The presence of CS may be the underlying cause of persistant pain experience in FMS patients despite routine treatment. Furthermore, our knowledge about CS and body awareness in FMS, which is characterized by chronic musculoskeletal pain, fatigue and other symptoms, is limited. Additionally, disease activity, which is frequently assessed in the clinical setting, may affect both CS and body awareness. So, we aimed to assess the impact of disease activity on CS and body awareness in FMS patients. The first hypothesis suggests that high disease activity is related to impaired body awareness. The second hypothesis proposes that disease activity is a determining factor on body awareness and CS.

MATERIALS and METHODS

This study was approved by Necmettin Erbakan University Drug and Non-Medical Device Research Ethics Committee (dated 01.03.2024 and numbered 2024/4831). All patients were informed about the study and then their written consent was obtained. The study was performed in regarding the Declaration of Helsinki's principles. This study was designed as a descriptive and cross-sectional study. Participants evaluated at Necmettin Erbakan University Hospital, Department of Rheumatology between April 2024 and July 2024.

Participants

Patients who were between the ages of 18 and 65, diagnosed with FMS by a specialized rheumatologist with 20 years of experience at Necmettin Erbakan University Hospital, Department of Rheumatology in line with the American College of Rheumatology's 2010 diagnostic criteria[20] and had chronic musculoskeletal pain for more than 3 months were included in this study. Patients were excluded if they had any neurological, cardiovascular and inflam-

matory joint diseases, musculoskeletal surgery, neuropsychiatric medical treatment, the presence of active malignancy, visual and hearing problems, pregnancy and regular exercise habit.

Outcome Measures

Information about sociodemographic, disease duration and medications were recorded. To assess self-reported pain severity was performed visual analog scale (VAS).[21] It consists of a solid line defined as 0 = "no pain" and 10 = "worst pain". Participants described their pain level on a line.

Disease Activity

The Turkish version of Fibromyalgia Impact Questionnaire (FIQ) was used to evaluate the degree of FMS symptoms and disease activity.[3] This self-reported questionnaire consists of 21 items evaluating physical impairment, well-being, work missed, and anxiety and depression. The total score was obtained from the sum of all subscales (general affect, activity level, and severity of symptoms); where higher scores indicated a high disease activity (0–100).

Central Sensitization

The Turkish version of Central Sensitivity Inventory (CSI) was used to evaluate the presence and severity of CS.[22] The questionnaire included 25 items assessing current symptoms related to CS. Each item is scored from 0 (never) to 4 (always). The total score is 100 points, with higher scores reflecting greater severity of symptoms. The cut-off point of CSI is 40 points.

Body Awareness

The Body Awareness Questionnaire (BAQ) includes four subgroups (changes in body processes, sleep-wake cycle, prediction at the onset of the disease, prediction of body reactions) and a total of 18 statements, aiming to determine the normal or abnormal sensitivity level of body composition. The patient is asked to give a score between 1 (not true for me at all) and 7 (completely true for me) for each statement. The total score varies between 18 and 126. A higher score indicates better body awareness. Turkish validity and reliability studies of this scale were conducted by Karaca et al.[23]

Statistical Analysis

The required sample size was determined using G Power software (Version 3.1.9.2, Franz Faul, University of Kiel, Kiel, Germany). The sample size of at least 41 individuals was found to have a power of 0.90, an effect size of 0.42 (medium effect d≥0.3), correlation test r2= 0.18, and an alpha value of 0.05 (one-tailed). The participant rate was calculated to be 10% higher in order to compensate for data losses in research process or statistical analysis process. As a result, 45 patients were participated in this study.

IBM SPSS (Statistical Package for the Social Sciences, ver. 22.0) was performed for statistical analyses. Shapiro Wilk test, probability plots and histograms were used to determine whether variables were normally distributed. Normally distributed variables were given as mean± standard deviation (SD), non-normal distributions were given as median (IQR), and non-numerical data were shown as frequency and percentage. The relationship between FIQ-VAS, CSI and BAQ was determined with Pearson's correlation analysis due to parametric conditions. The size of correlation coefficient was interpreted as following, very high; between 0.90 -1.00, high; between 0.90 and 0.71, good; between 0.70 and 0.51, moderate; 0.50 and 0.31, negligible; 0.3 or less.[24] Simple linear regression analyses were used to determine which of the independent variables (VAS, CS) could explain the dependent variables (FIQ) in presence of the significant correlations. P value <0.05 was accepted for statistical significance level.

RESULTS

Forty-five patients with FMS (mean age: 45.9 (6.9) years, median disease duration: 3 (2-6) years) were completed this study. Patients' demographic and clinical features are presented in Table 1. The median VAS score of all patients was 8 (5-8) cm. Twenty-four patients (53.3%) used analgesic medicine, eight patients (17.7%) used anti-depressant, and thirteen patients (29%) don't used any medicine prior to the study. The mean FIQ score of all patients was

53.4 (12.2) points. Patient' CSI score was 52 (41.5-57). The CS is positive in 82.2% of all patients. The mean BAQ score of all patients was 90 (9.6) points (Table 1).

Table 1. The demographic and clinical features of patients with fibromyalgia syndrome.

Variables		FMS (n=45)
Age (year), mean±SD)		45.9±6.9
BMI (kg/m^2), median (IQR)		28.7 (25.5-32)
Disease duration (year), median (IQR)		3 (2-6)
History of smoking, n (%)	None	40 (88.9)
	Active	5 (11.1)
Education (year), median (IQR)		8 (5-12)
Drug use (yes/no)		32/13
VAS (cm), median (IQR)		8 (5-8)
FIQ, mean±SD)		53.4±12.2
CS positive, n (%)		37 (82.2)
CSI (point), median (IQR)		52 (41.5-57)
BAQ (point), mean±SD)		90±9.6)

FMS: Fibromyalgia Syndrome, BMI: Body Mass Index, IQR: Iinterquartile Range, VAS: Visual Analogue Scale, FIQ: Fibromyalgia Impact Questionnaire, CS: Central Sensitization, CSI: Central Sensitivity Inventory, BAQ: Body Awareness Questionnaire.

Table 2. Linear regression analysis between the disease activity, central sensitization and pain severity of fibromyalgia syndrome patients.

					CSI				
Variables	**r**	**R^2**	**P**	**F**	**B coefficient**	**Std. error**	**β**	**t**	**p**
Constant					22.678	7.484	-	3.030	0.004*
Disease activity	0.539	0.291	<0.001*	17.650	0.618	0.147	0.539	4.201	<0.001*
					VAS				
Constant					33.052	6.473	-	5.106	<0.001*
Disease activity	0.445	0.198	0.002*	10.610	3.008	0.923	0.445	3.257	0.002*

CSI: Central Sensitization Inventory, VAS: Visual Analogue Scale, * Linear regression analysis.

FIQ is moderately correlated with the VAS score (r=0.445, R2=0.198, p=0.002) and is highly correlated with CSI (r=0.539, R2=0.291, p<0.001). There is no significant correlation between FIQ and BAQ (p=0.791). The simple linear regression analysis between the disease activity, central sensitization and pain severity is presented in Table 2. The VAS score is explained 19.8% of the variance and FIQ (r=0.445, p=0.002) significantly predicted pain severity. The CSI score is explained 29.1% of the variance and FIQ (r=0.539, p<0.001) significantly predicted CS (Figure 1).

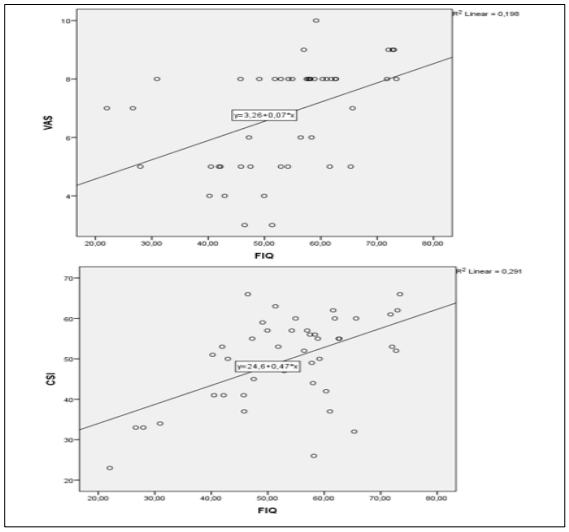

Figure 1. Scatter plots of disease activity, central sensitization, and pain severity.

DISCUSSION

The lack of understanding of the exact pathogenesis of FMS makes the diagnosis and treatment of this illness very difficult. This study purposed to to investigate the influence on disease activity on CS and body awareness in patients with FMS. We found that high disease activity adversely affected CS and pain severity. Moreover, disease activity is an important determinant of CS in patients with FMS. As the disease activity increased, pain intensity and CS deteriorated.

In a study conducted with healthy individuals, it was reported that the level of body awareness was directly related to pain and emotional state related to the musculoskeletal system.[25] Apaydın et al. reported that axial spondyloarthritis patients with high disease activity have poorer body awareness compared to low disease activity.[10] Previous studies suggested that body image perception may also be disturbed in chronic painful conditions.[26] Akkaya et al. reported that body image is deteriorated in patients with FMS compared to healthy individuals.[16] Additionally, it was found that body image was associated with FIQ and pain severity. Another study reported that FIQ associated with body image in patients with FMS.[27] Unlike previous

studies, our findings indicate that there is no significant association between FIQ and body awareness. In previous studies, body image was assessed using the Body Image Scale. However, we evaluated body awareness with BAQ. The contents of these two evaluation measurements differ from each other. Moreover, in this study, disease duration, disease activity and mean age of the patients and the sample size were lower. A recent systematic review suggests that body awareness therapies are holistic, body-focused interventions that enhance physical, mental and emotional well-being by promoting awareness of the body's function, behaviour and interactions with oneself and others. Moreover, this systematic review showed positive results in favor of body awareness treatments as adjunctive therapy to usual care in patients with FMS.[11] For this reason, adding body awareness exercises to the rehabilitation process in FMS patients might be effective in improving disease activity and pain.

In FMS, earlier studies already presented evidence for CS as the cause of chronic widespread pain.[6,8] Additionally, previous studies reported that CS was higher in patients with FMS than in healthy individuals.[28,29] Another study reported that mean CSI score of FMS patients was 70.7.[30] Moreover, Casas-Barragán et al. found that mean CSI score in FMS patients was 67.73.[28] In a study involving different rheumatic diseases, it was reported that CS syndromes were present in 94% of fibromyalgia patients, 41% of rheumatoid arthritis, 45% of axSpA patients, patients, and 62% of osteoarthritis patients.[31] In line with the literature, in this study presented clinical CS in 82.2% of patients with FMS. However, we found mean CSI score of patients as 52. Cultural differences and the smaller number of participants in our study may explain the lower CSI score. The presence of CS is a very common condition in patients with FMS and should be taken into account in the evaluation process, treatment management and patient follow-up.

Valera-Calero et al. showed that anxiety, depression and pain during daily living activities were all independently associated with CS in FMS.[30] Another study reported that clinical symptoms like pain, fatigue, and insomnia are adversely affects CS in patients with FMS.[32] Moreover, earlier studies demonstrated that years with pain and pain during daily life activities were positively associated with CS.[33,34] Salaffi et al. stated that worse disease activity, more pain, and symptom severity independently predict the development of CS in FMS.[35] Our results of the regression analysis presented that CS and pain were moderately associated. In addition, CS were highly correlated with disease activity. The pain severity and disease activity may predict the presence and severity of CS in patients with FMS, which is consistent with the previous studies. As the pain and disease activity increases, the severity of CS is also increased.

Limitation

The study has some limitations. Firstly, due to the cross-sectional design of our study, causal conclusions can not be drawn. Secondly, current study is included only women because the higher frequency of FMS among women. Therefore, our study results cannot be generalized to all FMS patients. Thirdly, the psychological status of the patients was not evaluated in this study, but body awareness and CS may be influenced by psychological factors. Lastly, patients' neuropathic pain profiles were not evaluated, which may be affect CS. An important strength of our study is the detailed investigation of the relationship of disease activity with FMS to body awareness and CS. Further studies are needed to confirm the findings shown here. In addition, future studies may evaluate the effects of body awareness therapies on disease activity, CS, psychological and emotional status and health-related quality of life.

Conclusion

To summarize, our study points out comprehensive evidence of the relationship between disease activity, pain, CS and body awareness in FMS patients. The present study focused on body awareness, CS and disease activity in patients with FMS, which are missing in the literature. Detection impaired CS and body awareness early in the disease would help in FMS treatment planning and management. In combination with routine pharmacological treatments and non-pharmacological treatments such as exercise and cognitive behavioral therapies, body awareness therapy can decrease pain, symptoms, and CS and improve body awareness. We suggest that body awareness and

breathing therapies, especially in addition to postural control exercises, may be beneficial in terms of CS, pain and disease activity in FM patients. In conclusion, clinicians should consider a multimodal biopsychosocial perspective in addition to routine treatments in the management of patients with high disease activity.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

This study was approved by Necmettin Erbakan University Drug and Non-Medical Device Research Ethics Committee (dated 01.03.2024 and numbered 2024/4831).

Authors' Contributions

Concept/Design: YM, AK. Data Collection and/or Processing: YM, AK. Data analysis and interpretation: YM, AK. Literature Search: YM. Drafting manuscript: YM, AK. Critical revision of manuscript: YM, AK.

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Investigation of Hepatic and Splenic Shear-wave Elastography Findings in Patients with Familial Mediterranean Fever

Ailevi Akdeniz Ateşi Hastalarında Karaciğer ve Dalak Shearwave Elastografi Bulgularının İncelenmesi

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ÖZ

Amaç: Ailevi Akdeniz Ateşi (AAA), iç organları etkileyebilen otoinflamatuar multisistemik bir hastalıktır. Bu çalışma, AAA'nın karaciğer ve dalak üzerindeki etkisini shear wave elastografisi (SWE) kullanarak değerlendirmeyi amaçlamaktadır.
Araçlar ve Yöntem: Çalışmamıza Tel-Hashomer kriterlerine göre AAA tanısı alan, 18 yaş ve üzeri, amiloidoz gelişmemiş, karaciğer ya da dalak dokusunu etkileyen herhangi bir durumu olmayan hastalar dahil edilmiştir. Elektronik tıbbi kayıtlar retrospektif olarak incelenmiştir. Shear wave elastografi incelemesi en az beş yıllık SWE deneyimi olan bir radyolog tarafından yapıldı. Shear wave elastografi bulguları AAA olguları ve sağlıklı grup arasında karşılaştırıldı.
Bulgular: Yaş ortalaması 32.3 yıl olan 51 AAA olgusu (25 kadın, 26 erkek) ile yaş ortalaması 36.9 yıl olan 14 sağlıklı birey (4 kadın, 10 erkek) incelendi. En sık görülen semptom ateş olup vakaların %98'inde görülürken, %64.7'sinde M694V gen mutasyonu vardı. Hasta ve kontrol grubunun ortalama SWE değerleri arasında anlamlı bir fark bulunmadı. Karaciğer sertliği ve yaş arasında hafif pozitif bir korelasyon olduğunu saptadık (r=0.319, p=0.023). Hastalık başlangıç yaşı, hepatik sertlik (r=0.474, p=0.001) ve hepatik velosite (r=0.386, p=0.007) ile koreleydi.
Sonuç: Ailevi Akdeniz Ateşi hastalarını takip etmek için non-invaziv yöntemler konusunda bir fikir birliği bulunmamaktadır. AAA'de dahil olmak üzere enflamatuar hastalıklardan etkilenen solid organlarda SWE ölçümlerinin kantitatif ve rutin olarak uygulanması için daha fazla çalışma yapılması gerekmektedir.

Anahtar Kelimeler: inflamasyon; otoinflamatuvar hastalık; sonoelastografi

ABSTRACT

Purpose: Familial Mediterranean Fever (FMF) is an autoinflammatory multisystemic disorder that may impact internal organs. This study aims to evaluate the impact of FMF on the liver and spleen utilizing shear wave elastography (SWE).
Materials and Methods: Our study included patients diagnosed with FMF according to the Tel-Hashomer criteria, aged ≥18 years, who did not have AA amyloidosis or any conditions affecting liver or spleen tissue. Electronic medical records were examined retrospectively. A radiologist with a minimum of five years of expertise in shear wave elastography conducted the procedure. Shear wave elastography results were compared between patients with FMF and healthy controls.
Results: We examined fifty-one cases of FMF (25 females, 26 males) with a mean age of 32.3 years, alongside 14 healthy persons (4 females, 10 males) with a mean age of 36.9 years. The predominant symptom was fever, observed in 98% of cases, whereas 64.7% had the M694V gene mutation. No significant difference was seen between the mean SWE values of FMF cases and the control group. A positive connection between hepatic stiffness and age was identified (r=0.319, p=0.023). The age at disease onset exhibited a correlation with hepatic stiffness and velocity (r=0.474, p=0.001; r=0.386, p=0.007, respectively).
Conclusion: A consensus on non-invasive methods to follow up patients with FMF is lacking. Further studies are necessary for the quantitative and routine application of SWE measurements in solid organs affected by inflammatory disorders, including FMF.

Keywords: autoinflammatory disease; inflammation; sonoelastography

Received: 19.03.2024; Accepted: 10.11.2024

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How to cite: Çabalak K, Çelik MM, Kayalı A, Pekdiker M. Investigation of hepatic and splenic shear-wave elastography findings in patients with familial mediterranean fever. Ahi Evran Med J. 2025;9(1):37-43. DOI: 10.46332/aemj.1455102

INTRODUCTION

Familial Mediterranean fever (FMF), which is the first described and most common autoinflammatory disease, usually affects Turks, Arabs, Armenians, and non-Ashkenazi Jews. There is a clear geographical clustering of the disease, and FMF originated from Middle Eastern countries.[1] FMF is characterized by recurrent episodes, including fever, serositis, and skin and joint inflammation that last 1-3 days and cease spontaneously. Patients with FMF are asymptomatic between episodes. The frequency and type of attacks can be variable depending on the individual.[2] The prevalence of FMF is 1/1000 in Turkey, and can rise to 1/395 in Central Anatolia.[3] The MEFV gene, which is situated on the short arm of chromosome 16 (16p13.3), is the most significant component in the pathophysiology of FMF. The MEFV gene encodes the 'pyrin' protein and is inherited as autosomal recessive. The association between the MEFV gene and FMF was first described in 1997.[4] Apart from the MEFV gene, other genetic factors (such as the MICA and SAA-1 genes) and environmental factors also take part in the pathogenesis of FMF.[5-9]

Colchicine is the cornerstone of FMF treatment. Colchicine leads to a decrease in the frequency and intensity of attacks, amyloidosis, renal failure, and mortality.[10] Anti-interleukin-1 agents are recommended for treating patients with colchicine-resistant FMF because interleukin-1 is the pivotal cytokine in FMF pathogenesis.[11] However, subclinical systemic inflammation continues in 30% of FMF cases. Chronic systemic inflammation in FMF patients increases complications such as normochromic normocytic anemia, growth retardation, decreased bone density, increased risk for infertility, and cardiovascular diseases.[12]

The primary predictor of prognosis and most prevalent FMF consequence is secondary amyloidosis (AA-type).[13] AA-amyloidosis is caused by the extracellular accumulation of an insoluble fibrillar protein named serum amyloid-A (SAA), especially in internal organs. So, AA-amyloidosis leads to organ dysfunction and failure. Patients with FMF having AA-amyloidosis are usually under 40 years of age and develop end-stage renal failure within five years after the initial diagnosis.[14] The diagnosis of amyloidosis is usually based on a renal biopsy, and currently, there is no accepted non-invasive test for follow-up or diagnosis. The early detection of AA-amyloidosis is essential for the effective management of FMF.

Elastography is an imaging method measuring tissue hardness.[15] Shear wave elastography (SWE) is a technique that uses very quick image sequences to develop a quantitative tissue stiffness map by perceiving shear wave (SW) waves, which are produced by applying transient mechanical impulses to the tissue under evaluation with a probe.[16] The hardness and elasticity of the tissue could be ascertained by measuring the velocity of the shear waves produced by the ultrasonic probe, and the speed of SW is higher in hard tissues.[17] Fibrosis causes tissue to become more rigid, which raises the shear wave velocity.[18]

Currently, there is increasing evidence for SWE in the medical literature. Published studies investigated the utilizability of SWE in solid organ parenchymal diseases or musculoskeletal injuries.[19-21] In this research, we aimed to investigate the effects of FMF on the liver and spleen without amyloidosis by examining splenic and hepatic SWE findings.

MATERIALS and METHODS

Patients' Selection

This study was approved by the Hatay MKU Tayfur Ata Sökmen Medical Faculty Clinical Research Ethics Committee (dated 24.10.2022 and numbered 09). The patients gave us their informed written consent.

Our research was a case-based retrospective study. A total of 65 participants; 51 patients with FMF and 14 participants as a control group were enrolled in the study. The study included patients who were referred to our rheumatology department between October 2022 and January 2023, were older than 18 years old, fulfilled the Tel-Hashomer classification criteria,[22] and did not develop amyloidosis. Exclusion criteria were having secondary amyloidosis, another systemic condition affecting the liver or spleen (e.g., non-alcoholic steatohepatitis, viral hepatitis), metabolic disorders including obesity, diabetes mellitus, and chronic liver and spleen diseases like cirrhosis. We also excluded patients who were pregnant or lactating. The control group consisted of adult admissions to the internal

medicine department without a history of chronic diseases or metabolic conditions.

Data Collection

Electronic patient files were retrospectively scanned. Baseline demographic, laboratory, clinical, and treatment data were noted. Our study included biochemical measures, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid-A (SAA), full urinalysis, spot urine protein, and creatinine. The patients' biochemical tests were carried out as part of a normal assessment upon admission. Blood tests are regularly assessed in routine visits during six-month period rheumatology visits. A shear wave elastography examination was conducted during admission for routine examination by a musculoskeletal radiologist. All patients and the control group adhered to legal procedures prior to the examination.

We used the LOGIQ E9 (GE Healthcare, Wauwatosa, WI, USA), a 1-6 MHz convex probe (XDClear C1-6-D) for grayscale and SWE evaluation. Pressure on the probe was avoided during measurement. Measurements were performed in the lateral decubitus position with breath holding (the left decubitus position was used for liver and the right decubitus position was used for spleen measurements). Individuals who could not hold their breath and could not obtain optimal measurements were excluded from the study. In each patient, 3 separate measurements of mean velocity (m/s) and mean stiffness (kPa) were taken by using a 0.8 mm diameter ROI (region of interest). The stiffness and velocity values from each measurement were taken, and the average of these 3 measurements was used for the study. SWE values and grayscale were taken from the recorded data at the time of the first inspection.

Statistical Analysis

Data analysis was conducted using the statistical package program, Statistical Package for the Social Sciences (SPSS), version 22.0. For descriptive statistics, the highest and lowest values, standard deviation, frequency (%), and mean value were utilized. The Shapiro-Wilk test was used to determine if the data were ordinarily distributed. Two distinct groups' worth of non-normally distributed quantitative data were analyzed using the Mann Whitney U test. The independent and qualitative data were analyzed using the chi-square test. Pearson Correlation analysis was used to assess the association between the SWE measurement values and the participants' ages as well as the patients' ages at disease onset. P-values less than 0.05 were regarded as significant in statistical studies.

RESULTS

We analyzed 65 participants; 78.5% of the participants were patients (n= 51; 25 females and 26 males), and 21.5% (n= 14; 4 females and 10 males) were in the control group. Among all participants, there were 29 females (44.6%) and 36 males (55.4%). The mean age was 32.33±10.57 years in the FMF group and 36.39±9.95 years in the control group. The mean body-mass index was 23.65±4.05 kg/m^2 in the FMF group and 24.75±2.96 kg/m^2 in the control group. Age, gender, and BMI were distributed uniformly in both the control group and the FMF patients (Table 1).

Table 1. Demographic data of patients and control group.

Variables	FMF group (n= 51)	Control group (n= 14)	p value
Age, mean±SD, years	32.33±10.57	36.39±9.95	0.893*
Male sex, n, (%)	26 (51%)	10 (71.4)	0.173**
Body-mass index, mean±SD, kg/m^2	23.65±4.05	24.75±2.96	0.347*

Abbrevations: FMF, Familial Mediterranean fever. *Student T test, **Chi-square test

In the FMF group, the mean age at disease onset was found to be 13.58±10.4 years (range 1-53 years). The most common clinical findings were fever in 98%, peritonitis in 86.3%, and arthritis in 66.7% of FMF cases. Pleuritis was present in 31.4%, erysipelas-like erythema in 17.6%, and pericarditis in 7.8% of FMF cases. The most common MEFV gene mutation was compound heterozygous with a rate of 39.2% (n=20). Homozygous MEFV gene mutations were detected as M694V (n=10), M680I (n=2), E148Q (n=1), and R202Q (n=1). Heterozygous mutations were M694V (n=11), E148Q (n=1) and V726A (n=1). Four cases had no mutation on the MEFV gene. The M694V mutation was present in 12 cases with compound heterozygous. As a result, M694V mutations were positive in 64.7% (n=33) of cases. The mean dosage of colchicine was

1.5 mg/day. Three patients were using Canakinumab treatment due to colchicine-resistant disease activity.

There was no significant difference between the patient and control groups' average SWE values (Table 2). Hepatic stiffness and age showed a weak positive correlation in the FMF group (r=0.319, p=0.023). In the control group, a high positive correlation was found between splenic velocity and age (r=0.721, p=0.004). Additionally, a weak positive correlation was found between the age of FMF onset and both hepatic stiffness and velocity in the patient group (r=0.474, p=0.001; r=0.386, p=0.007, respectively) (Table 3).

Table 2. Evaluation of SWE measurement results in patient and control groups.

Features		Median (kPa)	Min (kPa)	Max (kPa)	p*
Hepatic Stiffness	Patient	6.18	2.85	16.47	0.780
	Control	5.84	4.11	15.35	
Hepatic Velocity	Patient	1.40	0.96	2.08	0.655
	Control	1.37	1.14	2.08	
Splenic Stiffness	Patient	17.14	8.18	35.55	0.267
	Control	14.79	5.03	27.15	
Splenic Velocity	Patient	2.26	1.55	3.31	0.911
	Control	2.23	1.21	5.83	

Abbrevations: SWE, shear wave elastography; min, minimum; max, maximum *Mann-Whitney U test

Table 3: Relationship between participants' ages and the onset age of the disease with SWE values in the patient group.

Features		Hepatic Stiffness		Hepatic Velocity		Splenic Stiffness		Splenic Velocity	
		r*	p**	r*	p**	r*	p**	r*	p**
Age	Patient	0.319	0.023	0.248	0.080	-0.050	0.727	-0.159	0.264
	Control	0.095	0.747	0.065	0.824	0.147	0.616	0.721	0.004
Age at disease onset		0.474	0.001	0.386	0.007	2	0.988	-0.086	0.561

Abbrevations: SWE, shear wave elastography. * Correlation Coefficient **Pearson Correlational Analysis.

Table 4. Relationship between SWE value and laboratory findings.

Variables	Hepatic Stiffness		Hepatic Velocity		Splenic Stiffness		Splenic Velocity	
	r*	p**	r*	p**	r*	p**	r*	p**
Serum amyloid-A	0.017	0.906	0.060	0.684	0.141	0.333	0.141	0.332
Spot urine microprotein	-0.299	**0.049**	-0.308	**0.042**	-0.284	0.062	-0.243	0.111
Spot urine creatinine	-0.283	**0.049**	-0.242	0.094	-0.249	0.085	-0.204	0.159
Fibrinogen	0.158	0.2.79	0.104	0.478	0.046	0.753	0.009	0.949
Albumin	-0.114	0.424	-0.189	0.183	-0.076	0.594	-0.063	0.659
Total protein	-0.004	0.980	-0.039	0.790	-0.140	0.333	-0.104	0.471
BUN	0.218	0.128	0.204	0.156	-0.169	0.240	-0.139	0.337
Creatinine	-0.253	0.077	-0.300	**0.034**	-0.192	0.181	-0.175	0.223
CRP	0.002	0.990	0.044	0.761	0.134	0.347	0.123	0.391
ESR	0.286	**0.042**	0.285	**0.043**	0.082	0.567	0.055	0.701
SGPT	0.181	0.203	0.123	0.390	-0.048	0.737	-0.021	0.881
SGOT	0.025	0.863	-0.020	0.887	0.171	0.231	0.158	0.267
WBC	-0.207	0.144	-0.279	**0.047**	0.363	**0.009**	0.289	**0.040**
HGB	-0.088	0.537	-0.082	0.565	-0.096	0.502	-0.032	0.821
PLT	-0.078	0.586	-0.137	0.336	0.457	**0.001**	0.390	**0.005**

Abbreviations: SWE, shear wave elastography; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SGPT, Serum Glutamic Pyruvic Transaminase; SGOT, Serum Glutamic-Oxaloacetic Transaminase; WBC, white blood count; HGB, haemoglobin; PLT, serum platelet count.
*Correlation Coefficient **Pearson Correlation Analysis

We detected a weak negative correlation was found between spot urine microprotein value and hepatic stiffness and velocity values (r=-0.299, p=0.049; r=0.308, p=0.042, respectively). Additionally, there was a weak negative correlation between spot urine creatinine and hepatic stiffness (r=0.283, p=0.049) and a weak negative correlation between creatinine value and hepatic velocity (r=0.3, p=0.034). There was a weak negative correlation between leukocyte count and hepatic velocity (r=-0.279, p=0.047) and a weak positive correlation between splenic stiffness and velocity values (r=0.009, p=0.040). Besides, we found a weak positive correlation between erythrocyte sedimentation rate and hepatic stiffness and velocity values (r=0.286, p=0.042; r=0.285, p=0.043, respectively) and a weak positive correlation between platelet count and splenic stiffness and velocity values (r=0.00, p=0.005) (Table 4).

DISCUSSION

In this study, we investigated the changes in tissue stiffness in the liver and spleen and compared these results between FMF patients and healthy subjects. Additionally, we compared the SWE values with the laboratory findings in cases of FMF. Our study is a contribution to the literature that evaluates tissue elasticity together with laboratory parameters in patients with FMF. The mean SWE values in our study did not show a significant difference between the FMF cases and the healthy control group. However, there was a weak positive correlation between age at FMF onset and hepatic stiffness and velocity in the patient group.

In a multicenter study conducted in 2014 in our country, the mean age at FMF onset was 15.7± 9.6 years,[23] whereas in our study, the mean age at disease onset was 13.58±10.4 years. In our study, the M694V mutation was present in 64.7% of the cases. The most common finding in Turkish FMF patients, as well as in our patients, was fever. There are very few studies in the literature that evaluate FMF cases by using SWE. Bayramoğlu Z. et al. examined the stiffness level of solid organs in 38 pediatric FMF patients and 38 healthy individuals in the control group. Compared to control participants, the FMF group with amyloidosis had significantly higher median values for elasticity of the liver, spleen, kidney, and pancreas. The relevant study found no difference in the median liver stiffness values between FMF patients without amyloidosis and the control group.[24] In this study, stiffness values tend to show a moderate positive correlation with CRP, ESR, and SAA levels. We also excluded patients with amyloidosis, as they could potentially explain the differences in our results. In our study, a weak positive correlation was found between ESR and hepatic stiffness and velocity values. Furthermore, a weak correlation was found between the leukocyte count and the velocity and stiffness of the spleen. However, an analysis of the mean SWE values of the patient and control groups revealed no significant difference. According to Aktı S et al., liver stiffness values were significantly higher in adults with FMF compared to the control group. They also didn't leave out patients who had secondary amyloidosis related to FMF.[25]

Kayalı et al. performed a study with 35 adult patients with FMF and 23 healthy control groups. Renal stiffness in FMF cases was found to be considerably higher ($p< 0.001$) than in the control group.[26] Among solid organs, the kidneys are the primary targets of FMF. Ozmen Z et al. reported a study with 79 pediatric FMF cases, and they found out kidney stiffness values were higher ($p<0.001$) than the healthy control group.[27] Urfalı M et al. found a significant increase in parotid gland, thyroid, and renal parenchymal stiffness, as well as arterial vascular resistance values, in 35 FMF patients. They also showed that tissue stiffness and vascular resistance values were higher ($p<0.001$) in the group with the M694V homozygous mutation.[28] Previous results could be affected by the M694V homozygous mutation, which is related and associated with more severe disease and an enhanced risk of amyloidosis.[29] Bayramoglu Z et al. found that during an acute attack, the salivary and thyroid glands' median shear wave elasticity and velocity values were significantly higher in pediatric FMF cases than in the healthy control group. Additionally, a significant correlation was spotted between the elasticity values of the parotid gland ($r=-0.4$, $p=0.04$) and thyroid glands ($r=-0.6$, $p=0.008$) and CRP, as well as a moderately negative correlation between serum amyloid-A and thyroid gland elasticity ($r=-0.58$, $p=0.018$).[30]

Acute phase responses such as ESR, CRP, and SAA are used to measure inflammatory activity in the follow-up of FMF cases. However, there is no predictive test for the development of amyloidosis. Amyloidosis is associated with a family history of the disease, end-stage renal failure, the M694V mutation (particularly homozygous), male gender, chronic arthritis, and delayed diagnosis in Turkish FMF patients; the incidence of amyloidosis is 8.6%.[31] Since amyloidosis is the main determinant of prognosis in FMF patients. Non-invasive measurement methods, such as SWE, hold great promise.

Despite unique results, our study has some limitations. We were unable to collect the desired number of patients and control group data due to the Kahramanmaras-centered earthquakes that occurred during the study period. Our study has a small number of patients and control groups. Lack of data regarding family history of amyloidosis or end-stage renal failure, the exclusion of FMF patients having secondary rheumatic disorders (such as seronegative

spondyloarthritis), and the absence of a patient group having AA-amyloidosis were the major limitations of our study.

In conclusion, we investigated the splenic and hepatic SWE findings in FMF cases and the control group. This study found a positive association between hepatic stiffness velocity and age at FMF onset. Our results should be supported by larger-scale research. Monitorization and follow-up are essential in patients with FMF because of amyloidosis-related solid organ involvement. The stiffness and velocity of solid organs could be useful parameters for non-invasive imaging techniques in inflammatory conditions.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

This study was approved by the Hatay MKU Tayfur Ata Sökmen Medical Faculty Clinical Research Ethics Committee (dated 24.10.2022 and numbered 09).

Authors' Contributions

Concept/Design: MMÇ, MP, AÇ. Data Collection and/or Processing: AÇ, MMÇ, MP. Data analysis and interpretation: MP, AK, AÇ. Literature Search: AK, AÇ, MMÇ. Drafting manuscript: AÇ, AK, MP.

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BİLİMSEL ARAŞTIRMA MAKALESİ

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Obez Çocuk ve Ergenlerde Subklinik Hipotiroidi Sıklığı ve İlgili Parametrelerin İncelenmesi

An Examination of the Frequency of Subclinical Hypothyroidism and Relevant Parameters in Obese Children and Adolescents

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ÖZ

Amaç: Subklinik hipotiroidizm (SH), obez çocuk ve ergenlerde sık görülen bir tiroid hormon bozukluğudur. Bu çalışmada, obez çocuk ve ergenlerde subklinik hipotiroidi sıklığını belirlemek, TSH düzeyi ile antropometrik ve metabolik parametreler arasındaki ilişkinin araştırılması planlanmıştır.
Araçlar ve Yöntem: Çalışmaya yaşları 10-18 yaş aralığından değişen 100 obez grup, 70 kontrol grubu olmak üzere toplam 170 olgu alındı. Tüm olguların dosya kayıtlarından; cinsiyet, antropometrik ölçümleri (vücut ağırlığı, boy, beden kitle indeksleri) ve standart deviasyon skorları (SDS), tiroid fonksiyon testleri (TSH, sT4, sT3), insülin, açlık kan şekeri, total kolesterol (TK), yüksek dansiteli lipoprotein, kolesterol (HDL-K), trigliserid ve düşük dansitelilipoprotein kolesterol (LDL-K), HOMA-IR düzeyleri elde edildi.
Bulgular: Obez gruptaki 100 hastanın 7'sinde (% 7) SH saptandı. Obez grubun VA ve BKİ-SDS değerleri kontrol grubuna göre anlamlı derecede yüksek saptandı. (p=<0.01,<0.01, sırasıyla). Obez grupta sT4 düzeyi kontrol grubuna göre anlamlı düşük (p=0.04), HOMA-IR ve AST düzeyi de anlamlı olarak yüksek bulundu (p=<0.01, <0.01, sırasıyla). Serum TSH düzeyi ile HOMA-IR düzeyi arasında pozitif yönde düşük derecede korelasyon saptandı (r=0.15, p=0.049).
Sonuç: Obez çocuk ve ergenlerde SH normal popülasyona göre daha sık görülür, ancak çoğu olguda TSH 10 UI/ml'nın altında ve tedaviye ihtiyaç duyulmamaktadır. Obez çocuklarda Hashimato tiroiditi olmaksızın tiroid otoantikor pozitifliği görülebilir. TSH düzeyi ile insülin direnci arasında düşük derecede de olsa pozitif bir ilişki olduğundan, obez çocuklarda SH saptanması insülin direnci olasılığı konusunda klinisyen için uyarıcı olmalıdır.

Anahtar Kelimeler: beden kitle indeksi; insülin direnci; obezite; tiroid hormonları

ABSTRACT

Purpose: Subclinical hypothyroidism (SH) is a thyroid hormone disorder commonly observed in obese children and adolescents. In this study, it was aimed to determine the frequency of subclinical hypothyroidism in obese children and adolescents and to investigate the relationship between TSH levels and anthropometric and metabolic parameters.
Materials and Methods: A total of 170 patients aged 10-18 years were included in the study, 100 in the obese group and 70 in the control group. Gender, anthropometric measurements and laboratory data were obtained from the patients medical records.
Results: SH was detected in 7 of the 100 patients (7%) in the obese group. The BW and BMI SDS values were found significantly higher in the obese group compared to the control group (p=<0.01,<0.01, respectively).In the obese group, fT4 levels were significantly lower (p=0.04) than in the control group, and HOMA-IR and AST levels were significantly higher (p=<0.01, <0.01, re-spectively). A low positive correlation was found between serum TSH levels and HOMA IR levels (r=0.15, p=0.049).
Conclusion: Subclinical hypothyroidism (SH) is more common in obese children and adolescents compared to the general population; however, in most cases, TSH levels remain below 10 IU/mL, and treatment is not required. In obese children, thyroid autoantibody positivity may be observed without Hashimoto's thyroiditis. Since there is a weak but positive correlation between TSH levels and insulin resistance, the detection of SH in obese children should alert clinicians to the possibility of insulin resistance.

Keywords: body mass index; ınsulin resistance; obesity; thyroid hormones

Gönderilme tarihi: 15.07.2024; Kabul edilme tarihi: 11.11.2024

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Makaleye atıf için: Beştaş A, Ünal E. Obez çocuk ve ergenlerde subklinik hipotiroidi sıklığı ve ilgili parametrelerin incelenmesi. Ahi Evran Med J. 2025;9(1):44-50. DOI: 10.46332/aemj.1516640

GİRİŞ

Obezite, kalori alımı ve harcaması arasındaki dengesizlik nedeniyle vücutta anormal ve aşırı yağ birikimidir. Son 50 yılda çocukluk ve adölesan yaş grubunda obezite prevalansı dramatik bir şekilde artış göstermiştir. Bu da obeziteyle ilişkili dislipidemi, hipertansiyon, bozulmuş glukoz toleransı ve insülin direnci gibi çeşitli metabolik ve hormonal bozuklukların artmasına neden olmaktadır.[1]

Subklinik hipotiroidi (SH), serum serbest tiroksin (sT4) düzeyi normal olmasına rağmen serum tirotropin (TSH) düzeyinin referans değerlerin üzerinde olması olarak tanımlanır. Obez çocuk ve ergenlerde görülen en sık tiroid hormon bozukluğudur. Prevalansı erişkinlerde %4-20, çocuklarda %1.5-3 olarak rapor edilmiştir. Fazla kilolu ve obez çocuklarda ise SH prevelansı %7-36 arasında değişmektedir.[2] İyot eksikliği, otoimmün tiroid hastalığı, TSH reseptör gen mutasyonu, tiroid hormon direnci ve obezite subklinik hipotiroidi nedenleri arasında gösterilmektedir. Obez çocuk ve ergenlerde subklinik hipotiroidizmin oluşum mekanizması tam olarak bilinmemektedir. Ancak tiroid hormonlarında oluşan bu değişimin kilo alımındaki artışı engellemek için enerji harcamasını arttıran bir kompanzasyon mekanizması ile ilgili olduğu belirtilmektedir.[3]

Tiroid hormonları, lipid ve glukoz metabolizmasında rol oynayarak bazal metabolizmayı hızlandırır, vücut ağırlığı ve kompozisyonunu düzenlemektedir. Subklinik hipotiroidi ile lipid ve glukoz metabolizması arasındaki ilişkiyi araştıran erişkin çalışmalarında TSH düzeyi ile hem dislipidemi hem de insülin direnci arasında ilişki olduğu gösterilmiştir.[4] Ancak obez çocuklarda yapılan çalışmalarda TSH yüksekliğinin lipit profili ve insülin direnci üzerine olan etkisi net değildir. Bazı çalışmalarda TSH düzeyinin aterojenik lipitler ve insülin direnci ile pozitif yönde korelasyon gösterdiği, bazı çalışmalarda ise korelasyon göstermediği rapor edilmiştir.[5,6,7]

Bu çalışmada, obez çocuk ve ergenlerde subklinik hipotiroidi sıklığını belirlemek, TSH düzeyi ile antropometrik ve metabolik parametreler arasındaki ilişkinin araştırılması planlanmıştır.

ARAÇLAR ve YÖNTEM

Bu çalışma Sağlık Bilimleri Üniversitesi Gazi Yaşargil Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu onayı alındıktan sonra yapılmıştır (03.03.2023 tarih ve 2023/336 sayılı).

Bu çalışma Sağlık Bilimleri Üniversitesi Gazi Yaşargil Eğitim Araştırma Hastanesi Çocuk Endokrinolojisi Bölümünde yapıldı. Çalışmaya yaşları 10-18 yaş aralığından değişen 100 obez grup, 70 kontrol grubu olmak üzere toplam 170 olgu (106 kız, 64 erkek) alındı. Hipotiroidi, büyüme hormonu eksikliği, ilaç kullanım öyküsü olan olgular ile monojenik ya da sendromik obezite tanısı ile izlenen olgular çalışma dışı bırakıldı. Çalışmadaki tüm olguların antropometrik ölçümleri en az 8 saat açlığı takip eden günün sabahında yapıldı. Olguların vücut ağırlıkları (VA), kg cinsinden ölçüldü. Ölçümü yapan cihaz 0.1 kg'a kadar duyarlı idi (SECA marka dijital tartı). Olguların boyları ayakta iken ölçüldü ve ölçüm 0.1 cm aralıkla yapıldı (Harpenden stadiyometre). Beden kitle indeksi (BKİ), kilogram cinsinden vücut ağırlığın metre cinsinden boyun karesine bölünmesiyle hesaplandı. Boy, kilo, BKİ standart deviasyon skorları (SDS), ulusal verilere göre web tabanlı Child metric programı kullanılarak hesaplandı.[8] Çalışma grupları obez ve kontrol grubu olmak üzere 2 gruptan oluşturuldu. Obez gruba Dünya sağlık örgütü sınıflamasına göre BKİ >95. persantil veya BKİ–SDS değeri +2 ve üzerinde olan olgular alındı.[9] Kontrol grubu ise sağlıklı normal çocuklardan oluşturuldu. Obez gruptaki 100 olgunun 98'i, kontrol grubundan 70 olgunun 63'nün pubertal bulgularına dosya kayıtlarından ulaşıldı.

Çalışmaya dahil edilen olgulardan12 saatlik açlığı takiben kan örneği alındı. Tüm olgulardan tiroid fonksiyon testleri olarak; TSH, sT4 ve sT3 çalıştırıldı. Karaciğer enzimlerinden; aspartat amino transferaz (AST) ve alanin amino transferaz (ALT) enzim düzeylerine bakıldı. Ayrıca açlık kan glukoz ve insülin düzeyleri, total kolesterol (TK), yüksek dansiteli lipoprotein kolesterol (HDL-K) ve trigliserid ile düşük dansiteli lipoprotein kolesterol (LDL-K) değerleri ölçüldü. Tüm olguların, Homeostasic Model Assessment forInsulin Resistance (HOMA-IR) düzeyleri, (açlık insülin (mcU/ml) X açlık glukoz (mg/dl) / 405 formülüyle) hesaplandı. HOMA-IR düzeyi prepubertal olgularda >2.5

pubertal olgularda >3.16 olması insülin direnci olarak kabul edildi.[10] Subklinik hipotiroidi tanısı en az 4 hafta arayla yapılan 2 ölçümde, sT4 düzeyi normal referans aralıkta ve TSH düzeyi normal referans aralığın üzerinde (TSH: 5.5-10 µIU/Ml arasında) olması ile konuldu.[11]

İstatistiksel Analiz

Çalışmanın verileri değerlendirilirken istatistiksel analizler için 'Statistical PackageforSocialSciences (SPSS) for Windows v18.0.0' programı kullanıldı. Öncelikle çalışmadaki verilerin normal dağılıp dağılmadığına Shapiro-Wilk testi kullanılarak bakıldı. Normal dağılımla uyumlu olan veriler ortalama ± standart sapma (SS) ile gösterilirken, normal dağılmayan veriler ise ortanca (25-75 persantil) şeklinde gösterildi. Kategorik değişkenler sayı ve yüzde (%) ile belirtildi. Normal dağılan veriler değerlendirilirken Student's t-testi, normal dağılmayan veriler karşılaştırılırken ise Mann-Whitney U testi kullanıldı. İki değişken arasında herhangi bir ilişki varlığı ve ilişki varsa bu ilişkinin şiddetini değerlendirmek içinpearsonkorelasyon analizi kullanıldı. Yapılan tüm istatistiksel testlerde p değerinin < 0.05 olması halinde anlamlı kabul edildi.

BULGULAR

Çalışmaya ekzojen obezitesi olan 100 obez hasta ile 70 kontrol grubu olmak üzere toplam 170 olgu alındı. Obez gruptaki olguların 69'u (%69) kız, 31'i (%31) erkek, kontrol grubundaki olguların 37'si (%53) kız, 33'ü(%47) erkek cinsiyetteydi. Obezitenin kız cinsiyette daha fazla olduğu görüldü (p=0.033). Obez grubun yaş ortalaması 14.2±2.15, kontrol grubun 13.7±2.08 idi. Obez gruptaki olguların %92.9'u pubertal, %7.1'i prepubertal, kontrol grubundaki olguların %87.3'ü pubertal, %12.7'i prepubertaldi. Pubertal durum açısından karşılaştırıldığında gruplar arasında anlamlı bir fark bulunmadı (p=0.237). Obez gruptaki 100 hastanın 7'sinde (% 7) SH saptandı. Aynı grupta SH'si olan olguların HOMA-IR düzeyi 5.2 (4.20-9.70), SH'si olmayan olguların HOMA-IR düzeyi 3.8 (20.5-5.60) olarak bulundu, aralarındaki fark istatistiksel olarak anlamlı değildi (p=0.11). Subklinik hipotiroidi saptanan olguların klinik ve laboratuvar bulguları Tablo 1'de verilmiştir. Kontrol grubunda SH'li olgu yoktu. Grupların antropometrik parametreleri karşılaştırıldığında, obez grubun VA ve BKİ-SDS değerleri anlamlı ölçüde yüksek saptandı (p=<0.01,<0.01, sırasıyla). Obez grupta sT4 düzeyi anlamlı derecede düşük (p=0.04), HOMA-IR ve AST düzeyi ise yüksek bulundu (p=<0.01, <0.01, sırasıyla). Serbest T3 düzeyi obez grupta yüksek saptandı ancak aradaki fark anlamlı bulunmadı (p=0.85). TSH düzeyleri her iki grupta benzer bulundu (p=0.15). Grupların lipit profili karşılaştırıldığında, obez grupta TK düzey anlamlı yüksek, HDL-K düzeyi ise anlamlı düşük tespit edildi (p=0.04, <0.01, sırasıyla). İki grup arasında LDL-K ve Trigliserid değerleri açısından anlamlı bir fark tespit edilmedi (p=0.14, 0.14, sırasıyla). Grupların, antropometrik ve laboratuvar verileri Tablo 2'de özetlenmiştir. Çalışmadaki olguların Serum TSH düzeyi ile HOMA-IR düzeyi arasında pozitif korelasyon saptandı (r=0.15, p=0.049), TSH ile diğer parametreler arasında başka bir korelasyon bulunmadı (p>0.05). TSH düzeyinin antropometrik ve metabolik parametrelerle korelasyonu Tablo 3'de verilmiştir.

Tablo 1. Subklinik hipotiroidili olguların klinik ve laboratuvar bulguları.

Parametreler	Olgu-1	Olgu-2	Olgu-3	Olgu-4	Olgu-5	Olgu-6	Olgu-7
Yaş (yıl)	10.9	13.1	15.2	15.11	17.2	14.7	17.8
Cinsiyet	Kız	Kız	Kız	Kız	Kız	Erkek	Kız
VA-SDS	0.64	3.5	5.3	2	2.5	1.7	3.8
Boy-SDS	-2.25	1.2	1.5	-0.62	-1.8	-0.99	1.03
BKİ-SDS	2.04	2.7	3.6	2	3.1	2.3	2.9
TSH (mIU/mL)	8.1	9	5.7	5.9	6.8	6.3	9
sT4 (ng/ml)	1.4	1	1.1	0.9	1.2	0.9	1.3
sT3 (pg/mL)	3.9	5.3	4	2.4	3.7	4.4	3.04
AntiTPO (IU/mL)	19	12	60	15	52	14	47
HOMA-IR	2.7	9.7	12.7	5.2	5.9	4.5	4.2
TK (mg/dl)	149	120	113	149	204	156	137
LDL-K (mg/dl)	83	50	65	75	94	92	54
Trigliserid(mg/dl)	48	70	30	37	204	154	129
HDL-K (mg/dl)	51	66	37	61	49	36	51
AST (U/L)	22	19	15	21	15	32	10
ALT (U/L)	24	17	35	13	13	35	13

VA:Vücut ağırlığı, SDS: Standart deviasyon skoru, BKİ: Beden kitle indeksi, TSH: Tiroid uyarıcı hormon, sT4: Serbest tiroksin, sT3: Serbest triiyodotironin, HOMA-IR: Homeostasic model assessment of insülin resistance, TK: Total kolesterol, LDL-K: Düşük dansiteli lipoprotein kolesterol, HDL-K: Yüksek dansiteli lipoprotein kolesterol, AST: Aspartat amino transferaz, ALT: Alanin amino transferaz.

Tablo 2. Grupların antropometrik ve laboratuvar verilerinin karşılaştırılması.

Parametreler	Obez grup (n:100)	Kontrol grup (n:70)	P değeri
Yaş (yıl)	14.2 ± 2.15	13.7 ± 2.08	0.15[a]
Cinsiyet			0.033[b]
Kız, n, (%)	69 (69)	37(53)	
Erkek, n, (%)	31 (31)	33 (47)	
Pubertal durum			0.237[b]
Prepubertal, n, (%)	7 (7.1)	8 (12.7)	
Pubertal, n, (%)	91 (92.9)	55 (87.3)	
VA-SDS	2.59 (2-3.5)		<0.01[c]
Boy-SDS	0.14 (-0.64-0.88)	-0.29 (-1.33-1.08)	0.1[c]
BKİ-SDS	2.55 (2.12-3.09)	-0.27 (-0.99-0.68)	<0.01[c]
TSH (mIU/mL)	2.70 ± 1.68	2.77 ± 1.20	0.15[c]
sT4 (ng/ml)	1.20 (1.1-1.3)	1.30 (1.19-1.39)	0.04[c]
sT3 (pg/mL)	3.75 ±0.68	1.73 ±0.23	0.85[a]
HOMA-IR	4.05 (2.12-5.67)	2.76 (2-3.5)	<0.01[c]
TK (mg/dl)	96.5 (70-126.5)	81(64.75-108.25)	0.04[c]
LDL-K (mg/dl)	82.5 (67.25-96.25)	77.65 (65.17-90.75)	0.14[c]
Trigliserid (mg/dl	144.5±33.84	151.42 ± 24.10	0.14[a]
HDL-K (mg/dl)	45 (38-51)	55.95 (47.50-61.80)	<0.01[c]
AST (U/L)	16.50 (13-23)	13 (10-17)	<0.01[c]
ALT (U/L)	18 (14.25-21)	18 (16-24)	0.12[c]

VA:Vücut ağırlığı, SDS: Standart deviasyon skoru, BKİ: Beden kitle indeksi, TSH: Tiroid uyarıcı hormon, sT4: Serbest tiroksin, sT3: Serbest triiyodotironin, HOMA-IR: Homeostasic model assessment of insülin resistance, TK: Total kolesterol, LDL-K: Düşük dansiteli lipoprotein kolesterol, HDL-K: Yüksek dansiteli lipoprotein kolesterol, AST: Aspartat amino transferaz, ALT: Alanin amino transferaz. aStudent t-test, bPearsonChi-Square test, cMann-Whitney U-test

Tablo 3. TSH düzeyinin antropometrik ve metabolik parametrelerle korelasyonu.

	TSH	
Parametreler	r	P değeri
BKİ-SDS	-0.009	0.90
TK(mg/dl)	0.11	0.12
HOMA-IR	0.15	0.049
LDL-K(mg/dl)	0.06	0.38
HDL-K(mg/dl)	-0.002	0.98
Trigliserid(mg/dl)	0.11	0.12

TSH: Tiroid uyarıcı hormon, r: Korelasyon katsayısı, BKİ: Beden kitle indeksi, TK: Total kolesterol, HOMA-IR: Homeostasic model assessment of insülin resistance, LDL-K: Düşük dansiteli lipoprotein kolesterol, HDL-K: Yüksek dansiteli lipoprotein kolesterol.

TARTIŞMA

Tiroid hormonları lipit, karbonhidrat ve enerji metabolizmasını düzenlemede önemli bir role sahip olduğundan tiroid hormonları ile obezite arasındaki ilişki çok sayıda çalışmada incelenmiş ve bu çalışmalardan farklı sonuçlar elde edildiği bildirilmiştir.[12,13] Obez çocuklarda en sık rastlanan tiroid hormon bozukluğunun hafif TSH yüksekliği ile serbest T3 düzeyinde artışolduğu belirtilmektedir.[2,3,14] Obez olguların TSH düzeyi ile normal sağlıklı popülasyondan oluşan kontrol grubundaki olguların TSH düzeyini karşılaştırdığımız çalışmamızda gruplar arasında TSH düzeyinde anlamlı bir farklılık saptamadık. T3 düzeyini de literatür ile benzer olarak obez olgularda daha yüksek saptadık.[2,3] Duntas ve arkadaşları da yaptıkları çalışmada obez gruptaki olguların TSH düzeyini kontrol grubundaki olguların TSH düzeyi ile benzer saptadıkları bildirilmiştir.[15] Yapılan çalışmalar, Total ve serbest T4 düzeyinin bireylerin beslenme alışkanlıklarından etkilenmediğini göstermektedir.[12] Obez çocuklarda yapılan çeşitli çalışmalar, T4

hormonunun normal ya da hafifçe arttığını belirtilmektedir.[13] Çalışmamızda obez grupta ortalama sT4 düzeyi literatürdeki birçok çalışmadan farklı olarak, kontrol grubundan anlamlı olarak daha düşük bulundu. Obez bireylerde yağ dokusunda deiyodinaz enzim aktivitesi TSH etkisi ile artar. Artan deiyodinaz enzim aktivitesine bağlı olarak sT4'ün sT3'e dönüşümü artar ve bu durum sT4 değerinde azalma, sT3 değerinde artmayla sonuçlanır.[16] Çalışmadaki sT4 düşüklüğü ile sT3 yüksekliğinin artan deiyodinaz enzim aktivitesi ile ilgili olduğunu düşünmekteyiz. Önceki bazı çalışmalar, çalışmamızla benzer şekilde sT4 değerini normal popülasyondan daha düşük olduğunu bildirmiştir.[17]

Literatürde obez çocuk ve ergenlerde SH sıklığının %7-36 oranında değiştiği ve TSH'sı yüksek olan obez olgularda tiroid otoantikor pozitifliğinin daha fazla olduğu rapor edilmiştir. Obezlerde tiroid otoimmünitesini araştıran çalışmalarda, bu durumun otoimmün tiroidit hastalığı veya iyot eksikliği ile ilişkili olmadığı, tiroid bezine antijen sunumunun artmasıyla ilişkili olduğu gösterilmiştir. Bilindiği üzere yağ dokusunda artan leptin, lenfositlerde anti CD3 uyarısına yol açarak lenfositlerin Th1 yönünde prolifere olmasına neden olur. Artan Th1 lenfositler de proinflamatuar yolakları aktive eder.[18,19] Yaptığımız çalışmada obez grupta subklinik hipotiroidi sıklığını literatür ile benzer olarak % 7 oranında saptadık. TSH düzeyi > 5.5 UI/ml olan olgularımızın 3'ün de tiroid peroksidaz antikor düzeyi (olgu-3, olgu-5, olgu-7) yüksekti. Çalışmamız ile benzer olarak Stichel ve arkadaşlarının çalışmalarında da subklinik hipotiroidi sıklığı%7.5 ve TSH'si yüksek olan obez olgularda tiroid peroksidaz antikor düzeyinin daha yüksek olduğu gösterilmiştir.[20] Obezite ve tiroid hormonları arasındaki ilişkiyi inceleyen önceki çalışmalar, anti-tiroid antikor titreleri yüksek olan olgularda hipotiroidiye ilerleme riskinin artığını ve levotiroksin tedavisinin antikor titrelerini azalttığını belirtmiş olsa da, bu uygulamanın obez hastalarda herhangi bir klinik fayda sağlamadığı gösterilmiştir.[21] Biz çalışmamızda tiroid peroksidaz antikor düzeyi yüksek olan bir olgunun uygun diyet ve egzersiz programı uyguladıktan sonra yapılan 6.ay kontrolünde BKİ–SDS sindeki düşme ile beraber hem TSH hem de tiroid peroksidaz antikor düzeyinde düşme olduğunu saptadık (olgu-3). Yine González-Mereles ve arkadaşları da yapmış oldukları çalışmalarında levotiroksin tedavisinin kronik otoimmünt iroiditi olan obez olgularda vücut kompozisyonunu düzeltmede etkili olmadığını göstermiştir.[22] Bu nedenle subklinik hipotiroidisi olan obez hastalarda anti-tiroid-antikor titre yüksekliği mevcut olsa bile hemen levotiroksin tedavisi başlanmasının doğru olmadığı kanısındayız. Kilo kaybının sağlanması hem TSH değerinin düşmesine hem de anti-TPO antikor titresinin azalmasına yol açabilir.

Tiroid hormonları, vücut ağırlığı ve kompozisyonunu düzenlemede rol oynar. Bu nedenle TSH ile BKİ arasındaki ilişki çok sayıda çalışmada incelenmiş ve farklı sonuçlar elde edildiği bildirilmiştir. Literatürde TSH ile BKİ arasında pozitif bir ilişki olduğunu saptayan çok sayıda çalışma mevcuttur.[20,23] Ancak biz çalışmamızda TSH düzeyi ile BKİ arasında anlamlı bir korelasyon saptamadık. Çalışmamızla benzer olarak Dündar ve arkadaşları da çalışmalarında TSH ile BKİ arasında herhangi bir ilişki saptamamışlardır.[16] Tiroid hormonları glukoz ve lipit metabolizması için gereklidir. Aşikar hipotiroidi, obezite, insülin direnci ve dislipidemi ile ilişkilidir.[24] Subklinik hipotiroidinin de insülin direnci ve serum lipit profilinde değişikliklere yol açtığı çeşitli çalışmalarda belirtilmektedir.[14,24,25] Bazı çalışmalarda TSH düzeyi ile insülin direnci arasında anlamlı bir korelasyon saptandığı, bazı çalışmalarda da anlamlı bir korelasyon saptanmadığı rapor edilmiştir.[14,26,27] Bizim çalışmamızda TSH düzeyi ile insülin direnci arasında anlamlı korelasyon olduğu gösterilmiştir. Biz her ne kadar TSH ile insülin direnci arasında pozitif korelasyon saptasak da korelasyonun düşük derecede olduğu unutulmamalıdır. Çalışmamızla benzer olarak önceki bazı çalışmalarda da subklinik hipotiroidinin insülin direnci ile ilişkili olduğu, TSH düzeyi ile insülin direnci arasında pozitif yönde korelasyon olduğu rapor edilmiştir.[14,26] Literatürü incelediğimizde subklinik hipotiroidinin serum lipit profili üzerine olan etkisinin net olmadığını görmekteyiz.[14,16,27] Birçok çalışmada TSH düzeyinin serum lipit profilinde değişikliğe yol açmadığı belirtilmektedir.[27,28] Bizde çalışmamızda literatür ile benzer olarak TSH düzeyi ile lipit parametreleri arasında anlamlı olabilecek bir ilişki saptamadık. Hem tiroid hormonları hem de lipit profili kilo durumundan etkilenmektedir. Bu nedenle obezitede bu ikisi arasında nedensel bir ilişki olduğunu göstermek zordur. Çünkü uygun beslenme, egzersiz ve davranış tedavisi ile

BKİ kontrol altına alındıktan sonra hem TSH hemde lipit düzeylerinin azaldığı çeşitli çalışmalarda rapor edilmiştir.[5,29,30]

Çalışmamızın kısıtlı yönü hasta sayısının kısmen az olması ve güç analizinin yapılmamış olması olarak değerlendirilmiştir.

Sonuç olarak; bulgularımız obez çocuk ve ergenlerde subklinik hipotiroidinin normal popülasyona göre daha sık görüldüğünü, ancak olguların çoğunda TSH'nın 10 UI/ml'nin altında olduğu için tedaviye ihtiyaç duyulmadığını göstermektedir. Obez çocuklarda subklinik hipotiroidi ile birlikte Hashimato tiroiditi olmaksızın tiroid otoantikor pozitifliğinin de olabileceği gösterilmiştir. Ayrıca TSH düzeyi ile insülin direnci arasında düşük derecede de olsa pozitif yönde bir ilişki olduğu, bu nedenle obez çocuk ve ergenlerde subklinik hipotiroidi saptanması insülin direnci gelişimi açısından klinisyen için uyarıcı olmalıdır.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Etik Kurul İzni

Bu çalışma için Sağlık Bilimleri Üniversitesi Gazi Yaşargil Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu onay alınmıştır (03.03.2023 tarih ve 2023/336 sayılı).

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: EB EÜ. Veri toplama/İşleme: EB EÜ. Veri analizi ve yorumlama: EB EÜ. Literatür taraması: EB EÜ. Yazım: EB EÜ. Gözden geçirme ve düzeltme: EB EÜ. Danışmanlık: EÜ.

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Evaluation of Clinical and Laboratory Findings in Patients with Brucellosis

Brusellozlu Hastalarda Klinik ve Laboratuvar Bulgularının Değerlendirilmesi

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ÖZ

Amaç: Bu çalışmanın amacı bruselloz tanısı konulan hastaların demografik verilerini, klinik ve laboratuvar bulgularını ve organ tutulumlarını değerlendirmektir.
Araçlar ve Yöntem: Hastalar cinsiyete (kadın/erkek) ve yaşa (≤40 yıl/>40 yıl ve ≤30 yıl, 31-44 yıl, 45-59 yıl ve ≥60 yıl) göre gruplara ayrıldı.
Bulgular: Toplam 238 hasta değerlendirildi. Bunların %57.5'i (n=137) erkekti ve yaş ortalaması 43.8±15.0 yıldı. En sık görülen klinik semptomlar artralji (%93.7, n=223), miyalji (%84.9, n=202) ve yorgunluk (%84.5, n=201) idi. Kadın hastalarda miyalji (%92.1'e karşı %79.6, p=0.008), yorgunluk (%92.1'e karşı %78.8, p=0.005), baş ağrısı (%38.6'ya karşı %25.5, p=0.031) ve bulantı (%32.7'ye karşı %13.9, p=0.001) daha yaygındı, iştahsızlık (%43.5'e karşı %59.9, p=0.013) ise daha az yaygındı. Daha genç hastalarda (≤40 yaş) kilo kaybı (%48.0'e karşı %34.3, p=0.034) ve sakroileit (%13.2'ye karşı %5.0, p=0.029) daha yaygındı, spondilodiskit (%2.0'ye karşı %9.3, p=0.039) ise daha az yaygındı. Kilo kaybı ≤30 yaş grubunda 31-44 yaş grubuna (55.8% - %32.8, p=0.013) ve 45-69 yaş grubuna (55.8% - %35.3, p=0.019) göre daha yaygındı. Ateş ≤30 yaş grubunda 45-59 yaş grubuna (32.7% - %54.1, p=0.015) göre daha az yaygındı.
Sonuç: Endemik bölgelerde, artralji, miyalji, yorgunluk, lökopeni veya lökositoz ve yüksek ESR ve CRP'li hastaların ayırıcı tanısında bruselloz düşünülmelidir. Brusellozlu ≤40 yaş hastalar sakroiliit açısından değerlendirilmeli ve >40 yaş hastalar spondilodiskit komplikasyonları açısından değerlendirilmelidir.

Anahtar Kelimeler: brusella; cinsiyet; sakroileit; spondilodiskit; yaş

ABSTRACT

Purpose: The purpose of this study is to evaluate the demographic data, laboratory and clinical findings and organ involvement of patients diagnosed with brucellosis.
Materials and Methods: The patients were divided into groups according to sex (female/male) and age (≤40 years/>40 years and ≤30 years, 31-44 years, 45-59 years, and ≥60 years).
Results: A total of 238 patients were assessed. Among those, 57.5% (n=137) were male, and the mean age was 43.8±15.0 years. Arthralgia (93.7%, n=223), myalgia (84.9%, n=202), and fatigue (84.5%, n=201) were the most common clinical symptoms. In female patients, myalgia (92.1% vs. 79.6%, p=0.008), fatigue (92.1% vs. 78.8%, p=0.005), headache (38.6% vs. 25.5%, p=0.031), and nausea (32.7% vs. 13.9%, p=0.001) were more common, whereas loss of appetite (43.5% vs. 59.9%, p=0.013) was less common. Weight loss (48.0% vs. 34.3%, p=0.034) and sacroiliitis (13.2% vs. 5.0%, p=0.029) were more common, whereas spondylodiscitis (2.0% vs. 9.3%, p=0.039) was less common in younger patients (≤40 years). Weight loss was more common in the ≤30 age group compared to the 31-44 age (55.8% vs. 32.8%, p=0.013) and 45-69 age groups (55.8% vs. 35.3%, p=0.019). Fever was less common in the ≤30 age group compared to the 45-59 age group (32.7% vs. 54.1%, p=0.015).
Conclusion: In endemic areas, brucellosis should be considered in the differential diagnosis of patients with arthralgia, myalgia, fatigue, leukopenia or leukocytosis, and elevated ESR and CRP. Patients ≤40 years with brucellosis should be evaluated for sacroiliitis, and patients >40 years should be evaluated for spondylodiscitis complications.

Keywords: age; brucella; gender; sacroiliitis; spondylodiscitis

Received: 12.09.2024; Accepted: 12.11.2024

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How to cite: Mumcu N, Özdemir YE, Cıvak M, Damar N, Özdemir MŞ. Evaluation of clinical and laboratory findings in patients with brucellosis. Ahi Evran Med J. 2025;9(1):51-61. DOI: 10.46332/aemj.1549183

INTRODUCTION

Brucellosis is a zoonosis that can be transmitted to humans under certain conditions, affecting both farm animals and wildlife. Transmission to humans occurs through direct contact with infected animals, consumption of infected animal products, and inhalation of infected aerosols.[1,2] Recent studies estimate that the annual global incidence of brucellosis in humans is 1.6–2.1 million, which is 3-4 times higher than previously estimated.[3] The disease is endemic in regions such as the Middle East, the Mediterranean, and Central and South America.[4] Most patients with brucellosis present with nonspecific symptoms such as fever, sweating, fatigue, anorexia, nausea, weight loss, myalgia, and arthralgia. The lack of specific clinical findings may lead to misdiagnosis and delays in treatment. If the disease is not treated, it can progress to a chronic phase, and the risk of complications may increase.[1,5] Brucellosis is an infection that can affect almost any system. The most common systems involved are the musculoskeletal system, gastrointestinal system, central nervous system, hematological system, urogenital system, cardiovascular system, respiratory system and skin.[6] As a result of focal involvement, complications such as osteomyelitis, sacroiliitis, spondylodiscitis, septic arthritis, epidural abscesses and epididymo orchitis may occur. Focal involvement can be observed in more than half of patients, who sometimes require different and prolonged treatments.[1,2] In patients with focal brucellosis, delayed diagnosis and inadequate and ineffective treatment may lead to disease recurrence, organ damage and even death.[7] Brucellosis is diagnosed by the isolation of Brucella bacteria from blood or tissues or positive serology together with clinical findings suggestive of brucellosis. Among laboratory findings, the white blood cell count is usually low or normal, while erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) levels are variable.[5] Brucellosis is associated with a wide range of symptoms, ranging from mild to severe, and can affect many organs. Because the clinical symptoms of brucellosis vary widely, diagnosis is difficult.[1,5]

The purpose of this study is to evaluate the demographic data, laboratory and clinical findings and organ involvement of patients diagnosed with brucellosis. In addition, the clinical and laboratory findings of the patients were compared in terms of age and sex.

MATERIALS and METHODS

This study was approved by the Ethics Committee of Kafkas University protocol (dated 31.01.2024 and numbered 2024/01).

In this single-center, cross-sectional study, patients aged 18 years and over who were diagnosed with brucellosis and who applied to the Infectious Diseases and Clinical Microbiology outpatient clinic of Iğdır State Hospital, a secondary care hospital located in the Eastern Anatolia Region of Türkiye, between January 04, 2021, and December 29, 2023, were evaluated. The patients' age, sex, complaints, laboratory findings, and organ involvement were recorded on the prepared form. Patients were divided into groups according to sex (female/male) and age (≤40 years/>40 years and ≤30 years, 31-44 years, 45-59 years, and ≥60 years).

Diagnosis

Blood culture and standard tube agglutination (STA) test were used for diagnosis. In patients with clinical findings compatible with brucellosis, brucellosis was diagnosed with an STA ≥1/160, and/or *Brucella spp.* were isolated via blood culture. A BacT/Alert 3D automated system (bioMerieux) was used for blood culture. Routine laboratory tests, such as complete blood count, CRP, ESR, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine were performed on all patients upon admission. Patients with hip and low back pain were assessed with magnetic resonance imaging (MRI) for sacroiliitis and spondylodiscitis. Patients with swelling and pain in the scrotum were evaluated with ultrasonography for genitourinary system involvement. Osteomyelitis, arthritis and bursitis were diagnosed via MRI in addition to findings such as joint pain, redness, swelling, and limited joint movement.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 25.0 was used for statistical analysis. Categorical variables are presented as numbers (n) and percentages (%), and

continuous variables are presented as the mean ± standard deviation (sd). The chi-square test was used to compare categorical variables. The Mann–Whitney U test was used to compare non normally distributed continuous parameters, whereas the t test was used to compare normally distributed continuous parameters. If the p value was < 0.05, the results were considered statistically significant.

RESULTS

A total of 238 patients were included. Among these patients, 57.5% (n=137/238) were male, and the mean age was 43.8±15.0 years. There was a family history of brucellosis in 121 (51.8%) patients. The mean duration of complaints was 58±79 days. The most common symptoms were arthralgia (93.7%, n=223), myalgia (84.9%, n=202), fatigue (84.5%, n=201), low back pain (62.6%, n=149), loss of appetite (52.9%, n=126), and fever (43.7%, n=104). STA titer was ≥1/640 in 52.1% of patients. The laboratory parameters of the patients are shown in Table 1. Brucella bacteraemia was detected in 33 (13.9%) patients, and focal involvement was detected in 47 (19.7%) patients. Among the patients with focal involvement, 42.5% (n=20/47) had sacroiliitis, 31.9% (n=15/47) had spondylodiscitis, 14.9% (n=7/47) had epididymoorchitis, 6.4% (n=3/47) had peripheral arthritis, and 4.3% (n=2/47) had bursitis (Table 1).

The mean duration of complaints was longer in female patients than in male patients (64±75 vs. 54±81, p=0.016). In female patients, myalgia (92.1% vs. 79.6%, p=0.008), fatigue (92.1% vs. 78.8%, p=0.005), headache (38.6% vs. 25.5%, p=0.031), and nausea (32.7% vs. 13.9%, p=0.001) were more common, whereas loss of appetite (43.5% vs. 59.9%, p=0.013) was less common. In addition, leukocyte count (6611±1806 vs. 7807±2456, p<0.001), neutrophil count (3519±1351 vs. 4402±2084, p<0.001), hemoglobulin (13.8±3.2 vs. 14.4±3.8, p<0.001), NLR (1.46±0.71 vs. 1.76±0.97, p=0.007), urea (26±8 vs. 32±10, p<0.001), creatinine (0.65±0.12 vs. 0.82±0.19, p<0.001), ALT (29±24 vs. 34±25, p=0.001), AST (26±19 vs. 26±19, p=0.007), total bilirubin (0.46±0.27 vs. 0.55±0.30, p=0.018), and CRP (10±15 vs. 20±26, p=0.009) were lower, and the platelet count (293±96 vs. 267±80, p=0.022), PLR (122±54 vs. 107±46, p=0.015), and ESR (27±20 vs. 23±20, p=0.030) were higher. The frequency of Brucella bacteremia was similar (13.9% vs. 13.9%, p=0.999) between the two groups, and focal involvement was less common (13.9% vs. 24.1%, p=0.050) in female patients (Table 1).

When patients were evaluated according to age group, weight loss (48.0% vs. 34.3%, p=0.034) was more common in younger patients (≤40 years) than in older patients (>40 years). In addition, urea (25±7 vs. 32±10, p<0.001) and creatinine (0.72±0.15 vs. 0.77±0.20, p=0.014) values were lower and STA titers were higher (61.2% vs. 45.7%, p=0.018) in younger patients. Moreover, sacroiliitis was detected more frequently in younger patients (13.2% vs. 5.0%, p=0.029), whereas spondylodiscitis was detected more frequently in older patients (2.0% vs. 9.3%, p=0.039) (Table 2). The distribution of symptom frequencies according to age group in brucellosis patients is shown in Table 3. Weight loss was more common in the ≤30 years age group than in the 31–44 years (55.8% vs. 32.3%, p=0.013) and 45–69 years age groups (55.8% vs. 35.3%, p=0.019). Fever was less common in the ≤30 years age group than in the 45-59 years age group (32.7% vs. 54.1%, p=0.015). Headache was more common in the 31-44 year age group than in the 45–59 year age group (41.8% vs. 23.5%, p=0.017). There was no statistically significant difference in the distribution of other symptoms between age groups (Figures 1, 2).

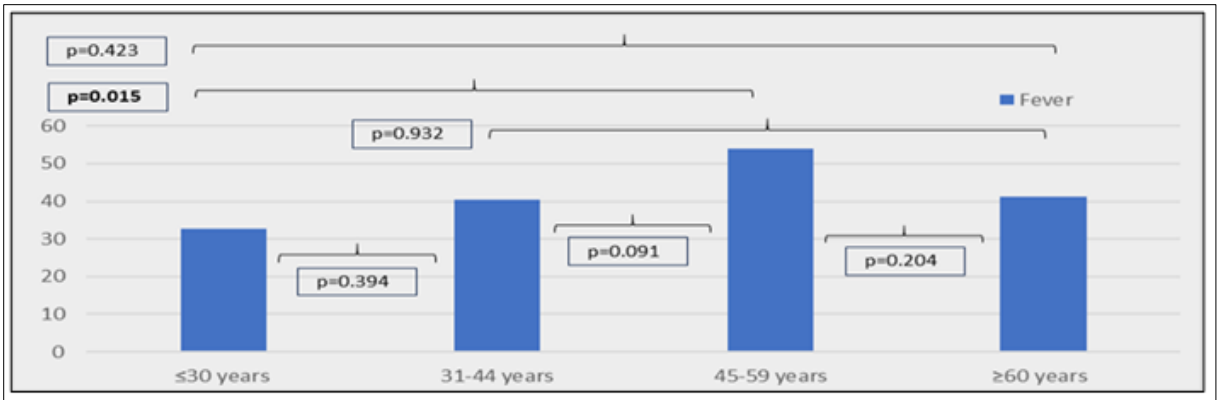

Figure A

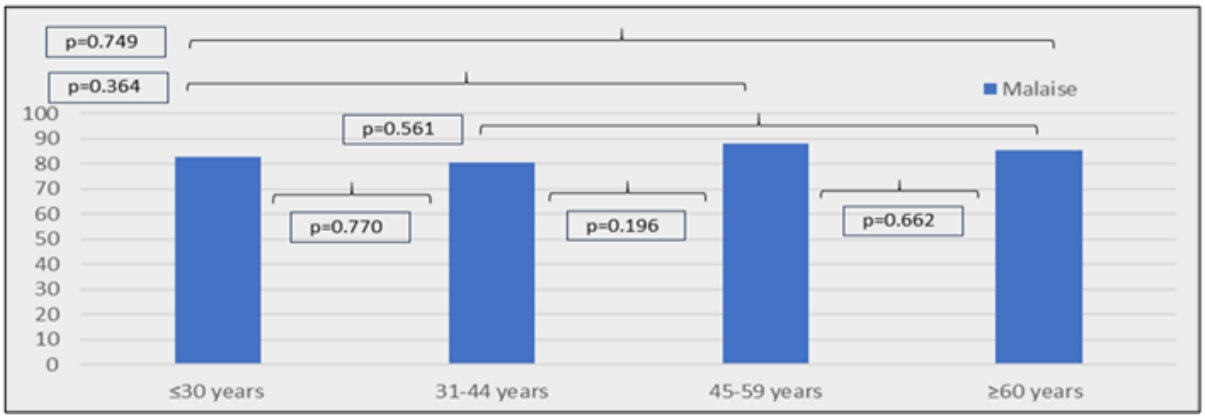

Figure B

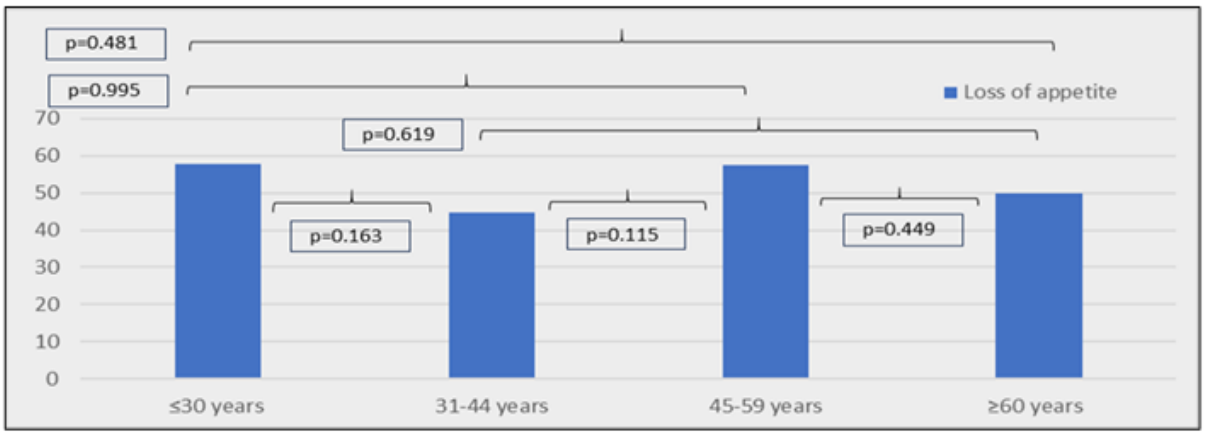

Figure C

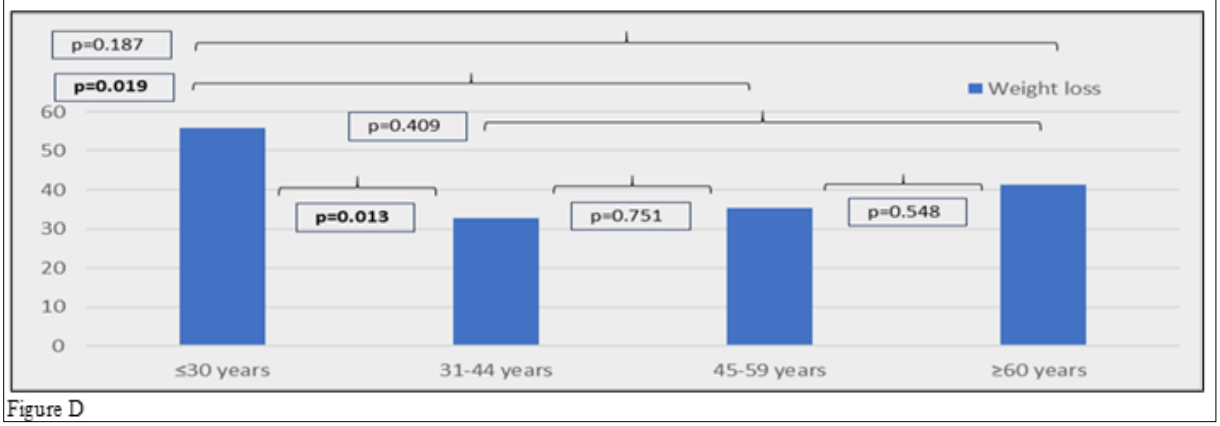

Figure D

Figure 1. Comparison of complaints of fever, fatigue, loss of appetite, and weight loss according to age groups.

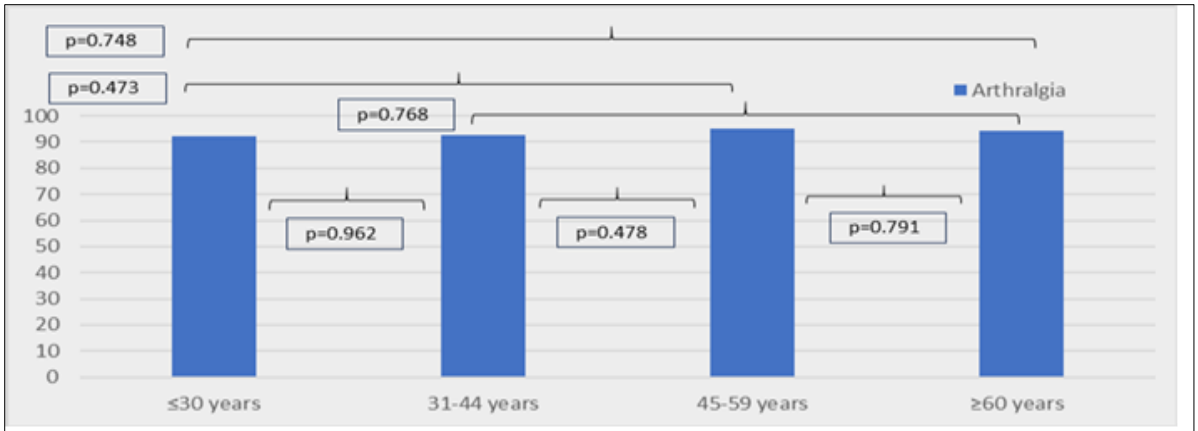

Figure A

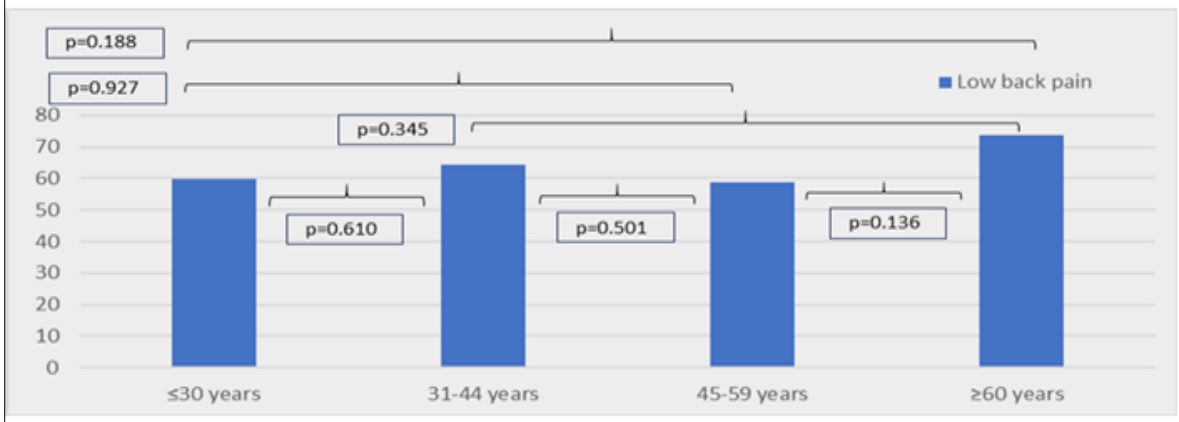

Figure B

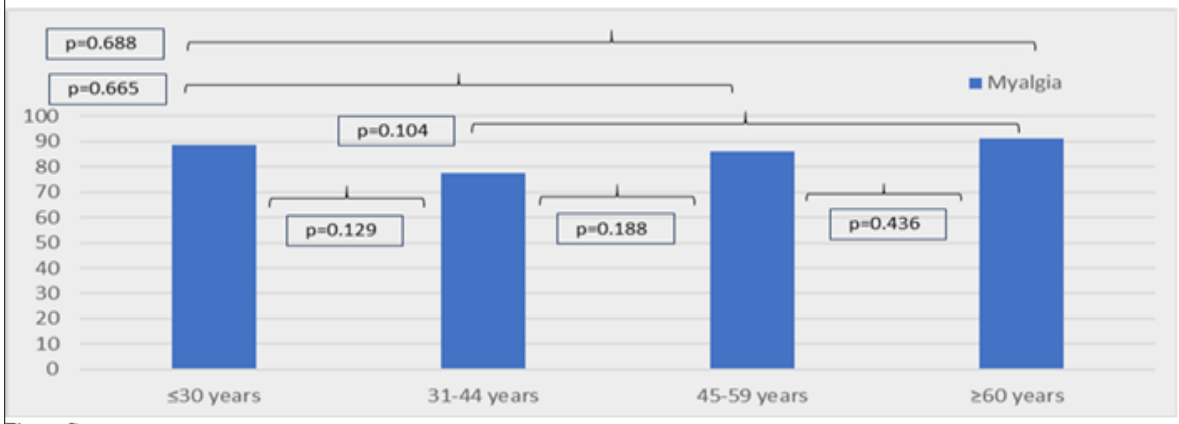

Figure C

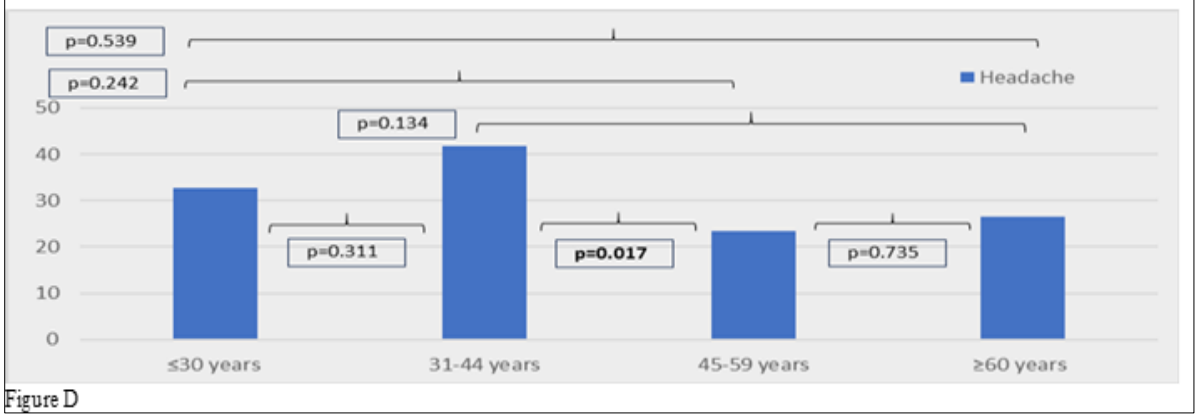

Figure D

Figure 2. Comparison of complaints of arthralgia, myalgia, headache and low back pain ac-cording to age groups.

Table 1. Comparison of demographic characteristics, clinical findings and laboratory parameters of patients diagnosed with brucellosis according to sex.

Parameters	Total (n=238) n (%) / mean ± sd		Male (n=137) n (%) / mean ± sd		Female (n=101) n (%) / mean ± sd		p	OR
Demographic characteristics								
Age	43.8±15.0		44.2 ± 14.9		43.3 ± 15.1		0.540	
Height	168±9		173±7		162 6		<0.001	
Weight	73±12		75±11		69±13		0.029	
BMI (kg/m²)	27.7±24.3		25±3		31±38		0.089	
Smoking	71	29.8	54	39.4	17	16.8	<0.001	3.21
Family History	121	51.8	64	46.7	57	56.4	0.138	0.67
Clinical findings								
Arthralgia	223	93.7	128	93.4	95	94.1	0.844	0.89
Myalgia	202	84.9	109	79.6	93	92.1	0.008	0.33
Fatigue	201	84.5	108	78.8	93	92.1	0.005	0.32
Low back pain	149	62.6	82	59.9	67	66.3	0.307	0.75
Loss of appetite	126	52.9	82	59.9	44	43.5	0.013	1.93
Fever	104	43.7	62	45.3	42	41.6	0.573	1.16
Weight loss	95	39.9	58	42.3	37	36.6	0.375	1.27
Headache	74	31.1	35	25.5	39	38.6	0.031	0.54
Nausea	52	21.8	19	13.9	33	32.7	0.001	0.33
Cough	16	6.7	8	5.8	8	7.9	0.526	0.72
Vomitting	15	6.3	7	5.1	8	7.9	0.378	0.62
Diarrhea	5	2.1	2	1.5	3	3.0	0.422	0.48
Rash	3	1.3	2	1.5	1	1.0	0.748	1.48
Duration of complaint (day)	58±79		54±81		64±75		0.016	
Laboratory parameters								
White blood cells (/µl)	7297±2277		7807±2456		6611±1806		<0.001	
Leukocytosis	15	6.3	13	9.6	2	2.0	0.018	5.23
Leukopenia	5	2.1	0	0.0	5	5.0	0.009	1.05
Neutrophil count (/µl)	4026±1857		4402±2084		3519±1351		<0.001	
Lymphocyte count (/µl)	2715±1187		2807±1411		2591±782		0.377	
Lymphocytosis	50	21.0	33	24.1	17	16.8	0.174	1.56
NLR	1.63±0.88		1.76±0.97		1.46±0.71		0.007	
Hemoglobin (g/dL)	14.2±6.1		14.4±3.8		13.8±3.2		<0.001	
Anemia	30	12.6	13	9.6	17	16.8	0.096	0.52
Platelet count (103/µl)	278±88		267±80		293±96		0.022	
Thrombocytopenia	4	1.7	3	2.2	1	1.0	0.472	2.25
PLR	113±50		107±46		122±54		0.015	
Urea (mg/dl)	29±10		32±10		26±8		<0.001	
Creatinine (mg/dl)	0.75±0.18		0.82±0.19		0.65±0.12		<0.001	
ALT (IU/L)	32±25		34±25		29±24		0.001	
ALT >40 (IU/L)	58	24.4	39	28.7	19	18.8	0.081	1.73
AST (IU/L)	28±18		28±16		26±19		0.007	
AST >40 (IU/L)	33	13.9	21	15.4	12	11.9	0.434	1.35
Total bilirubin (mg/dl)	0.51±0.28		0.55±0.30		0.46±0.27		0.018	
CRP (mg/L)	16±232		20±26		10±15		0.009	
CRP >5 (mg/L)	127	53.4	83	60.6	45	44.5	0.013	1.92
ESR (mm/hour)	25±20		23±20		27±20		0.030	
ESR > 20 (mm/hour)	115	48.3	59	43.1	56	55.4	0.059	0.61
STA titer ≥ 1/320	199	83.6	115	83.9	84	83.2	0.873	1.5
STA titer ≥ 1/640	124	52.1	73	53.3	51	50.5	0.670	1.11
Focus of İnfection								
Bacteremia	33	13.9	19	13.9	14	13.9	0.999	1.00
Focal involvement	47	19.7	33	24.1	14	13.9	0.050	1.97
Sacroiliitis	20	8.4	14	10.2	6	5.9	0.245	1.80
Spondylodiscitis	15	6.3	9	6.6	6	5.9	0.843	1.11
Epididymoorchitis	7	2.9	7	5.1	0	0.0	0.093	11.6
Peripheral arthritis	3	1.3	2	1.5	1	1.0	0.749	1.48
Bursitis	2	0.8	1	0.7	1	1.0	0.735	0.82
Endocarditis	0	0	0	0.0	0	0.0	0.879	0.73
Meningitis	0	0	0	0.0	0	0.0	0.879	0.73

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, NLR: Neutrophil / lymphocyte ratio, PLR: Platelet / lymphocyte ratio, STA: Standard tube agglutination,

Table 2. Comparison of demographic characteristics, clinical findings and laboratory parameters of patients diagnosed with brucellosis according to age.

Parameters	Total (n=238)		≤40 years (n=98)		>40 years (n=140)		p	OR
	n (%) / mean±sd		n (%) / mean±sd		n (%) / mean±sd			
Demographic characteristics								
Sex (Female)	137	57.5	52	53.1	85	60.7	0.540	0.73
Height	168±9		169±9		168±9		0.738	
Weight	73±12		69±12		76±11		0.001	
BMI	27.7±24.3		24±4		31±332		<0.001	
Smoking	71	29.8	28	28.2	43	30.7	0.722	0.90
Family History	121	51.8	56	57.1	65	46.8	0.104	1.54
Clinical findings								
Arthralgia	223	93.7	89	90.8	134	95.7	0.126	0.44
Myalgia	202	84.9	80	81.6	122	87.1	0.243	0.65
Malaise	201	84.5	79	80.6	122	87.1	0.171	0.61
Low back pain	149	62.6	61	62.2	88	62.9	0.923	0.97
Loss of appetite	126	52.9	49	50.0	77	55.0	0.447	0.82
Fever	104	43.7	36	36.7	68	48.6	0.070	0.61
Weight loss	95	39.9	47	48.0	48	34.3	0.034	1.76
Headache	74	31.1	36	36.7	38	27.1	0.116	1.55
Nausea	52	21.8	25	25.5	27	19.3	0.253	1.43
Cough	16	6.7	6	6.1	10	7.1	0.757	0.85
Vomitting	15	6.3	7	7.1	8	5.7	0.655	1.26
Diarrhea	5	2.1	3	3.1	2	1.4	0.387	2.17
Rash	3	1.3	1	1.0	2	1.4	0.781	0.71
Duration of complaint (day)	58±79		54±81		64±75		0.016	
Laboratory parameters								
White blood cells	7297±2277		7510±2331		7150±2235		0.156	
Leukocytosis	15	6.3	7	7.2	8	5.7	0.640	1.28
Leukopenia	5	2.1	3	3.1	2	1.4	0.381	2.20
Neutrophil count	4026±1857		4201±1942		3904±1793		0.228	
Lymphocyte count	2715±1187		2692±798		2731±1394		0.487	
Lymphocytosis	50	21.0	19	19.4	31	22.1	0.608	0.84
NLR	1.63±0.88		1.68±0.97		1.56±0.82		0.374	
Hemoglobin	14.2±6.1		14.7±9.3		13.8±1.4		0.874	
Anemia	30	12.6	15	15.5	15	10.7	0.280	1.52
Platelet count	278±88		282±92		275±84		0.682	
Thrombocytopenia	4	1.7	0	0	4	2.9	0.093	0.15
PLR	113±50		112±43		114±55		0.940	
Urea	29±10		25±7		32±10		<0.001	
Creatinine	0.75±0.18		0.72±0.15		0.77±0.20		0.014	
ALT	32±25		35±27		30±23		0.110	
ALT >40	58	24.4	30	30.9	28	20.0	0.054	1.79
AST	28±18		29±18		27±17		0.199	
AST >40	33	13.9	16	16.5	17	12.1	0.341	1.42
Total bilirubin	0.51±0.28		0.51±0.28		0.52±0.28		0.458	
C-reactive protein	16±232		16±23		16±22		0.722	
CRP >5 mg/dL	128	53.8	57	58.1	71	50.7	0.435	1.25
ESR	25±20		24±19		25±202		0.611	
ESR >20	115	48.3	46	46.9	69	49.3	0.721	0.91
STA titer ≥ 1/320	199	83.6	84	85.7	115	82.1	0.464	1.30

STA titer ≥ 1/640	124	52.1	60	61.2	64	45.7	0.018	1.87
Focus of İnfection								
Bacteremia	33	13.9	18	18.4	15	10.7	0.093	1.87
Focal involvement	47	19.7	23	23.5	24	17.1	0.228	1.48
Sacroiliitis	20	8.4	13	13.2	7	5.0	0.029	2.90
Spondylodiscitis	15	6.3	2	2.0	13	9.3	0.039	0.20
Epididymoorchitis	7	2.9	4	4.1	3	2.1	0.391	1.94
Peripheral arthritis	3	1.3	3	3.0	0	0.0	0.124	10.2
Bursitis	2	0.8	1	1.0	1	0.7	0.388	2.89
Endocarditis	0	0	0	0.0	0	0.0	0.859	1.42
Meningitis	0	0	0	0.0	0	0.0	0.859	1.42

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, NLR: Neutrophil / lymphocyte ratio, PLR: Platelet / lymphocyte ratio, STA: Standard tube agglutination,

Table 3. Comparison of the clinical findings of patients diagnosed with brucellosis according to age group.

Parameters		**≤30 years (n=52)**		**31-44 years (n=67)**		**45-59 years (n=85)**		**≥60 years (n=34)**	
		n	%	n	%	n	%	n	%
Fever	Yes	17	32.7	27	40.3	46	54.1	14	41.2
	No	35	67.3	40	59.7	39	45.9	20	58.8
Malaise	Yes	43	82.7	54	80.6	75	88.2	29	85.3
	No	9	17.3	13	19.4	10	11.8	5	14.7
Loss of appetite	Yes	30	57.7	30	44.8	49	57.6	17	50.0
	No	22	42.3	37	55.2	36	42.4	17	50.0
Weight loss	Yes	29	55.8	22	32.8	30	35.3	14	41.2
	No	23	44.2	45	67.2	55	64.7	20	58.8
Arthralgia	Yes	48	92.3	62	92.5	81	95.3	32	94.1
	No	4	7.7	5	7.5	4	4.7	2	5.9
Low back pain	Yes	31	59.6	43	64.2	50	58.8	25	73.5
	No	21	40.4	24	35.8	35	41.2	9	26.5
Myalgia	Yes	46	88.5	52	77.6	73	85.9	31	91.2
	No	6	11.5	15	22.4	12	14.1	3	8.8
Headache	Yes	17	32.7	28	41.8	20	23.5	9	26.5
	No	35	67.3	39	58.2	65	76.5	25	73.5
Nausea	Yes	11	21.2	18	26.9	16	18.8	7	20.6
	No	41	78.8	49	73.1	69	81.2	27	79.4
Vomitting	Yes	5	9.6	3	4.5	5	5.9	2	5.9
	No	47	90.4	64	95.5	80	94.1	32	94.1
Diarrhea	Yes	1	1.9	2	3.0	1	1.2	1	2.9
	No	51	98.1	65	97.0	84	98.8	33	97.1
Cough	Yes	3	5.8	9	9.0	5	5.9	2	5.9
	No	49	94.2	58	91.0	80	94.1	32	94.1
Rash	Yes	0	0.0	1	1.5	2	2.4	0	0.0
	No	52	100	66	98.5	83	97.6	34	100

DISCUSSION

In this study, the demographic data, clinical and laboratory findings and organ involvement of brucellosis patients were evaluated according to the age and sex of the patients. Accordingly, the duration of complaints was significantly longer in women. Weakness, myalgia, headache and nausea were significantly more common in women, and loss of appetite was significantly more common in men. Re-

garding laboratory values, leukocytosis, NLR, hemoglobin, CRP elevation and mean CRP values were significantly higher in men, and leukopenia, PLR and mean ESR values were significantly higher in women. Weight loss and sacroiliitis were more common, and spondylodiscitis was less common in patients aged ≤40 years. Additionally, high STA titers (≥1/640) were higher in patients aged ≤40 years.

Brucellosis can be detected at any age, but the age group in which brucellosis is frequently detected varies from country to country and according to the studies conducted. It usually affects the productive age group. Buzgan et al.[8] reported the age range in which patients are frequently 13--34 years, whereas Jiang et al.[9] reported the age range of 41--65 years. In addition, in other studies, the average age of patients with brucellosis varies between 27 and 46 years.[10-12] A study conducted in California reported that the incidence of brucellosis was greater in individuals aged 65 and over than in other studies.[13] In this study, most of the infected individuals were middle-aged patients between the ages of 45 and 60, and the average age of all patients was 43.8 years. The reason why the age at which brucellosis is frequently observed varies according to studies may be related to differences in the age of animal husbandry from society to society.

We observed different results in studies on the relationship between brucellosis incidence and sex. In contrast to studies reporting that sex is associated with the occurrence of brucellosis in humans,[14-16] other studies reporting that it is not associated with brucellosis.[17,18] In general, community-based studies report that brucellosis is detected at equal or very close rates in men and women and that it is more common in men in societies where occupational exposure is more common.[19-24] In this study, most of the brucellosis patients (57.5%) were men. This result was consistent with studies reporting that brucellosis is more common in males.[16,24-27] The change in brucellosis incidence according to sex may be related to occupational exposure and the mode of transmission of the disease.[23]

The clinical symptoms of brucellosis vary considerably.[8] Most patients with brucellosis have nonspecific symptoms such as fever, sweating, fatigue, anorexia, nausea, weight loss, myalgia, and arthralgia.[1,5] Although the most common symptoms vary from study to study and according to the stage of the disease, fever, sweating, fatigue, and arthralgia are generally the most frequently reported complaints.[8,9,28] In this study, consistent with the literature, arthralgia, myalgia, and fatigue were the most common clinical symptoms. When we evaluated the clinical symptoms of patients with brucellosis according to sex and age in this study, fatigue, myalgia, headache, and nausea were significantly more common in women, anorexia in men, and weight loss in individuals under the age of 40. Hasanjani et al.[23] reported that arthralgia was significantly more common in women, Zaks et al.[29] reported that myalgia was significantly more common in men and that the frequency of other clinical symptoms was the same in both genders. Another study reported that headache, arthralgia, myalgia, and fatigue were more common in women.[30] Fritz et al. reported that fever, sweating, and headache complaints were more common in patients under 65 years of age.[13] Another study reported that fever, headache, joint pain, and fatigue were more common in individuals aged 20-44 years and that myalgia, night sweats, and weight loss were more common in individuals aged 45 years and over.[30] In this study, weight loss was more common in individuals under 30 years of age, headache was more common in the 31-44 years age group, and fever was more common in the 45-69 years age group. However, the role of geographic region, age, sex, ethnicity, or other factors in the clinical symptoms of brucellosis has not yet been clarified.

Brucella infection can involve any organ or tissue in the body. Focal involvement can be observed in more than half of patients.[2] Osteoarticular involvement is the most common.[2,8,19] The prevalence of osteoarticular involvement has been reported to be between 10% and 85%, depending on the study, age, duration of the disease and infection with Brucella species.[5] In this study, 19.7% of the patients had focal involvement, and 85.1% of them had osteoarticular involvement. Among areas with osteoarticular involvement, peripheral arthritis, sacroiliitis and spondylitis are the most commonly affected areas.[5,8,19,23] Hasanjani et al.[23] reported that focal involvement and spondylitis were significantly more common in men than in women, whereas Zaks et al.[29] reported that osteoarticular involvement was similar in both sexes. In this study, focal involvement was

more common in men, but there was no significant difference in osteoarticular involvement. While spondylitis is usually observed in elderly men, sacroiliac joint involvement is observed in both sexes, young and old.[5] In this study, the most common osteoarticular involvements were sacroiliitis (50%) and spondylodiscitis (37.5%). Sacroiliitis was significantly more common in patients under 40 years of age, whereas spondylodiscitis was significantly more common in individuals over 40 years of age.

Among the laboratory findings of brucellosis, the white blood cell count is generally normal or low, whereas the levels of AST, ALT, ESR and CRP are variable.[5,8] Among the hematological findings, anemia, leukocytosis, leukopenia, thrombocytosis, thrombocytopenia and pancytopenia are relatively common. Hematological findings may be associated with hypercellularity, hemophagocytosis and granulomas, disseminated intravascular coagulation and hypersplenism in cases where the bone marrow is involved.[2] In previous studies, leukocytosis was reported as 5.6-15.2%, leukopenia as 3-37.1%, thrombocytopenia as 2-26%, anemia as 7-55%, CRP elevation as 36-66.2%, and ESR elevation as 38-77.8%.[8,19,23,31-33] In our study, when laboratory abnormalities were taken into consideration, 6.3% of our patients had leukocytosis, 2.1% had leukopenia, 12.6% had anemia, 1.7% had thrombocytopenia, 53.4% had CRP and 48.3% had ESR elevation. Leukocytosis, NLR, hemoglobin CRP elevation and mean CRP values (20±26) were significantly greater in male patients, and leukopenia, PLR and mean ESR values (27±20) were significantly greater in female patients. Demiraslan et al.[31] reported that leukopenia and anemia were more common in females and that leukocytosis was more common in males.

Brucellosis is diagnosed by the isolation of Brucella bacteria from blood or tissues or by positive serology together with clinical findings suggestive of brucellosis.[5] All patients in this study had STA titers of ≥1:160, and *Brucella spp.* were isolated from the blood cultures of 33 (13.9%) patients. A total of 52.1% of patients had STA tests of ≥1:640, which was significantly greater in individuals under 40 years of age than in individuals over 40 years of age.

Although the fact that the study was conducted in a region where mostly small livestock farms are performed and that it was a single center may limit the generalizability of the results, the fact that all brucellosis cases in the region were collected in this center contributes to the homogeneous distribution of the cases, which makes our results generalizable.

As a result, the clinical symptoms, laboratory values and complications of brucellosis vary significantly. Some of them were found to be related to age and sex. In regions where brucellosis is endemic, it should be considered in the differential diagnosis of patients with arthralgia, myalgia, weakness, leukopenia or leukocytosis, and elevated ESR and CRP. In particular, patients ≤40 years with brucellosis should be evaluated for sacroiliitis, and patients >40 years should be evaluated for spondylodiscitis complications.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

This study was approved by the Ethics Committee of Kafkas University protocol (dated 31.01.2024 and numbered 2024/01).

Authors' Contributions

Concept/Design: NM, YEO, MÇ, ND, MSO. Data Collection and/or Processing: NM, YEO, MÇ, ND, MSO. Data analysis and interpretation: NM, YEO, MÇ, ND, MSO. Literature Search: NM, YEO. Drafting manuscript: NM, YEO. Critical revision of manuscript: NM, YEO

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Relationship between RT-PCR Threshold Cycle Values and Thorax CT Severity Score in COVID-19 Patients

COVID-19 Hastalarında RT-PCR CT Değerleri ile Toraks BT Şiddet Skoru Arasındaki İlişki

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Deniz ÖZKAN[4]

ÖZ

Amaç: Bu çalışmada, viral yük hakkında bilgi veren RT-PCR Cycles Threshold (Ct) değerleri ile akciğer tutulumunu göstermek için kullanılan Bilgisayarlı Tomografi şiddet skoru (BTŞS) arasındaki ilişkinin araştırması amaçlandı.
Araçlar ve Yöntem: 1 Ocak 2021 ile 31 Kasım 2021 tarihleri arasında akciğer oskültasyon bulguları ve/veya posteroanterior akciğer grafisinde şüpheli bulguları olan ve RT-PCR testi pozitif çıkan toplam 162 hasta çalışmaya dahil edilmiştir. Olguların viral yükleri, akciğer tutulumu ve mortalite oranları hastaneye yatırıldıkları birimlere göre analiz edildi. Ayrıca, COVID-19, BTŞS, RT-PCR Ct viral yük değerleri ve yaşa eşlik eden komorbid hastalıklar arasındaki korelasyon incelendi.
Bulgular: BTŞS yaş ile pozitif ve anlamlı bir korelasyon göstermiştir (p=0.017). İstatistiksel analiz, viral yük ile torasik tutulum arasında anlamlı bir korelasyon olmadığını ortaya koymuştur (p=0.663).
Sonuç: Bu çalışmaya göre, COVID-19 hastalığının tanısında önemli bir yer tutan RT-PCR Ct değerleri ile toraks BT tutulumu arasında anlamlı bir korelasyon bulunmazken, akciğer tutulumu prevalansı ve olguların ölüm oranı yaşla birlikte artmıştır. Ayrıca, CT-CS skoru ile yaş arasında anlamlı bir korelasyon gözlenmiştir. Bu bulgular, bu alanda gelecekte yapılacak derinlemesine araştırmaların önünü açarak konunun daha iyi anlaşılmasını sağlayacaktır.

Anahtar Kelimeler: bilgisayarlı tomografi; COVID-19; tomografi; torasik tutulum; viral yük

ABSTRACT

Purpose: In this study, we aimed to investigate the relationship between RT-PCR Cycles Threshold (Ct) values, which provide information about the viral load, and CT severity score (CTSS), which is used to demonstrate lung involvement.
Materials and Methods: Between January 1, 2021 and November 30, 2021, a total of 162 patients with lung auscultation findings and/or suspicious findings on posteroanterior chest radiography, along with a positive RT-PCR test, were included in the study. Viral loads, lung involvement, and mortality rates of the cases were analyzed based on the units in which they were hospitalized. Additionally, we investigated the correlation between comorbid diseases associated with COVID-19, CTSS (CT severity score), RT-PCR Ct viral load values, and age.
Results: The CTSS showed a positive and significant correlation with age (p=0.017). Statistical analysis revealed no significant correlation between viral load and thoracic involvement (p=0.663).
Conclusion: According to the present study, no significant correlation was found between RT-PCR Ct values, which play a crucial role in the diagnosis of COVID-19, and thoracic CT involvement. However, the prevalence of lung involvement and the mortality rate of the cases increased with age. Additionally, a significant correlation was observed between the CT severity score (CT-SS) and age. These findings pave the way for future in-depth research in this field, fostering a better understanding of the subject matter.

Keywords: computed tomography; COVID-19, thoracic involvement; tomography; viral load

Received: 11.03.2024; Accepted: 15.11.2024

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How to cite: Akıneden A, Çiçek C, Türkel S, Kararmaz NB, Özkan D. Relationship between RT-PCR threshold cycle values and thorax ct severity score in COVID-19 patients. Ahi Evran Med J. 2025;9(1):62-67. DOI: 10.46332/aemj.1450874

INTRODUCTION

SARS CoV-2 (COVID-19), the causative agent of coronavirus disease, is transmitted through the respiratory tract and close contact.[1] The real-time reverse transcriptase polymerase chain reaction (RT-PCR), used in diagnostic purposes, provides a quantification of viral load in the sample through the cycle threshold (Ct) value.[2] The Ct value is an important determinant in assessing the likelihood and severity of disease transmission.[3,4] Lung involvement is the main cause of morbidity and mortality in COVID-19 patients.[2] Due to its wide availability and rapid examination time, the role of chest computed tomography (CT) is increasingly complementary to RT-PCR in patients with COVID-19 pneumonia.[5] Chest CT examination holds significance not only for the prompt diagnosis of COVID-19 but also for disease monitoring and assessing the effectiveness of treatment.[6,7] The utilization of Computed Tomography Severity Scoring (CTSS) is recommended for quantifying pulmonary involvement in patients with COVID-19 and establishing correlations with clinical classifications.[6] The objective of this study was to examine the correlation between RT-PCR Ct values, serving as viral load markers, and CTSS values among hospitalized patients with COVID-19.

MATERIALS and METHODS

This study was conducted with the approval of the Ministry of Health, General Directorate of Health Services Scientific Study Platform (Decision No: T21-31-28, Date: 11-10-2021) Approval for this study was obtained from Aksaray University Clinical Research Ethics Committee (dated 16.12.2021 and numbered 2021/17-03).

Collection of Samples

The study included patients aged 18 and above, with confirmed positive RT-PCR tests, and without any known pre-existing lung disease, who were admitted to the COVID-19 service and intensive care unit during the period of January 1, 2021, to November 30, 2021. In the study, the cases were analyzed in terms of demographic information (age, gender), comorbid diseases (diabetes, hypertension, cardiovascular diseases, etc.), CTSS, RT-PCR Ct values, the unit of hospitalization (ward-intensive care unit) and the outcome of the disease (non-survivor/survivor).

Molecular Studies and RT-PCR

Naso-oropharyngeal swab samples were collected with a COVID-19 transfer tube (vNAT, Bioeksen, Istanbul, Turkey) and sent to the laboratory. Nucleic acid extraction and PCR reaction was performed without modification according to the manufacturers' instructions contained in the kit inserts (Bio-Speedy COVID-19 RT-qPCR Detection Kit) (Bioeksen, Turkey). Amplification was performed on a Bio-Rad CFX96 Touch™ (Bio-Rad, USA). RT-PCR Ct values <25 were determined as high, 25-30 as moderate and >30 as low viral load.[8]

Determination of Lung Involvement and Severity Scores by CT

Multidetector CT device (GE Medical Systems, USA) was used for CT scanning. CT scanning was performed according to the manufacturer's recommendations. Images were reconstructed to include coronal and sagittal planes with 1-mm slice thickness. In the determination of computed tomography total severity score (CT-CS), a semi-quantitative scoring system was used to determine the lung involvement of COVID19-related abnormalities.[6] Each lung lobe was scored from 0 to 5 (0: No lobe involvement; 1: <5% of the lobe; 2: 5-25% of the lobe; 3: 26-50% of the lobe; 4: 51-75% of the lobe; 5: >75% of the lobe involved). Along with this scoring; total severity scoring was performed on CT. Values of 8 and below were accepted as mild, values between 9 and 15 as moderate and values above 15 as severe lung involvement.[9] In addition, the patients were grouped as Group I without lung involvement, Group II with mild involvement (Figure I), Group III with moderate involvement (Figure II)and Group IV with severe involvement (Figure III).[10]

Statistical Analysis

IBM Statistics for Windows, Version 26.0 package program was used to evaluate the data. Parametric and/or nonparametric test methods were used for comparison of continuous variables between groups according to Shapiro Wilk normality test. Student's t test or Mann

Whitney U test were used to compare two independent groups, and One-Way ANOVA and Kruskal Wallis tests were used to compare more than two independent groups. If the difference was found to be significant, the groups that caused the difference were identified by using appropriate posthoc multiple comparison tests. The difference was defined with letter indices placed on the means or medians. As descriptive statistics, mean±St.deviation median (minimum-maximum) was used to summarize continuous variables, while frequency distributions and percentages were used for categorical variables. Multiple Logistic Regression method (Backward LR option) was used to evaluate the risk factors affecting mortality and the results are presented with odds ratios and confidence intervals.

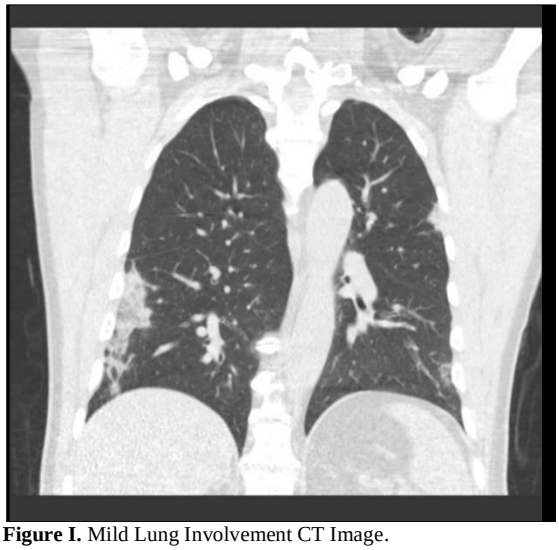

Figure I. Mild Lung Involvement CT Image.

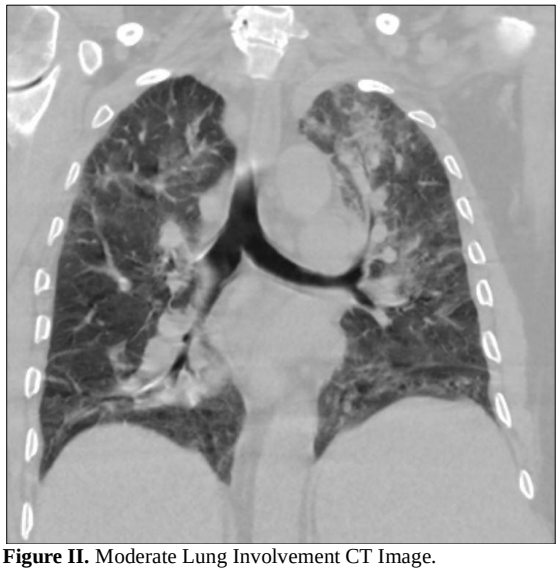

Figure II. Moderate Lung Involvement CT Image.

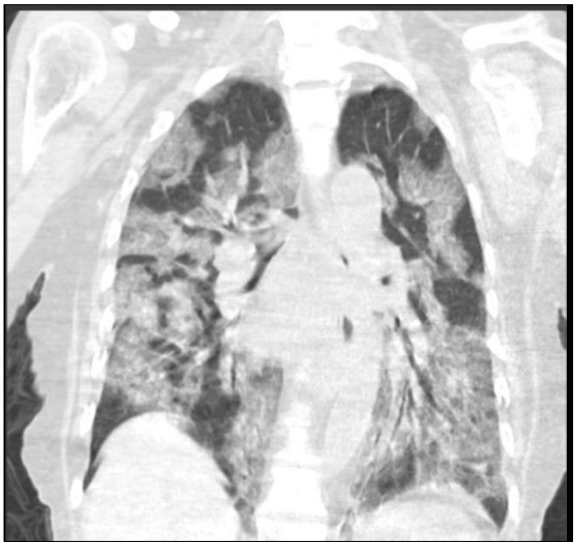

Figure III. Severe Lung Involvement CT Image.

RESULTS

A total of 162 patients, 77 females and 85 males, who were positive for COVID-19 RT-PCR, aged 18 years or older, had lung listening findings on physical examination and/or suspicious findings on posteroanterior chest radiography were included in the study. In addition, the cases were divided into 3 groups as low (Ct>30), intermediate (Ct 25-30) and high (Ct<25) viral load according to RT-PCR Ct value. The mean age of the patients was 63.42 years, 133 were hospitalized in the ward and 29 in the intensive care unit (Table 1).

Lung involvement rates and RT-PCR Ct values of cases were compared. No association was observed between lung involvement and viral load, although it was observed that mortality increased as lung involvement increased (Table 2).

It was determined that COVID-19 patients had comorbid diseases (diabetes mellitus, hypertension, cardiovascular diseases, malignancy, rheumatologic diseases, renal diseases, obesity, neurologic diseases and endocrine disorders). The most common comorbid diseases were hypertension (n=63, 38.88%), cardiovascular disease (n=44, 27.16%), diabetes mellitus (n=36, 22.22%) and chronic obstructive pulmonary disease (n=11, 6.79%). The correlation between these diseases, CTSS and RT-PCR Ct viral load values and age were analyzed. A significant positive correlation was found between CTSS score and age (r=0.188, p=0.017) (Table 3).

We compared the variables of Ct viral load, age, and number of chronic diseases with CT severity categories, and found that the difference was significant only for age. The mean age of the group with mild viral load was statistically lower than the group with moderate and severe viral load (Table 4).

Table 1. Viral loads of the cases.

Parameters	Viral loads	High <25 n (%)	Mild 25-30 n (%)	Low >30 n (%)	Total n (%)
ICU	Man	6	5	7	18
	Woman	3	6	2	11
Ward	Man	29	20	18	67
	Woman	27	20	19	66
Total	Man	35	25	25	85 (52.47)
	Woman	30	26	21	77 (47.53)
	Total	65 (40.12)	51 (31.48)	46 (28.40)	162 (100)

ICU: Intensive Care Unit

Table 2. CT Lung involvement, viral loads and non-survivor rates.

Groups	Lung Involvement	Viral Load (Ct)	Non-survivor rates n (%)	Survivor rates n (%)	Total n (%)
I	No involvement	20-32	0 (0)	2 (100)	2 (100)
II	Mild	16-39	2 (4)	48 (96)	50 (100)
III	Moderate	12-38	11(18.97)	47 (81.03)	58 (100)
IV	Severe	17-39	16 (30.77)	36 (69.23)	52 (100)
Total			29 (17.9)	133 (82.1)	162 (100)

Table 3. Correlation between CTSS, Ct viral load, age and comorbid diseases.

Parameters		CTSS	Ct Viral Load	Age	Number of Comorbid Disease
CTSS	**r**		0.035	**0.188**	-0.001
	p		0.663	**0.017**	0.990
	n		162	162	124
Ct Viral Load	**r**	0.035		-0.021	-0.059
	p	0.663		0.792	0.513
	n	162		162	124
Age	**r**	**0.188**	-0.021		0.135
	p	**0.017**	0.792		0.136
	n	162	162		124
Number of Comorbid Disease	**r**	-0.001	-0.059	0.135	
	p	0.990	0.513	0.136	
	n	124	124	124	

CTSS: Computed Tomography Severity Scoring, r:Pearson's correlation coefficient (rho),p:p value, n:number of cases

Table 4. Comparison of CT viral load, age and number of chronic diseases variables and CT severity score categories.

CT Severity Categories	Mild	Moderate	Severe	p
Ct Viral Load	26.9±6.07 27(16-38)	26.69±6 27(12-39)	26.86±5.39 26(17-39)	0.977
CTSS	4.58±2.07 5(1-8)[a]	12.15±2.83 12(8-17)[b]	20.74±1.83 21(18-25)[c]	<0.001
Age	55.78±20.01[a] 60(18-87)	65.76±14.1[b] 67(18-90)	66.94±12.93[b] 66(38-88)	0.001
Number of Chronic Diseases Variables	1.85±0.73 2(1-3)	1.75±0.85 2(1-4)	1.77±1.01 1.5(1-5)	0.969*

CTSS: Computed Tomography Severity Mean±St.Dev. and Median (Min.-Max.),*; p value from Kruskal Wallis test and all others from ANOVA
[a,b,c]; indices such as a,b and c shows statistically difference of means or medians.

DISCUSSION

In this study, we investigated the relationship between RT-PCR Cycles Threshold (Ct) values, which provide information about the viral load carried by the individual, and CT-CS, used to demonstrate lung involvement. Our findings revealed that no significant correlation was found between RT-PCR Ct values, which play an essential place in the diagnosis of COVID-19 disease, and thoracic CT involvement, whereas the prevalence of pulmonary involvement and the mortality rate of cases increased with age.

The detection of COVID-19 relies on the reference method of reverse transcription polymerase chain reaction (RT-PCR), which allows for the identification of specific viral RNA sequences.[7] The Ct value obtained from this test is inversely correlated with the viral load carried by the patient.[11,12] In a study by Calle et al. involving 455 patients, a higher respiratory risk was associated with higher viral load, as indicated by lower Ct values.[13] Simi-

larly, Singh et al. found that symptomatic COVID-19 patients had significantly lower RT-PCR Ct values compared to those without clinical symptoms.[12] In another study conducted by Shah et al. in India with 219 patients, lower Ct values were found to be indicative of increased disease severity.[14] In a study conducted in Mersin, it was observed that symptomatic patients had a higher mean age compared to asymptomatic patients, and their Ct values were lower.[5] Similarly, Bakir et al. conducted a study in Ankara involving 158 patients, and like our study, they reported no association between Ct values and age, gender, or mortality.[15] These findings collectively highlight the importance of Ct values in assessing viral load and the clinical implications of such measurements.

Our study did not find any significant relationship between RT-PCR Ct values and lung involvement.

In cases with COVID-19 pneumonia, imaging using CT is important in the detection and evaluation of lung infection.[16,17] In COVID-19 pneumonia, CT findings are similar to those seen in other viral pneumonias. These CT manifestations predominantly present as areas of ground-glass opacities and consolidations.[7,18] The CTSS value is used to rapidly and objectively assess the severity of pulmonary involvement in COVID-19 patients.[7] In a study conducted by Yağcı et al. including 284 patients, although the CTSS value was found to be higher in hospitalized patients, an inverse relationship was found between viral load and thoracic severity score, and it was found that viral load was not an effective factor in hospitalization and mortality.[19] Similar to this study, we did not find a significant correlation between CTSS value and viral load. We observed that all deceased patients were in intensive care units, and the probability of mortality increased with advancing age. Francone et al. found that the mortality risk was higher in patients with a CTSS of 18 or higher and Li et al. found that the mortality risk was higher in patients with a CTSS of 15 or higher.[20,21] According to Saeed et al, a severe clinical picture occurs in patients with a CTSS of 25 and above.[9] Similar to this situation in our study, we found a significant positive correlation between CTSS and age. Bakir et al. did not find a significant relationship between the amount of viral load detected in patients with COVID-19 pneumonia and CTSS value.[15] Similar to this study, we did not find a significant relationship between CT score and viral load in our study.

In patients with comorbid conditions, including diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular diseases, hypertension, and malignancy, COVID-19 infection has the potential to escalate into a life-threatening condition.[22] In a study conducted by Gülbudak et al., comorbid diseases were found at a higher rate in symptomatic patients compared to asymptomatic patients. According to this study, hypertension, diabetes mellitus, chronic respiratory disease and cardiovascular diseases were found most frequently in symptomatic patients.[5] According to Singh et al. chronic renal failure, diabetes mellitus, chronic liver disease, chronic lung disease and chronic cardiovascular disease were found more frequently in symptomatic COVID-19 patients.[12] Although hypertension, cardiovascular disease, diabetes mellitus and chronic obstructive pulmonary disease were more common in our study, no significant correlation was observed between the number of comorbidities and CTSS.

Our study revealed no association between COVID-19 diagnosis based on RT-PCR test Ct values and chest CT involvement as indicated by the CTSS. However, a significant correlation was observed between the CTSS and age. These findings pave the way for future in-depth researches in this domain, fostering a better understanding of the subject matter.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Acknowledgements

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Committee Permission

Approval for this study was obtained from Aksaray University Clinical Research Ethics Committee (dated 16.12.2021 and numbered 2021/17-03).

Authors' Contributions

Concept/Design: AA, CÇ. Data Collection and/or Processing: DÖ, ST. Data analysis and interpretation: DÖ, CÇ, ST. Literature Search: CÇ, NBK. Drafting manuscript: NBK. Critical revision of manuscript: AA, DÖ, ST, NBK. Danışmanlık: AA, DÖ.

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Investigation of the Agreement between Glucose Meters Used for Glucose Measurement and Central Laboratory Measurements

Glukoz Ölçümünde Kullanılan Glukometreler ile Merkez Laboratuvar Ölçümleri Arasındaki Uyumun Araştırılması

Esra YILMAZ[1] Medeni ARPA[1] Bayram SEN[2] Mehmet CİNGİRT[3]

Amaç: Kan şekeri ölçümü farklı klinik birimler, farklı hastalık ve hasta gruplarında komplikasyonların önüne geçilmesi, mortalite ve morbiditenin azaltılmasında büyük önem taşımaktadır. Bu çalışmada, hastane alımlarına esas teşkil etmesi adına glukometreler ve otoanalizör arasındaki uyumun değerlendirilmesi amaçlanmıştır.
Araçlar ve Yöntem: Çalışmada kırk yedi venöz kan örneği kullanıldı. G1 ve G2 glukometreleri ile glukoz ölçümü yapılmasının ardından otoanalizör ile glukoz ölçümü yapıldı. Sonuçların değerlendirilmesinde korelasyon ve Passing Bablok regresyon analizi ve Bland-Altman farklar grafiği kullanıldı. Klinik uyumun değerlendirilmesinde Clarke Error Grid (CEG) analizi kullanıldı. $p<0.05$ değeri istatistiksel olarak anlamlı kabul edildi.
Bulgular: Korelasyon analiz sonuçları G1 için r=0.929 (% 95 CI, 0.876-0.960) ve G2 için r=0.947 (%95 CI, 0.907-0.971) idi. Passing Bablok regresyon eşitliği G1 için y=1.1235x+3.4662 iken G2 için y=0.8846x+10.0076 idi. CEG analizinde verilerin %99 oranında A ya da B zonunda olması kriteri iki glukometre için de karşılandı.
Sonuç: CLSI'ın POCT12-A3 dokümanında yer alan kriterlere göre hedef değere göre <100 mg/dl'deki sonuçların %95 ve daha fazlası ±12 mg/dl arasında olması gerekir iken G1 için oran %38, G2 için %94'tü. Hedef değere göre >100 mg/dl'deki sonuçların %95 ve daha fazlası ±%12.5 arasında olması gerekir iken G1 için oran %47, G2 için %100 idi. Hedef değere göre <75 mg/dl'de ±15 mg/dl'yi, ≥75 mg/dl'de ise ±%20 sınırını aşan sayı <%2 olmalı idi. Bu oran G1 için %54, G2 için %0 idi. Bu çalışma da glukometreler performans hedeflerini tam olarak karşılamamaktaydı. CEG'e göre klinik performans yeterli olsa da alım sonrası glukometrelerin yakından takip edilmesi gerektiği düşünüldü.

Anahtar Kelimeler: hasta başı test; hiperglisemi; glukometre

ABSTRACT

Purpose: Blood glucose measurement is of great importance in preventing complications and reducing mortality and morbidity for several diseases. Glucometers are used by any healthcare professionals. We conducted this study to show the compatibility between glucometers and autoanalyzers as a basis for hospital procurement.
Materials and Methods: Fourty seven venous samples were used. Correlation, Passing Bablok regression analysis, and Bland-Altman difference plot were used to evaluate the results (glucometers and autoanalyzer). Clarke Error Grid analysis was used to assess the clinical agreement ($p<0.05$).
Results: The correlation coefficient for G1 was 0.9294 ($p<0.001$; 95% CI: 0.8761-0.9603) and 0.9473 ($p<0.001$; 95% CI: 0.9069-0.9705) for G2. Regression equations were G1 y=1.1235x+3.4662 G2 y=0.8846x+10.0076. In Clarke Error Grid analysis, the criterion of 99% of the data being in zone A or B was met for both glucometers.
Conclusion: According to the relevant document, based on the result obtained with the reference method as the target value, 95% of all results less than 100 mg/dl should be within ±12 mg/dl of the target value. 95% of all results above 100 mg/dl should be within ±12.5% of the target value. In addition, the ratio of the sum of results less than 75 mg/dl exceeding ±15 mg/dl and results greater than 75 mg/dl exceeding ±20% of the target value to all results should be less than 2%. Glucometers didn't fully meet the performance targets. We think that glucometer analysis results should be closely monitored and verified after procurement.

Keywords: glucometer; hyperglycemia; point of care testing

Received: 21.03.2024; Accepted: 22.11.2024

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How to cite: Yılmaz E, Arpa M, Şen B, Çingirt M. Investigation of the compatibility between glucometers that used in glucose measurement and the central laboratory. Ahi Evran Med J. 2025;9(1):68-73. DOI:10.46332/aemj.1456343

INTRODUCTION

Blood glucose measurement is of great importance in preventing complications and reducing mortality and morbidity in different clinical units, diverse diseases, and patient groups. Accurate measurement of blood glucose levels by healthcare professionals in myocardial infarct, stroke, major trauma, burn, sepsis patients who are hyperglycemic due to stress in emergency department clinics, in neonatal ward patients at risk of hypoglycemia, in intensive care patients whose blood glucose regulation is of great importance is extremely crucial for proper treatment practices. Additionally, in patients with diabetes, where hyperglycemia is more commonly observed, and in individuals prone to hyperglycemia, such as pregnant women, accurate and practical self-monitoring of blood glucose levels at home is crucial for predicting and preventing potential complications.[1-3]

Blood glucose measurements are crucial in the follow-up of DM, which affects a large number of people worldwide and whose prevalence is increasing rapidly, in terms of its consequences and complications.[3] The International Diabetes Federation (IDF) estimates that 382 million adults worldwide have diabetes and the number of patients with DM in Türkiye is around 7 million. According to the 2021 estimates of the IDF, the number of patients with DM between the ages of 20-79 in 2035 is estimated to be 592 million.[4 5] Considering the number of individuals affected by the disease, monitoring and management of DM by healthcare professionals and patients with POCT devices has recently been of increasing importance. The American Diabetes Association (ADA) also recommends blood glucose monitoring with self-monitoring of blood glucose (SMBG) in patients with DM on insulin therapy.[6] In clinics or in the case of SMBG, glucometers are preferred due to their simple and pratic use, low blood sample requirement, and the fact that their use does not require much technical knowledge.[7]

Several international standards have been developed to determine the analytical performance of glucometers. Although different analytical targets are proposed in guidelines such as ADA, ISO, FDA, and CLSI, there is no consensus on the criteria.[8-9] While CLSI specifies its recommendations for healthcare professionals in hospitals, the ISO 15197-2013 Standard includes suggestions for glucometer manufacturers. The most current recommendation is ISO15197-2015 and it has an important position in device selection in our country.[3]

The performance of glucometers is analyzed in two parts: analytical and clinical accuracy. In this study, we aimed to examine the performance of two glucometers that are planned to be used in our hospital, by comparing them with the biochemistry autoanalyzer before approval.

MATERIALS and METHODS

This study was approved by Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (Decision number: 2023/44 dated 02/03/2023). Forty-seven venous blood samples collected in a Becton Dickenson vacuum tube containing K_2EDTA were used. The glucose concentrations were measured with two glucometers (G1 and G2) and an autoanalyzer (Beckman Coulter AU5800, enzymatic UV hexokinase, Beckman Coulter, Brea, USA) respectively as groups of five within a maximum of five minutes to minimize glucose instability from the plasma obtained by centrifugation at 3000×g for 10 minutes. The autoanalyzer reagent measurement range was 10-800 mg/dl, the CV at low glucose concentration was 0.6% (mean: 116 mg/dL), CV at high glucose concentration was 0.7% (mean: 294 mg/dL), and total CV was 2.28%. The total allowable error for the autoanalyzer was calculated as 5.29%.[10]

Glucometer G1 and Glucometer G2 use the glucose oxidase (amperometric) method with a measurement range of 20-600 mg/dl and 10-600 mg/dl respectively. The agreement between autoanalyzer and glucometers was analyzed.

Statistical Analysis

Statistical analysis was performed using the SPSS 22.0 program (SPSS; Chicago, USA) and Med-Calc Statistical Software (Version 20.113, Med-Calc Software, Belgium). Passing Bablok regression analysis and Bland-Altman difference plot were used to evaluate the differences between groups. Clarke Error Grid (CEG) analysis

was used to evaluate clinical compliance. According to CEG, the criterion of 99% of the data being in zone A or B was met.p<0.05 was considered statistically significant.

RESULTS

The evaluation (although our study was not a pure method comparison study) was performed according to the criteria recommended in the CLSI document POCT12-A3. The total number of acceptable results for both glucometers was determined as a percentage. According to the relevant document, based on the result obtained with the reference method as the target value, 95% of all results less than 100 mg/dl should be within ±12 mg/dl of the target value. 95% of all results above 100 mg/dl should be within ±12.5% of the target value. In addition, the ratio of the sum of results less than 75 mg/dl exceeding ±15 mg/dl and results greater than 75 mg/dl exceeding ±20% of the target value to all results should be less than 2% (Figure 1).

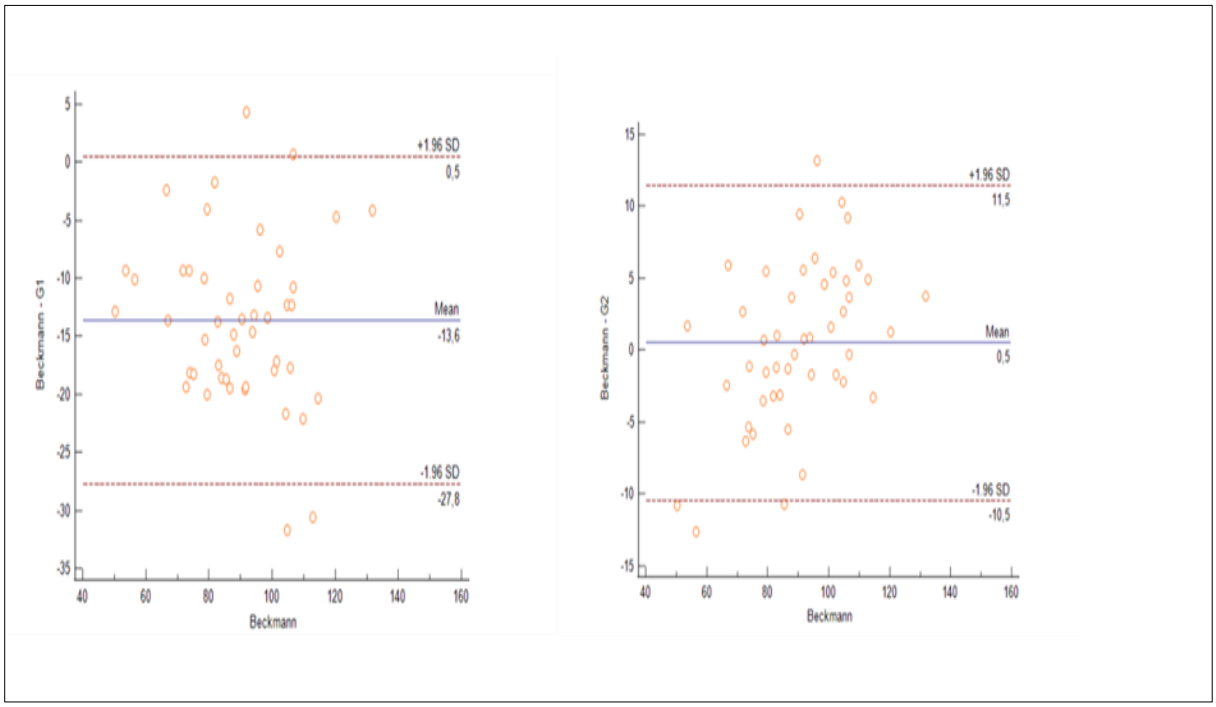

Figure 1. Comparison Between Glucometers and Autoanalyzer (Bland & Altman Plot).

The recommended minimum number of 40 samples in concordance studies was achieved with 47 samples. The results calculated based on the CLSI document are given before and the regression analyzes between glucometers and autoanalyzer were presented in Table 1.

Table 1. Regression analysis between glucometers and autoanalyzer.

Variables	Regression equation	Slope (95% CI)	Intercept (95% CI)	p Value
Beckman(x) G1(x)	y=1.1235x+3.4662	11.236 (0.9901-1.2804)	34.663 (-10.4354-15.0351)	<0.0001
Beckman(x) G2(y)	y=0.8846x+10.0076	0,8846 (0.7748+0.9830)	10,077 (0.6579-20.0242)	<0.0001

The correlation analysis between glucometers and autoanalyzer performed. The correlation coefficient for G1 was 0.9294 (p<0.001; 95% CI: 0.8761-0.9603) and 0.9473 (p<0.001; 95% CI: 0.9069-0.9705) for G2. In our study, all data were in zones A and B for both glucometers (Figure 2).

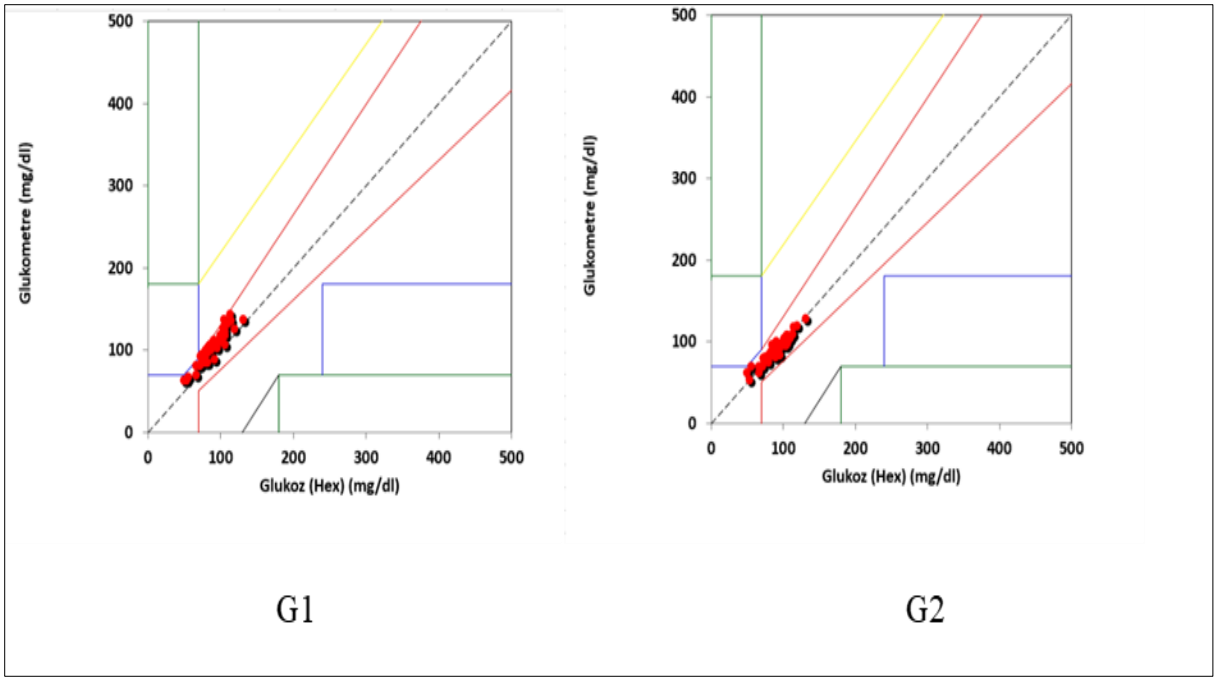

Figure 2. Clarke Error Grid Analysis of G1 and G2.

DISCUSSION

Since glucometers can be decisive in emergency clinical decisions, it is essential to select them appropriately. Two points should be considered; the first is to select control materials suitable for the functionality of the analysis and the second is to confirm the measurements made with POCT devices with the central laboratory.[11]

The quality control materials provided by manufacturers for glucometers do not mimic fresh human blood. They are only used to monitor whether the measurement is within the acceptable range. This acceptable range is too wide to be used as a guide for interpreting the results generated. A standardized laboratory method for quality control of glucometers is therefore required.[12]

In order to provide a basis for hospital procurement, we conducted this study aiming to compare glucometers with autoanalyzer with a protocol we prepared using CLSI's POCT12-A3 document.[13] Technical (reproducibility, consistency, correlation, linear regression) and clinical (error grid analysis) assessment was performed. An experienced laboratory staff was recruited. In the autoanalyzer operating with the glucose hexokinase method that we use in the clinical laboratory, results close to the values specified by the manufacturer were achieved with the control materials. Appropriate CV values were also calculated in the precision (CV1:2.294 CV2:2.259).

Since the electrochemical method used glucometers are highly sensitive to temperature and pH changes, the analyzes were performed immediately, and contact with air and exposure to light was minimized. Hemolyzed, icteric, and lipemic samples were also excluded to avoid major interferences. Capillary, arterial, and venous blood samples may differ in glucose concentrations for the same patient. It is inevitable that glucometers give different results from venous/arterial samples used in the reference laboratory method due to the difference between whole blood and plasma. The use of capillary blood in these devices has been reported to result in lower glucose measurements about 10-15% than plasma.[14] Solnica et al. developed a percentage error formula for capillary measuring devices and the cut-off value for the percentage error was set at 20%.[15] We also used venous whole blood and venous plasma in this study.

Differences in sample and reagent components (lot-to-lot variation etc.) may be difficult to distinguish from variability due to the measurement method. This should be taken into account when designing the study and establishing the acceptability requirements.[3] In our study, glucometer strips and autoanalyzer reagents were used with the same lot. The utilization of glucose strips and reagents with the same lot number can be considered as a

limitation of the study. Another limitation of our study is that although glucometers are bedside devices, in our study, measurements were made from whole blood and plasma after the samples were delivered to the laboratory.

Drawing attention to operator error, the FDA has reported that laboratory assessments can be misleading in determining clinical safety.[16] For example, in a study, CV values calculated from patients' own measurements were found to be considerably higher than those obtained from the laboratory staff.[17] Our study was completed with the same laboratory personnel following the same procedure.

Another parameter affecting the measurement in glucometers is hematocrit. In our study, sample hematocrit was maintained between 20-55%. Since the diffusible plasma volume will be decreased in the presence of high hematocrit, false low values may be observed and false high values may be observed in the presence of anemia.[18] Since our institution does not have a pediatric clinic, clinical usage characteristics for the pediatric age group, in which hematocrit can be an important variable, were not investigated. In diabetic ketoacidosis, high values were not included in the study because false low values may be obtained due to a marked increase in viscosity due to dehydration.

In our study, EDTA was used as an anticoagulant since EDTA is reported to cause less variability in glucose measurements by glucose hexokinase and glucose oxidase method compared to heparin.[19]

Correlation and regression analyses were performed to compare the results of glucometer venous whole blood and autoanalyzer plasma values. The observation of good correlation and agreement in the analysis is not sufficient to assess clinical accuracy. CEG analysis should be used to assess the clinical usefulness and accuracy of the data.[20] In CEG, data are classified into five zones according to the degree of clinical accuracy. Acceptable zones are A and B, while values in zones C, D, and E are unacceptable, misleading, and require urgent intervention. 99% of the data should be in zone A or B.[21] In our study, all data were in zones A and B for both glucometers.

Conclusion

Both hypoglycemia and fluctuation in blood glucose are among the factors with the strongest association with mortality in critically ill patients.[18] In critically ill patients, conditions such as poor blood flow to peripheral capillaries due to shock and/or vasopressor use, fluid overload, or anasarca may affect the analytical accuracy of POCT devices, leading to erroneous or inadequate treatment.[7] On the other hand, in neonates, hyperglycemia can lead to complications such as osmotic dehydration, intracranial hemorrhage, and increased susceptibility to infection.[18] All these considerably contribute to neonatal morbidity and mortality.

In this study, conducted to serve as a basis for hospital procurement, the measurement results of glucometers and autoanalyzers were evaluated as compatible. However, it was demonstrated that glucometers require careful monitoring, taking into account their usage characteristics and the clinical situations where their use is essential

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Acknowledgements

This study was shared in National 4th Hereditary Metabolic Diseases Laboratory Symposium (2022/10/5) as an oral presentation (Antalya, Türkiye).

Ethics Committee Permission

This study was approved by Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (Decision number: 2023/44 dated 02/03/2023).

Authors' Contributions

Concept/Design: MA, BS, MC, EY. Data Collection and/or Processing: MA, BS, MC, EY. Data analysis and interpretation: MA, BS, MC, EY. Literature Search: MA, BS, EY. Drafting manuscript: EY. Critical revision of manuscript: MA, BS. Supervısor: MA.

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BİLİMSEL ARAŞTIRMA MAKALESİ

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Kronik Miyeloid Lösemi Hastaları'nda miR-21, miR-150, miR-155 Ekspresyon Düzeylerinin Araştırılması

Investigation of miR-21, miR-150, miR-155 Expression Levels in Chronic Myeloid Leukemia Patients

Hüseyin AVCILAR[1] Hatice ALTIN[2] Sevil ŞİMŞEK[2] Leylagül KAYNAR[3]

ÖZ

Amaç: MikroRNA (miRNA)'lar proteinlere translasyonu gerçekleşmeyen, hücrede biyolojik mekanizmaları etkileyen RNA moleküleridir. miRNA ekspresyon düzeylerinin qPCR ile belirlenmesi KML hastalarının tedavisinin takibinde bilgi verebilir. Bu çalışmada KML hastalarının takibinde kullanılabilecek miR-21, miR-150, miR-155 ekspresyonlarının KML ile ilişkisi araştırılması amaçlanmıştır.
Araçlar ve Yöntem: Bu çalışma, imatinib, nilotinib, dasatinib ilaçlarıyla tedavi edilen 22 KML hastası ve 5 sağlıklı kontrolden elde edilen plazma örneklerinde yapıldı. Hasta ve kontrol periferik kan örneklerinden RNA ve miRNA eldesi Genaxxon miRNA pürifikasyon kiti kullanılarak gerçekleştirildi. Wiz ScriptcDNA Sentez Kiti kullanılarak cDNA eldesi yapıldı. cDNA örneklerinden hedeflenen miRNA ekspresyonlarının düzeyleri gerçek zamanlı PCR yöntemi ile analiz edildi.
Bulgular: Kontrol grubu miRNA ekspresyon düzeyleri 1.0 olarak belirlendi. KML yeni tanı grubunda miR-21 kat değişimi ortalama 0.6, miR-150 kat değişimi 0.3 ve miR-155 kat değişimi 0.5 bulundu. İmatinib tedavi grubunda miR-21, miR-150 ve miR-155 için kat değişimi sırasıyla 1.4, 0.5 ve 2.4 kat olarak bulundu. Nilotinib tedavi grubunda miR-21 düzeyi 3.5, miR-150 düzeyi 0.5 ve miR-155 düzeyi 4.3 bulundu. Dasatinib tedavi grubunda miR-21 kat değişimi 0.8, miR-150 kat değişimi 2.1 ve miR-155 kat değişimi 0.5 bulundu. Yapılan çalışmada miR-21 düzeyi ortalama 3.2, miR-150 düzeyi 1.0 ve miR-155 düzeyi 2.8 bulundu. miR-150 düzeyleri yeni tanı grubunda, İmatinib grubunda ve Nilotinib grubunda kontrol örneklerinden daha düşük oranda bulundu. Bu fark istatistiksel olarak yeni tanı grubunda (p=0.07484) ve Nilotinib grubunda (p=0.01541) anlamlıdır. Hasta ve kontroller arasında miR-21 ve miR-155 düzeyleri yönünden istatiksel olarak anlamlı bir farklılık bulunmadı.
Sonuç: Bu sonuçlar miRNA-150'nin KML hastalarının izleminde kullanılabileceğini ve ilaç direncinin erken dönemde tespitinde katkı sağlayabileceğini desteklemektedir.

Anahtar Kelimeler: kronik miyeloid lösemi; mikroRNA; mikroRNA-21; mikroRNA-150; mikroRNA-155

ABSTRACT

Purpose: In this study, the relationship between CML and the expression levels of miR-21, miR-150, and miR-155, which could be used in the follow-up of CML patients, was investigated.
Materials and Methods: RNA and miRNA were extracted from peripheral blood samples of patient and control samples. Targe-ted miRNA expression levels from cDNA samples were analyzed by real-time PCR method.
Results: miRNA expression level was determined as 1.0 in the control group. In the newly diagnosed group, the mean miR-21 fold change was 0.6, miR-150 fold change was 0.3, and miR-155 fold change was 0.5. fold changes for miR-21, miR-150 and miR-155 were found to be 1.4, 0.5 and 2.4 fold, respectively, in the imatinib treatment group. In the nilotinib treatment group, miR-21 level was 3.5, miR-150 level 0.5, and miR-155 level 4.3. In the dasatinib treatment group, fold change was 0.8 for miR-21, 2.1 for miR-150, and 0.5 for miR-155. The mean miR-21 level was found to be 3.2, miR-150 level 1.0 and miR-155 level 2.8. MiR-150 levels were found to be lower in the newly diagnosed group, imatinib group and nilotinib group than in the control samples. This difference between the new diagnosis group (p=0.07484) and the nilotinib group (p=0.01541) is statistically signi-ficant. No significant difference was found between patients and controls in terms of miR-21 and miR-155 levels.
Conclusion: These results support that miRNA-150 can be used as a parameter in the monitoring of treatment of CML patients and can contribute to the early detection of drug resistance.

Keywords: chronic myeloid leukemia; microRNA; microRNA-21; microRNA-150; microRNA-155

Gönderilme tarihi: 30.08.2023; Kabul edilme tarihi: 06.12.2024

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Makaleye atıf için: Avcılar H, Altın H, Şimşek S, Kaynar L. Kronik miyeloid lösemi hastaları'nda miR-21, miR-150, miR-155 ekspresyon düzeylerinin araştırılması. Ahi Evran Med J. 2025;9(1):74-81. DOI: 10.46332/aemj.1327364

GİRİŞ

Kronik Miyeloid Lösemi (KML) kemik iliğinde myeloid hücrelerin çoğalması, periferik kanda olgun ve genç miyeloid seri hücrelerinin aşırı artması, kan profilinde bazofili ve trombositozis splenomegali ile seyreden bir hemotopoetik kök hücre hastalığıdır. KML myeloproliferatif hastalık sınıfına girer. Tüm lösemilerin %15'lik kısmını, yetişkin lösemilerinin %20'sini KML oluşturur. KML insidansı 1/100.000'dir, yaşla görülme sıklığı artar, çocuklarda nadiren görülür, erkeklerde kadınlara göre daha sıktır.[1,2] KML tanısı konulan hastaların %92'sinde Philadelhia (Ph) kromozomu pozitiftir. KML moleküler patogenezinde BCR-ABL1 füzyon geni etkisiyle 9. ve 22. kromozomlar arasında oluşan translokasyon sonucunda Ph kromozomu meydana gelir. BCR/ABL gen füzyonu, artmış tirozin kinaz aktivitesine neden olarak; hücre çoğalma, maturasyon ve adezyon sinyal yolaklarının aktivitesine neden olarak apoptozu inhibe eder ve malign hücre transformasyonuna yol açar. Bu da KML patogenezinin temelini oluşturur.[3,4]

Hastalığın seyri, erken tanı konulması, yeni tedavi yöntemleriyle iyileşmiş ve yaşam süresi uzamıştır. KML tedavisinde yaygın olarak hidroksiüre, interferon, kemoterapi ve allojenik kök hücre nakli yöntemleri kullanılırken 2000'li yıllarda bu tedavilerin yerini BCR/ABL1 proteinini hedef alan tirozin kinaz inhibitörleri (TKI) almıştır. KML patogenezinde BCR/ABL1 önemli bir rol oynadığının bulunması bu proteini hedef alan spesifik tedavilerin geliştirilmesini sağlamıştır. BCR-ABL1'nin hedefleyen TKI'leri KML tedavisinde altın standart haline gelmiştir. Toplamda beş TKI, KML'nin birinci basamak tedavisi için onaylanmıştır. Bu moleküller imatinib dasatinib nilotinib, bosutinib ve ponatinib tedavileridir.[5] TKI'leri KML tedavisinde devrim yaratmış fakat bazı hastalarda TKI'lerine karşı direnç gelişmiştir. KML'deki TKI direnci BCR-ABL'ye bağımlı ve BCR-ABL'den bağımsız mekanizmalar olmak üzere iki temel mekanizma üzerinden gelişir. Birincil direnç oluşma nedeni *BCR-ABL* proteininin aşırı ekspresyonu ve TKİ bağlanma bölgesinde nokta mutasyonları oluşmasıdır. *BCR-ABL* proteininin bağlanma bölgesindeki nokta mutasyonları sonucu TKİ'nin bağlandığı bölgede konformasyonel değişiklik gelişir ve ilaç afinetesinde azalma sonucu bağlanma gerçekleşmez. Bunun sonucunda hücre sinyal yolaklarının aktivasyonu sonucu lösemik transformasyonda ve hücre proliferasyonunda artma, apoptosisde azalma oluşur.[6] *BCR-ABL* bağımsız direnç mekanizmaları lösemik kök hücreleri ve ilaç farmakokinetiğindeki değişikler sonucu gelişir. TKİ'lerin gastrointestinal sistemdeki emilim bozukluğu ilaç plazma düzeyinin düşmesine ve ilaç etkinliğinin azalmasına neden olur. İlacın hücre içi konsantrasyonunu ayarlayan influx ve efflux pompalarının aşırı çalışması da ilaç hücre içi konsantrasyonunun azalmasına neden olarak ilaç etkinliğini azaltır. Her iki mekanizma da klinik dirence neden olabilir.[7]

Genom üzerinde protein kodlamayan alanda, RNA genlerinden trankripsiyonu sağlanan, proteinlere translasyonu gerçekleşmeyen fonksiyonel RNA moleküllerine mikroRNA (miRNA) denir.[8] miRNA'lar hedef gen ekspresyonunu etkileyerek protein sentezinin düzenlenmesinde ve birçok biyolojik süreçde rol alırlar.[9-10] miRNAlar enfeksiyon, kardiyovasküler, nörodejeneratif hastalıklar ve kanser gibi birçok hastalığın patogenez mekanizmalarında da önemli rol alırlar.[11] Yapılan çalışmalarda miRNA ifadesinin bozulmasıyla kanser mekanizması arasında güçlü bir bağ olduğu bulunmuştur. Kanser mekanizmalarında önemli rolü olan hücre ölümü, gelişmesi, büyümesi, farklılaşması ve metabolizması gibi süreçlerde miRNA'ların düzenleyici rolü vardır.[12-13] miRNA'lar karsinogenezde onkogen veya tümör baskılayıcı olarak görev alırlar.[14-15] miRNA'ların anormal ekspresyonu KML hastalığının patogenezinde, kliniğinde ve ilaç direnç mekanizmalarında rolüne dair çalışmalar vardır.[16] miRNA'lar hem BCR-ABL'ye bağımlı ve BCR-ABL'den bağımsız mekanizmaları etkileyerek TKI ilaç direncinde rol oynar. Bazı miRNA'ların ekspresyon düzeylerindeki değişiklikler TKİ ilaç direnci hakkında bilgi verebilir. miR-29, miR-30a, miR-196, miR-203, miR320a, miR424 'ün BCR::ABL1 ekspresyon seviyelerini regülasyonunda rol oynar. Bu miRNA'ların ekspresyonunu artması BCR::ABL1 ekspresyon seviyelerini azaltarak hücre proliferasyonunu inhibe ederken, ekspresyon seviyelerinin azalması tedaviye dirençle ilişkilidir. miR-221, miR-153-3p, miR-577, miR-214 BCR-ABL'den bağımsız mekanizmaları etkileyerek TKI ilaç direncinde rol oynarlar.[17]

miRNA'ların ekspresyonun disregülasyonu kanser hücrelerinde onkogenik veya tümör baskılayıcı etkilerin ortaya çıkmasına neden olur. Tümör hücrelerinde onkogenik miRNA ekspresyonun artması karsinogenesin başlamasına ve tümör progresyonuna neden olur. Tümör baskılayıcı miRNA'lar ise kanser gelişimine engel olurlar. Bu miRNA'ların ekspresyonunun azalması onkogen aktivasyonuna ve tümör gelişimine neden olur.[18-19] miRNA'lar kanser tiplerinde kontrolsüz büyüme ya da anti-apopotik özellik gösterirler. MiR155 hem ilk keşfedilen onkogenik miRNA'lardan olup lenfoma ve lösemi oluşumunu arttırdığı belirtilmiştir. Yapılan çalışmalarda ise miR-155'in B hücreli lenfoma, meme, pankreas, akciğer ve Hodgkin lenfoma gibi kanser tiplerinde artmış ekspresyonu belirtilmiştir.[20] MiR-21 antiapoptotik özellik gösteren, akciğer, kolon, esofagus ve pankreas kanserlerinde ekspresyonu artan onkogenik özellik gösteren miRNA'dır.[21] KML hastalarında eksperesyonun arttığı gösterilmiştir.[22] MiR-150, megakaryositik-eritroid öncül hücreler, lenfoid hücreler ve NK hücrelerin gelişiminde rol alan miyeloid hücre farklılaşmasında rol almayan miRNA olarak tanımlamıştır. MiR-150'nin hedefi, lenfosit gelişiminin birden fazla aşaması için kritik öneme sahip c-Myb transkripsiyon faktörüdür. Yapılan çalışmalarda miR-150 ekspresyonu KML hastalarında azaldığı bulunmuştur.[23] Yapılan miRNA ilişkili çalışmalar hematolojik malignitelerde miRNA'ların belirteç olarak önemini göstermiştir. KML hastalarının tedavi sürecinin izleminde miRNA analizleri belirteç olarak kullanılabilmektedir. KML hastalarında miRNA düzeylerinin qPCR ile gen ekspresyonun belirlenmesi KML tedavi seyri açısından ek bilgi verebilir.[24] Bu çalışmada KML hastalarının takibinde kullanılabilecek ve regülatör görevi olabileceğini düşünülen miR-21, miR-150, miR-155 ekspresyonlarını qPCR ile araştırarak KML ile ilişkilerinin ortaya konması amaçlandı.

ARAÇLAR ve YÖNTEM

Hasta Örnekleri

Bu çalışma Erciyes Üniversitesi Tıp Fakültesi Hastanesi Hematoloji-Onkoloji Bilim Dalı'nda takibi yapılan 18-85 yaş aralığında, KML tanısı konulmuş onkolojik ve hematolojik başka malignitesi olmayan 22 hasta üzerinde Mayıs 2018-Eylül 2019 tarihleri arasında yapıldı. ''Herhangi bir onkolojik ve hematolojik malignitesi, nörolojik/kronik hastalık öyküsü olmayan 18-85 yaş aralığında kadın ve erkekten oluşan 5 birey, sağlıklı kontrol grubu olarak seçildi. (Güven aralığı %95, testin gücü %99 olacak şekilde örneklem büyüklüğü 5 olacak şekilde hesaplandı). Hasta ve kontrol grubundaki bireyler bilgilendirilmiş gönüllü olur formunu imzaladıktan sonra çalışmaya dahil edildi. Bu çalışma için Erciyes Üniversitesi Klinik Araştırmalar Etik Kurulundan onay alındı (26.01.2018 tarih ve 2018/52 sayı). Bu çalışma Erciyes Üniversitesi Bilimsel Araştırma Projeleri Birimi tarafından TYL 2018-8012 kodlu bilimsel araştırma projesi ile desteklenmiştir. Bu araştırma Erciyes Üniversitesi Tıp Fakültesi İmmünoloji Anabilim Dalı Laboratuvarı'nda yürütüldü. Çalışma için hastalardan ve kontrol grubundan miRNA çalışmaları için EDTA'lı tüpe 10 cc kan alındı. Örnekler -20'de çalışma zamanına kadar saklandı.

Tam Kandan Serum Eldesi Total RNA ve RNA'dan miRNA İzolasyonu

EDTA'lı tüpte 10 cc alınan tam kan örneği 3500 gx'de 10 dk santrifüj edildi. Santrifüj sonrası oluşan süpernatant şeffaf sıvı kısım 2 mL'lik ependorf tüpe alındı, pellet atıldı. Örneklerden RNA ve miRNA eldesi Genaxxon miRNA Purifükasyon kiti (lot no:585873) kullanılarak üretici firma protokolü uygulanarak gerçekleştirildi. İzole edilmiş miRNA ve RNA'lar -20 ° C'de buzdolabında saklandı. Total RNA, miRNA kalite ve miktarı Nano-Drop (Thermo Fisher Scientific, USA) kullanılarak değerlendirildi.

Revers Transkripsiyon ile miRNA'dan cDNA Eldesi

Çalışma hsa-miR-21, hsa-miR-150, hsa-mir-155 'nin primerleri (Suarge Biyoteknoloji, Ankara, Türkiye) kullanılarak Wiz ScriptcDNA Sentez Kiti (Wiz Script, katalog no: W2211-1) ile yapıldı. Her örnekten çift çalışma yapıldı. Ters transkripsiyon 25 °C de 10 dakika, 25°C'de 120 dakikada gerçekleştirildi. Son olarak 85 °C de 5 dakika bekletilerek Ters transkriptaz enziminin denatürasyonu sağlandı. Elde edilen cDNA örnekleri %2'lik agaroz jelde koşuldu. Hemen kullanılmayan cDNA'lar +4 ºC de saklandı.

Q-PCR (Kantitatif-PCR)

Gerçek-zamanlı PCR (qPCR) işlemi için Amplifyme SG Universal Mix (BLIRT, Polonya) ve miRNA qPCR SL Assay (Suarge Biyoteknoloji, Türkiye) qPCR primerleri kullanıldı. qPCR işlemi StepOnePlus™ Real-Time PCR System (Thermo Scıentıfıc, ABD) cihazında gerçekleştirildi. hsa-miR-21, hsa-miR-150, hsa-mir-155 ve endojen kontrol olarak U6 kullanılara kuyucuk başına 1,5 µL cDNA eklendi. qPCR ile elde edilen Ct değerleri U6 endojen kontrole göre normalize edilip $2^{-\Delta\Delta Ct}$ yöntemi ile değerlendirildi. Sentezlenen cDNA'lara RT-SYBR Green qPCR kiti kullanılarak denatürasyon (95 °C' de 20 saniye), hibridizasyon ve primer bağlanması (95 °C' de 20 saniye ve 60 °C' de 30 saniye (45 döngü)) ve polimerizasyon ve erime eğrisi (95 °C' de 15 saniye ve 60 °C'de 1dk) ve uzama (95 °C' de 15 saniye) basamaklarından oluşan 40 tekrarlık PCR protokolü uygulandı. Referans gen olarak U-6 kullanıldı.

mi-RNA seviyeleri için $2^{-\Delta\Delta Ct}$ Analizi ile Kat Değişimlerinin Hesaplanması

Gerçek zamanlı PCR çalışmasından sonra tüm örneklerin Cycle threshold (Ct) değerleri ile excel dosyası hazırlandı. U6 25 civarında, miR21 35 civarında, miR150 36 civarında, miR155 36 civarında cycle (Ct) değerleri gösterdi. Bütün Ct değerleri 25 ile 40 arasında dağılım gösterdi. Çıkan Ct değerleri referans gen Ct değerleri oranlanarak normalleştirildi. Kat-değişimi ($2^{-\Delta\Delta Ct}$); test örneğindeki normalize gen ekspresyonunun ($2^{-\Delta\Delta Ct}$), kontrol örneğindeki normalleştirilmiş gen ekspresyonuna ($2^{-\Delta\Delta Ct}$) oranıdır. Kat değişim değerleri <1 ise azalmış (aşağı regüle) olarak kabul edildi. Kat değişim değerleri >1 ise artmış (yukarı regüle) olarak kabul edildi. Örneklerin referans gene göre normalizasyonu yapıldı. Kontrol grubundaki genlerinden elde edilen $2^{-\Delta\Delta Ct}$ değerleri ile hasta grubu değerleni karşılaştırmak için student t-testi kullanıldı ve p değerleri buna göre hesaplandı.

İstatiksel Analiz

Gerçek zamanlı PCR veri analizi, Gen Globe Veri Analiz Merkezi (https://geneglobe.qiagen.com/us/analyze) kullanılarak analiz yapıldı. ΔΔCt metoduyla ham veriler, U6 housekeeping geni kullanılarak normalleşme yapıldı. Sonuçlar Student t-testi uygulanarak p değerleri hesaplandı. %95 güven aralığında "p<0.05" olan sonuçlar istatistiksel olarak anlamlı kabul edildi. Hasta grupları ve kontrol grubu yaş ve cinsiyet bakımından değerlendirilmesi One Way Anova tek yönlü varyans analiz yöntemiyle yapıldı.

BULGULAR

Hasta ve Kontrol Grubunun Özellikleri

Bu çalışmaya hasta grubu olarak 22 birey, kontrol grubu olarak 5 birey olmak üzere toplam 27 birey alındı. Çalışmaya katılan hasta ve kontrol bireylerin 14'ü kadın, 13'ü erkektir. Cinsiyetler açısından değerlendirildiğinde hasta ve kontrol gruplarında bulunan kadınların yaş ortalamaları 46±4 yıl, erkeklerin ise 48±4 yıl olarak hesaplanmıştır. KML tanısı alan hastalar yeni tanı ve ilaç grubu olarak ayrıldı. İlaç grubuna daha önceden ilaç tedavisi olarak imatinib, nilotinib ve dasatinib verilen KML tanısıyla takip edilen hastalar dahil edildi.

Çalışmamızda yer alan 22 KML tanılı hastanın 5 tanesi henüz tedavi almadan yeni tanı aldığında, 5 tanesi imatinib, 8 tanesi nilotinib ve 4 tanesi dasatinib tedavisinde iken çalışmaya dahil edildi. Nilotinib tedavisi alan 8 KML hastasından 4 'ü tanı konulduğunda direk nilotinib tedavisi başlanan, diğer 4'ü ise imatinib direnci görülerek nilotinibe geçilen hasta örnekleridir. Dasatinib tedavisi alan 4 KML hastası öncesinde imatinib ve nilotinibe direnç geliştirerek yanıt alınamayan hasta örnekleridir.

Gruplara Göre miRNA Ekspresyon Düzeyleri

Hasta ve kontrol grupları örneklerinde gerçek zamanlı PCR yöntemiyle miR-21, miR-150, miR-155 ekspresyon düzeylerine, housekeeping gen U6 ekspresyon düzeyine bakıldı. $2^{-\Delta\Delta Ct}$ analizi ile kat değişimleri hesaplandı. Hasta grupları ilaç kullanımlarına göre ayrılarak; kontrol grubuna göre kat değişimleri hesaplandı.

Çalışmada miR-21 kat değişimi yeni tanı grubunda 0.6 (p=0.2602), imatinib grubunda 1.4 (p=0.6121), nilotinib grubunda 3.5 (p=0.08872) ve dasatinib grubunda 0.8 (p=0.35) olarak bulundu. miR-150 kat değişimi yeni tanı grubunda 0.3 (p=0.007484), imatinib grubunda 0.5

(p=0.2688), nilotinib grubunda 0.5 (p=0.01541) ve dasatinib grubunda 2.1 (p=0.1463) olarak bulundu. miR-155 kat değişimi yeni tanı grubunda 0,5 (p=0.2601), imatinib grubunda 2.4 (p=0.2445), nilotinib grubunda 4.3 (p=0.09963) ve dasatinib grubunda 0.5 (p=-0.1863) olarak bulundu.

Yeni tanı grubu, kontrol grubuna göre karşılaştırıldığında miR-150 açısından anlamlı bir farklılık tespit edildi (p=0.007484). miR-155 ve miR-21 açısından yeni tanı ve kontrol grubu arasında fark tespit edilmedi (Tablo 1). **İmatinib tedavi grubu** hastalar ve kontrol grubu karşılaştırıldığında her üç miRNA içinde anlamlı bir fark saptanmadı (Tablo 2). **Nilotinib tedavi grubu** hastalar ve kontrol grubu karşılaştırıldığında miR-150 ile arasında anlamlı bir fark saptandı, fakat miR-21 ve miR-155 açısından anlamlı bir fark tespit edilmedi (Tablo 3). **Dasatinib tedavi grubu** hastalar ve kontrol grubu karşılaştırıldığında her üç miRNA içinde anlamlı bir fark saptanmadı (Tablo 4). Tüm gruplar birlikte edeğerlendirildiğinde yeni tanı grubunda miR-150, miR-155 ve miR-21 seviyeleri en düşük bulundu. miR-155 ve miR-21 için yüksek seviyeler nilotinib tedavi grubunda, miR-150 için ise dasatinib tedavi grubunda yüksek olarak bulundu (Şekil 1).

Çalışılan miRNA'lardan miR-21 ve miR-155 yeni tanıda düşük seviyede ölçülürken hem imatinib hem nilotinib kolunda yukarı regüle bulundu. Ancak sonuçlar arasında istatistiksel olarak bir anlamlılık bulunmadı (p>0.05). miR-21 kat değişimi 1.4 (imatinib), 3.5 (nilotinib) bulundu. **miR-155** kat değişimi=2.4 (imatinib), 4.3 (nilotinib); Sonuçlarımız bu ilaç gruplarındaki hastalarda yanıt sağlanmadığı şeklinde yorumlandı.

Tablo 1. Yeni tanı grubunun kontrol grubuna göre kat değişimleri ve p-değerleri.

Grup 1 (Yeni Tanı Grubu)		
Gen Adı	**Kat-Değişimi**	**p-değeri**
U6	1	Housekeeping gen
miR-21	0.6	0.2602
miR-150	**0.3**	**0.007484**
miR-155	0.5	0.2601

Tablo 2. Tedavi kolunda İmatinib grubun kontrol grubuna göre kat değişimleri ve p-değerleri.

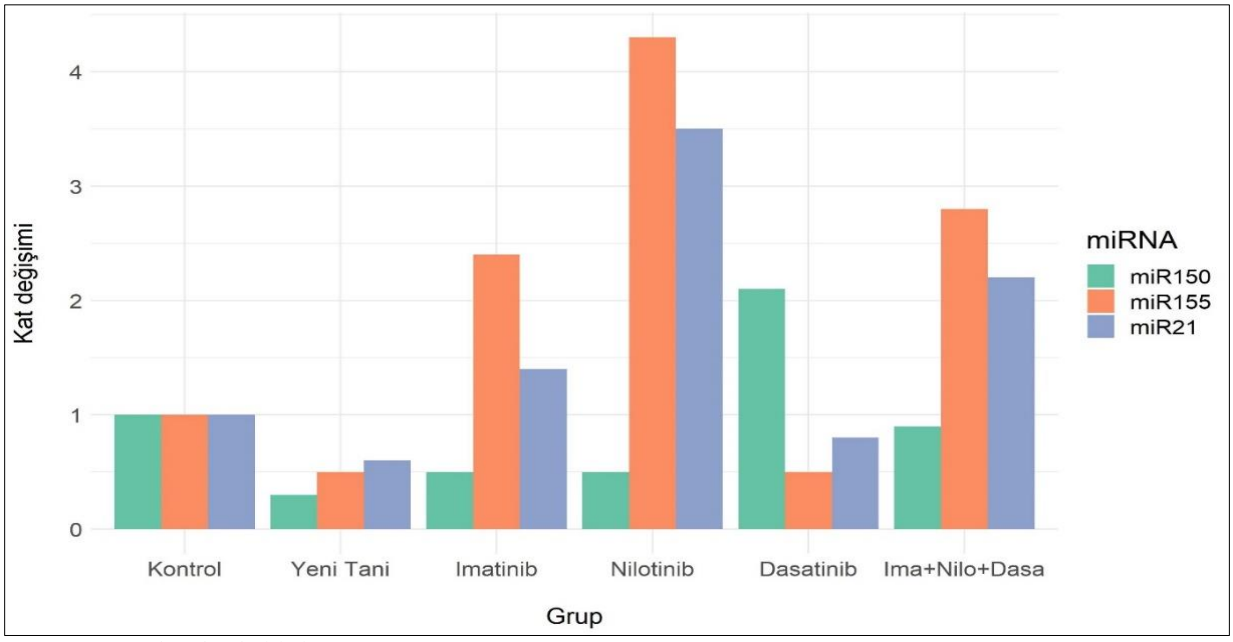
Grup 2 (Imatinib)		
Gen Adı	**Kat-Değişimi**	**p-değeri**
U6	1	Housekeeping gen
miR-21	1.4	0.6121
miR-150	0.5	0.2688
miR-155	2.4	0.2445

Tablo 3. Tedavi kolunda Nilotinib grubun kontrol grubuna göre kat değişimleri ve p-değerleri.

Grup 3 (Nilotinib)		
Gen Adı	**Kat-Değişimi**	**p-değeri**
U6	1	Housekeeping gen
miR-21	3.5	0.08872
miR-150	0.5	0.01541
miR-155	4.3	0.09963

Tablo 4. Tedavi kolunda Dasatinib grubun kontrol grubuna göre kat değişimleri ve p-değerleri.

Grup 4 (Dasatinib)		
Gen Adı	**Kat-Değişimi**	**p-değeri**
U6	1	Housekeeping gen
miR-21	0.8	0.35
miR-150	2.1	0.1463
miR-155	0.5	0.1863



Şekil 1. Tüm grupların kat değişimi.

TARTIŞMA

KML, periferik kanda miyeloid, eritroid ve trombosit hücrelerinde artışa neden olan, kemik iliğinde belirgin miyeloid hiperplaziye yol açan, Philadelphia kromozomu %95 pozitifliği ile karakterize edilen malign bir klonal hematopoietik kök hücre hastalığıdır. MikroRNA'lar, ökaryot hücrelerinde yaygın olarak eksprese edilen protein kodlamayan gen ekspresyonunu düzenleyen küçük mRNA moleküllerdir. mikroRNA'lar hücrelerin gelişiminde, farklılaşmasında, apoptozda ve çoğalma gibi kritik biyolojik süreçlerde rol oynarlar. Son zamanlarda yapılan çalışmalarda farklı mikroRNA moleküllerinin KML patogenezinde rol oynadığı bulunmuştur.[25]

Bu çalışmada, yeni KML tanısı almış ve imatinib, nilotinib, dasatinib tedavisi alan KML hastalarında miR-21, miR-150, miR155 ekspresyon seviyeleri araştırıldı. Hasta ve sağlıklı kontrol grubu miRNA düzeylerinin belirlenmesindeki amaç miRNA'ların KML tanısı konulma aşamasında ya da uygulanan ilaç tedavisinin etkinliğinin takibi esnasında farklılıklara bakılarak ilaç değişimi ya da direnç durumunun belirlenmesinde miRNA'ların rolünü araştırmaktı. Daha önceki araştırmaların ışığında, miRNA'ların KML tanı aşamasında bir biyobelirteç olarak kullanımı, KML hastalarının tedavi sürecinde miRNA'ların yeri ve anlamı açısından değerlendirilmesi üzerine yoğunlaşıldı. KML hastalarında belirli aralıklarla miR-21, mi-R150 ve mir-155 düzeylerine bakılarak ilaç yanıtının değerlendirilmesi açısından fikir verebileceği öngörüldü. Kanser gelişim mekanizmalarında miRNA'ların apoptozda rol oynadığının bulunması kanser oluşumlarında da miRNA'ların etkili olduğunu düşündürmüştür. Bir miRNA'nın kanserli hücrede sentezlenme miktarı kanserin tanısında ve tedavi süreçlerinde önemli rol oynar.[26]

miR-21 önemli tümör süpresör genleri hedef alarak çeşitli neoplazmaların gelişiminde rol alır. Kronik lenfositik lösemi (KLL), Akut miyeloid lösemi (AML) gibi hematolojik maligniteler, prostat, akciğer, kolon, karaciğer ve meme gibi kanser türlerinde miR-21 in ekspresyonun fazla seviyede olduğu görülmüştür.[27] miR-21'in hematolojik malignitelerde arttığı bulunmuş, birçok çalışmada malign transformasyonu arttırarak hastalık ilerlemesinin patogenezinde rol alır. Mirza ve arkadaşları tarafından yapılan çalışmada yeni tanı ve tedavi alan KML hastalarında miR-21 seviyeleri arasında anlamlı bir kat artışı bulunmuştur. İmatinib tedavisi alan KML hastalarında miR-21 ekspresyonu yaklaşık 9 kat arttığı gözlenmiştir. Bu çalışmada yeni tanı ile kronik faz hastaları arasında anlamlı farklılık saptanmıştır. Kronik faz ile blastik ve akselere faz değerlendirildiğinde 3-5 kat artış tespit edilmiştir.[28] Bizde çalışmamızda miR-21 açısından yeni tanı ile tedavi kolu karşılaştırıldığında, imatinib ve nilotinib kolunda katsayı anlamında fark tespit edilmiştir. miR-21'in yeni tanı almış grupta azaldığını, (yeni tanı:0.6) imatinip (1.4) ve nilotinip (3.5) tedavi grubunda kat artışı gösterdiği, dasatinip tedavi grubunda (0.8) düşük düzeyde olduğu bulundu.

miR-150, lenfoid farklılaşması açısından önemli bir miRNA'dır. miR-150 T ve B hücrelerinde eksprese edilirken progenitör hücrelerinde eksprese edilmez. miR-150 için lenfopoezde pre-B hücrelerinin mature B hücrelerine geçtiği basamakta rol alır. Transgenik farelerle yapılan çalışmalarda miR-150 lenfosit gelişimine etki ettiği ve mature B hücrelerinin alt grup hücrelerinin gelişiminde rol aldığı belirlenmiştir.[27]

Yapılan çalışmalarda KML teşhis ve tedaviye yanıtında biyobelirteç olarak miR-150' nin; KML ve AML'yi ayırt etmek için miR-155'in ve apoptoz aktivitesi için miR-21'in rolünün olduğu ileri sürülmüştür. Yeh ve arkadaşları, KML hastaları için iyi ve kötü prognostik belirteç olabilecek miRNA'ları göstermişlerdir. Yapılan çalışmada KML'de en sık bozulan miRNA'larının içerisinde miR-150'nin de olduğu bulmuşlardır.[24] KML hastalarında, teşhis ve tedavi yanıtında biyobelirteç olarak miR-150'nin, teşhis için biyobelirteç olarak miR-203'ün, KML ve AML'yi ayırt etmek içi miR-17'nin, teşhis ve ilaç yanıtı için miR-10'un, ilaç direnç takibi tespitinde biyobelirteç olarak miR-29a/b'nin rolü olabileceği ileri sürülmüştür.[29] miR-150 ifadesinin KML'nin yeni tanı aşamasında azaldığını gösteren çalışmalar vardır. Srutova ve arkadaşları yaptıkları araştırmada miR-150 seviyelerinde kontrol grubuyla kıyaslandığında KML grubunda miR-150 seviyesinde azalma bulmuşlardır.[30] Yeni tanı konmuş 50 KML hastasında RT-PCR yöntemi ile yapılan çalışmada miR-150'nin azalmasının KML'nin tanısal bir biyobelirteç olarak kullanılabileceği gösterilmiştir.[31] Yeni tanı konmuş KML hastaların mononükleer hücrelerinde ve kemik iliğinden bakılan CD34 + hücrelerinde miR-150'nin

azalmasını sağlıklı donörlere göre anlamlı bulmuştur. Tedavi edilmeyen KML hastalarında miR-150'nin da azalmış olduğu bulunmuştur.[32] Bizim de çalışmamızda, miR-150 gen ifadesi yeni tanı grubunda kat değişimi ve istatistiksel olarak anlamlı bulundu (kat değişimi=0.3, p=0.007484). Tedavi alan hasta grubu miR-150 gen ifadesi kontrol grubuna göre değerlendirildiğinde nilotinib kolunda istatistiksel olarak anlamlı bulundu (p=0.01541). (Tablo 3).

miR-155 ile yapılan çalışmalarda, çeşitli malignitelerde arttığı tespit edilmiştir. KML tanısı konulan hastalarda miR-155 seviyesinin sağlıklı bireylere göre daha yüksek olduğu bulunmuştur. Srutova ve arkadaşları KML hastalarında miR-155 ekspresyon seviyelerini kontrol grubuna göre daha yüksek bulmuştur.[30] Biz de çalışmamızda sağlıklı bireyler ve ilaç grubundaki miR-155 seviyesini karşılaştırdığımızda; imatinib ve nilotinib tedavi kollarında anlamlı kat artışı bulduk (imatinib:2.4, nilotinib:4.3). Bizim çalışmamızda ilaç grupları arası farklılıklar göstermekle beraber, net bir kat artışı ve miRNA-155 seviyesinde artış tespit edilememiştir.

Çalışmamızda miR-21 için yeni tanı ile dasatinib ilaç grubu arasında bir farklılık bulunmazken, imatinib ve özellikle nilotinib kolunda kat sayı açısından fark tespit edildi. Ancak sonuçlar istatiksel açıdan anlamlı bulunmamıştır (p=0.6121 imatinib, p=0.08872 nilotinib). Hasta öyküsüyle değerlendirildiği durumlarda ve hasta sayısının arttığı çalışmalarla desteklenmesiyle birlikte miR-21 hastalık ilerleyişi ve yanıt açısından bir parametre olarak kullanılabilir. Tedaviye yanıtı olmayan KML hastalarında miR-150 ifade düzeylerinin azalmasının tedavi direnci ile ilişkisinin ek çalışmalarla doğrulanması gereklidir. Yeni tanı grubunda sonuçlar bu durumu doğrulamaktadır. Örnek grupları arasında nilotinib kolundaki ifade düzeyinin azalması istatiksel açıdan anlamlı bulunmuştur (p=0.01541). Bu sonuçların örnek sayısının artırıldığı yeni çalışmalarla desteklenmesi, miR-150 gen ifadesinin tanı anında bakılması ve tedavi sürecinde izlenmesi, ilaç direnci takibi açısından önemli olabilir. KML hastalarında miR-155'nın prognostik belirteç olarak kullanılabilmesi için örnek sayısı arttırılmış yeni çalışmalara ihtiyaç vardır. Çünkü miR-155 ifade düzeyi, yeni tanı ile tedavi alan gruplar karşılaştırıldığında, ilk basamak tedavilerle son basamak tedavi arasında kat farklılık bulunmuştur. Yeni tanı ile dasatinib kolunda ise benzer oranlar elde edilmiştir. Ancak daha sağlıklı veri elde edebilmek için örnek sayısı arttırılmış yeni çalışmalarla desteklenmesi gerekmektedir.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Bilgilendirme

Çalışma Erciyes Üniversitesi Bilimsel Araştırma Projeleri Birimi tarafından TYL 2018-8012 kodlu bilimsel araştırma projesi ile desteklenmiştir.

Etik Kurul İzni

Bu çalışma için Erciyes Üniversitesi Klinik Araştırmalar Etik Kurulundan onay alındı (26.01.2018 tarih ve 2018/52 sayı).

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: HA, LK. Veri toplama/İşleme: HA, HA, SÖ, LK. Veri analizi ve yorumlama: HA, HA, SÖ. Literatür taraması: HA, HA, LK. Yazım: HA, HA, SÖ. Gözden geçirme ve düzeltme: HA, HA, LK. Danışmanlık: HA, LK.

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BİLİMSEL ARAŞTIRMA MAKALESİ

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Hemşirelik Son Sınıf Öğrencilerinin Stres Algısı ile Sosyal Yeterlilik ve Sonuç Beklentisinin Değerlendirilmesi

Evaluation of Stress Perception, Social Competence and Result Expectation of Senior Nursing Students

Müjgan SOLAK[1] Sevcan TOPÇU[2] Zuhal EMLEK SERT[2]

ÖZ

Amaç: Bu çalışma hemşirelik son sınıf öğrencilerinin stres algıları ile sosyal yeterlilik ve sonuç beklentisi düzeylerini belirlemek ve stres algıları ile sosyal yeterlilik sonuç beklentisi düzeyi arasındaki ilişkiyi incelemek amacı ile yapılmıştır.
Araçlar ve Yöntem: Tanımlayıcı-ilişki arayıcı tipte olan bu çalışma, bir devlet üniversitesinin Hemşirelik Fakültesi'nde yapılmıştır. Araştırmanın evrenini fakültede öğrenim gören hemşirelik son sınıf öğrencileri (N=288) oluşturmuştur. Çalışma araştırmaya katılmayı kabul eden 180 öğrenci ile tamamlanmıştır. Veri toplamada "Öğrenci Tanıtım Formu", "Hemşirelik Öğrencileri İçin Algılanan Stres Ölçeği" ve "Sosyal Yeterlilik ve Sosyal Sonuç Beklentileri Ölçeği" kullanılmıştır. Verilerin değerlendirilmesinde non-parametrik testler kullanılmıştır.
Bulgular: Öğrencilerin Algılanan Stres Ölçeğinden (HÖASÖ) aldıkları puan ile cinsiyet, sigara kullanımı, klinik yeterlilik ve kendini tanımlama arasında istatistiksel olarak anlamlı farklar bulunmuştur ($p<0.05$). Öğrencilerin sosyal güvencesinin olması, gelir düzeylerinin yüksek olması ve klinikte kendilerini yeterli olarak görmelerinin Sosyal Yeterlik ve Sosyal Sonuç Beklentileri (SYSSB) puanlarını arttırdığını ve bu farkın önemli olduğunu göstermiştir ($p<0.05$). HÖASÖ ve SYSSB Ölçekleri arasında negatif bir ilişki saptanmıştır ($r=-0.163$, $p=0.05$).
Sonuç: Öğrencilerin klinik olarak kendilerini yeterli hissetmelerinin ve sakin yapıya sahip olmalarının stres düzeyini azalttığı, uygulamalarda kendilerini yeterli bulmalarının sosyal yeterlik ve sosyal sonuç düzeylerini yükselttiği bulunmuştur. Öğrencilerin uygulamalara başlamadan, yeterliliklerinin arttırılması, kendilerini klinik uygulamalarda yeterli hissetmelerini sağlayacak özellikle yeni ve teknoloji tabanlı eğitim tekniklerinin kullanılması önerilir.

Anahtar Kelimeler: hemşire; sosyal yeterlilik; öz yeterlilik; algılanan stres

ABSTRACT

Purpose: This study was conducted to determine the stress perceptions and social competence and outcome expectation levels of senior nursing students and to examine the relationship between stress perceptions and social competence outcome expectation levels.
Materials and Methods: This descriptive-correlation type study was conducted at the Faculty of Nursing of a state university. The research population consisted of senior nursing students (N=288) studying at the faculty. The study was completed with 180 students who agreed to participate in the research. "Student Introduction Form", "Perceived Stress Scale for Nursing Students" and "Social Competence and Social Outcome Expectations Scale" were used in data collection. Non-parametric tests were used to evaluate the data.
Results: Statistically significant differences were found between the student's scores on the Perceived Stress Scale and gender, smoking, clinical competence, and self-definition ($p<0.05$). It has been shown that students' social security, high-income levels, and seeing themselves as competent in the clinic increase their Social Competence and Social Outcome Expectations scores, and this difference is significant ($p<0.05$). A negative relationship was found between HÖASÖ and SYSSB Scales ($r=-0.163$, $p=0.05$).
Conclusion: It was found that students' feeling clinically competent and having a calm nature reduced their stress levels, and finding themselves competent in practice increased their social competence and social outcome levels. It is recommended that students use new and technology-based training techniques to increase their proficiency before starting practice and to make them feel competent in clinical practice.

Keywords: nursing; social efficacy; self efficacy; perceived stress

Gönderilme tarihi: 19.09.2024; Kabul edilme tarihi: 10.12.2024

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Makaleye atıf için: Solak M, Topçu S, Emlek Sert Z. Hemşirelik son sınıf öğrencilerinin stres algısı ile sosyal yeterlilik ve sonuç beklentisinin değerlendirilmesi. Ahi Evran Med J. 2025;9(1):82-91. DOI: 10.46332/aemj.1553145

GİRİŞ

Stres, kişinin davranışsal uyum gerektiren koşullara bedenin psikolojik ve psikososyal tepkisidir.[1,2] Stres, günlük hayatın akışında değişiklik yaratan ve bireyi zor duruma sokan olaylara tepki olarak, kişinin dışarıya yansıtmadan kendi içinde yaşadığı bir deneyimdir.[3] Algılanan stres ise, bireyin belirli zamanlarda ne kadar strese maruz kaldığı konusunda sahip olduğu duygu ve düşüncelerdir.[4] Kişinin stresi algılama biçimi, kişinin kişilik yapısı, fiziksel özellikleri, sosyal becerileri gibi faktörlerle yakından ilişkilidir.[5] Her birey, kişisel deneyimlerinden, ailesel özelliklerinden, eğitim düzeyinden ve değerlerinden etkilenerek karşılaştığı olayları farklı şekillerde algılar ve farklı anlamlar yükler. Bir kişinin, bir durumu algıladığı stres düzeyi, olayla ilgili duyguları ve düşünceleri ne kadar olumsuzsa o kadar yüksek olabilir.[6]

Üniversite çağındaki gençler için, sınavların olması, aileden ayrı olma, mali problemler, gelecek kaygısı gibi faktörler stres kaynakları arasında yer alır. Ayrıca tıp fakültesi, diş hekimliği ve hemşirelik fakültesinde okuyan öğrencilerin staj programları esnasında hasta ile iletişimleri, pratik eğitimin getirdiği zorluklar, mezuniyet sonrasında yaşanılan iş bulma kaygısı ve çalışma şartlarının belirsizliği gibi düşünceler de strese neden olabilmektedir.[7,8] Hemşirelik eğitim programı, hemşirelik alanında bilgi, beceri ve yetkinlik kazanmalarını sağlayarak öğrencilerin mesleki kimliklerini geliştirmeyi amaçlar. Öğrenciler, gerçek yaşam deneyimlerinin yaşandığı uygulama alanına adım attıklarında, alışık olmadıkları yeni bir sosyal ortama girmekte ve eğitim sürecinin başlangıcından itibaren ölümle ya da ölüm riski taşıyan hastalarla karşılaşma gibi travmatik deneyimler yaşamaktadırlar. Ayrıca, kurum içindeki diğer kişilerle olan ilişkiler (doktorlar, hemşireler vb.), hata yapma, hastaya zarar verme, yanlış yapma korkusu, tıbbi aletleri kullanma sorunları, uygulamadaki bilgi ve yetenek eksiklikleri gibi faktörler, öğrencilerin kaygı düzeylerini artırmaktadır.[8,9,10]

Stres normal düzeyde kişiyi olumlu yönde etkiler. Yüksek stres düzeyi ile mücadele etmeyi bilmeyen öğrencilerin stresi daha yoğun yaşadığı ve bu strese bağlı olarak arkadaş ilişkilerinde, çevre uyumunda, akademik başarılarında yaşadıkları olumsuzlukların yanında, benlik saygısında azalma, fiziksel ve mental sağlık sorunlar yaşadıkları belirtilmektedir.[11,12] Dolasıyla stres, kişisel ve mesleki gelişimi de etkilemektedir.[13]

Bireyin stresle başa çıkma yeteneğini yansıtan bir özellik olan öz-etkililik ve yeterlilik algısı, kişinin kendine olan güveniyle ilgilidir.[14] Sosyal yeterlilik ise bireylerin çeşitli sosyal ortamlarda davranış başlatma, iletişim kurma, sürdürme, belirli davranışları başlatma ve tamamlama becerilerine olan inançlarına odaklanır.[15] Bu kavram, farklı sosyal becerilere ve yeteneklere sahip olma durumunu ifade eder. Ayrıca, sosyal yeterlilik kavramı, sosyal davranışın belirlenmesinde rol oynar. Sosyal yeterlilik; sosyal motivasyonlar, beceriler, algı, alışkanlıklar ve bilgi ile ilişkilendirilir.[16] Öğrencilerin sağlıklı ilişkiler geliştirmesinde sosyal yeterlik önemli bir role sahiptir. Güçlü sosyal yeterlilik algıları öğrencilerin daha güvenli ve başarılı sosyal etkileşimlerde bulunmalarını sağlar.[15]

Bireylerin sosyal yeterliliği ve becerileri geliştikçe; diğer insanlarla olan ilişkileri daha başarılıdır. Sosyal beceri ve yeterlilikleri yeterince gelişmemiş kişiler ise ilişkilerinde, sosyal yaşamlarında başarısız olma riski altındadırlar.[16] Bu durum, öğrencilerin kariyerleriyle ilgili planlarını ve mesleki sonuç beklentilerini olumsuz yönde etkiler.[17]

Sonuç beklentisi, kişinin belirli davranışları gerçekleştirmenin sonuçları veya çıktıları hakkındaki inançlardır.[18] Mesleki sonuç beklentisi, yeni beceriler edinme, gelir, statü gibi başarının uzun vadeli sonuçlarına yönelik inancıdır.[17] Buna göre, insanlar daha verimli ve başarılı olacaklarına inandıkları meslekleri seçtiklerinde, daha olumlu sonuçlar elde ederler.[19] Mesleki beklentileri karşılanan bireylerin güdülenme, iş doyumu ve meslekte performans düzeyleri yüksek olmaktadır. Aynı zamanda bu bireylerin başarılı ve üretken kişiler oldukları görülmektedir.[20]

Ülkemizde üniversite öğrencilerinin mesleki gelişiminde karşılaştıkları zorluklar arasında, kişisel farkındalıklarının düşük olması nedeni ile kendilerine uygun hedefler belirlemede güçlük yaşamaktadırlar.[21] Bu durum, öğrencilerin kariyer planlaması ve mesleki yönelimlerinde önemli engeller oluşturabilir. Hemşirelik öğrencilerinin eğitim sürecinden maksimum fayda sağlayabilmesi ve olumlu bir profesyonel kimlik geliştirebilmesi için stresle başa çıkma becerilerini geliştirebilmeleri son derece önemlidir. Öğrencilerin iletişim biçimlerini belirleyen ve sosyal

ortamdaki davranışlarını etkileyen diğer bir faktör ise sosyal yeterlik düzeyleridir. Öğrencilerin daha başarılı ve güvenli sosyal etkileşimlerde bulunmalarında güçlü sosyal öz yeterlik algılarının olmasının önemli bir yeri vardır. Öğrenciler klinik uygulama ortamında çeşitli derecelerde stres yaşamaktadır. Hastane ortamını, beceride yetersiz olma duygusunu, uygulamada sürekli hoca ile birlikte çalışmayı stres nedenleri olarak belirtmişlerdir.[14] Özellikle de hastanelerde görev alacak hemşirelik öğrencilerinin sosyal yeterliliklerinin gelişmiş olması hizmet sunduğu bireylerle ve diğer tüm sağlık personeli ile etkili iletişim kurabilmelerini sağlar. Bu nedenle, bu çalışma hemşirelik son sınıf öğrencilerinin stres algıları ile sosyal yeterlilik ve sonuç beklentisi düzeylerini belirlemek ve stres algıları ile sosyal yeterlilik ve sonuç beklentisi düzeyi arasındaki ilişkiyi incelemek amacı ile yapıldı. Bu araştırma ile aşağıdaki sorulara cevap aranmıştır: Hemşirelik son sınıf öğrencilerinin;

1. Hemşirelik son sınıf öğrencilerinin stres algı düzeyleri nasıldır?

2. Sosyal sonuç beklentisi ve sosyal yeterlik düzeyi nasıldır?

3. Stres algıları ile sosyal yeterlilik ve sonuç beklentisi düzeyi arasında ilişki var mıdır?

ARAÇLAR ve YÖNTEM

Araştırmanın Etiği

Çalışma "Helsinki Bildirgesi" nin ilkeleri ile tam bir uyum içinde yürütüldü. Bu çalışma için Ege Üniversitesi Sağlık Bilimleri Bilimsel Araştırma ve Yayın Etiği Kurulundan onay alındı (01.12.2022 tarih ve 13/07-1719 sayılı). Katılımcılara araştırmanın amacı, kapsamı, potansiyel riskleri ve faydaları hakkında açık ve anlaşılır bilgi verilmiştir. Katılımcıların araştırmaya katılımının tamamen gönüllü olduğunu ve diledikleri zaman katılımı sonlandırma hakkına sahip oldukları vurgulanmıştır. Araştırmada toplanan verilerin gizliliğinin sağlanacağı, bireysel bilgilerin gizli tutulacağı ve yalnızca araştırma amaçları için kullanılacağı belirtilmiştir. Araştırmaya katılmayı kabul eden gönüllü öğrencilerden yazılı bilgilendirilmiş onam alınmıştır.

Araştırmanın Tasarımı

Bu çalışma, hemşirelik son sınıf öğrencilerinin stres algıları, sosyal yeterlilikleri ve sonuç beklentilerini belirlemek amacıyla, tanımlayıcı ve ilişki arayıcı tasarım kullanılarak gerçekleştirilmiştir. Çalışma, belirli bir kurumda yer alan hemşirelik son sınıf öğrencileri arasında yürütülmüş olup, veri toplama süreci anketler aracılığıyla gerçekleştirilmiştir. Araştırma, öğrencilerin stres algı düzeylerini, sosyal sonuç beklentilerini ve sosyal yeterlilik düzeylerini belirlemeyi amaçlamaktadır.

Araştırmanın Yapıldığı Yer

Bu çalışma, bir devlet üniversitesinin Hemşirelik Fakültesi'nde gerçekleştirilmiştir. Bu hemşirelik fakültesinde son sınıf öğrencileri yedinci ve sekizinci yarıyıllarda uygulamalı sekiz farklı hemşirelik alanında (hemşirelik temel ilke ve uygulamaları, dahiliye hemşireliği, cerrahi hemşireliği, çocuk hemşireliği, kadın doğum hemşireliği, psikiyatri hemşireliği, halk sağlığı hemşireliği) eğitim almaktadırlar. Her yarıyılda haftada 32 saat uygulamalı eğitim almaktadırlar. Araştırmanın yapıldığı fakültede entegre eğitim modeli uygulanmaktadır. Bu nedenle son sınıf öğrencileri araştırma kapsamına alınmıştır.

Araştırma Evreni ve Örneklemi

Araştırmanın evrenini, 2022-2023 eğitim-öğretim yılı bahar yarıyılında öğrenim gören hemşirelik son sınıf öğrencileri (N=288) oluşturmaktadır. Araştırmanın örneklem sayısının belirlenmesinde evreni bilinen örneklem hesabı formülü kullanılmıştır. Yapılan hesaplama sonucunda %90 güven aralığı %5 hata düzeyinde alınması gereken örneklemin minimum 165 öğrenci olması gerektiği belirlenmiştir.[22] Veri toplama formları tüm son sınıf öğrencilerine Google Forms ile çevrimiçi gönderilmiştir. Hemşirelik son sınıf öğrencisi olan, araştırmaya katılmayı kabul eden, veri toplama formlarını eksiksiz tüm öğrenciler çalışma kapsamına alınmıştır. Çalışma araştırmaya katılmayı kabul eden 180 öğrenci ile tamamlanmıştır.

Veri Toplama Araçları

Veri toplamada "Öğrenci Tanıtım Formu", "Hemşirelik Öğrencileri İçin Algılanan Stres Ölçeği" (HÖASÖ) ve

"Sosyal Yeterlik ve Sosyal Sonuç Beklentileri Ölçeği" (SYSSB) kullanılmıştır.

Öğrenci Tanıtım Formu: Öğrencilerin sosyo-demografik özelliklerinden yaş, cinsiyet, medeni durum, gelir durumu vb. bilgileri içeren 18 soruluk bir formdur. Bu form, literatürden yararlanılarak oluşturulmuştur. [3,7,8,10,12]

Hemşirelik Öğrencileri İçin Algılanan Stres Ölçeği (HÖASÖ): Sheu ve arkadaşları(2002) tarafından geliştirilen, ölçek 29 maddeden oluşmaktadır.[23] Türkiye'de bu ölçeğin geçerliliği ve güvenirliği Karaca ve arkadaşları tarafından 2015 yılında yapılmıştır. Yapılan çalışmada, genel toplam düzeyinde Cronbach's alfa katsayıları 0,67 ile 0,93 arasında değişmektedir. Ayrıca, iki haftalık test-tekrar test güvenilirliği ise 0,96 olarak bulunmuştur. Ölçek, 0-4 puan alan Likert tipi bir ölçektir ve altı alt boyutu vardır. Ölçeğin puan aralığı 0-116'dır. Puanın yüksek olması, stres derecesinin yükseldiğini gösterir.[12] Bu araştırmada Cronbach Alfa katsayısı 0.91 bulunmuştur.

Sosyal Yeterlik ve Sosyal Sonuç Beklentileri Ölçeği (SYSSB): Bakioğlu ve Türküm (2017) tarafından geliştirilen ölçek, Sosyal Yeterlik ve Sosyal Sonuç Beklentisi olmak üzere iki alt boyut ve toplamda 19 maddeden oluşmaktadır. Ölçeğin her bir alt boyutundan alınan yüksek puan, bireyin ilgili alt boyuta ilişkin özelliğe sahip olduğu düzeyini ifade eder. Ölçeğin tüm maddelerinden alınan toplam puan ise sosyal yeterlik ve sonuç beklentileri düzeyini yansıtır. Puanın yükselmesi, sosyal yeterlik ve sonuç beklentileri düzeyinin de arttığını gösterir. [24] Bu araştırmada Cronbach Alfa katsayısı 0.94 bulunmuştur.

Veri Toplaması

Araştırmanın verileri 15 Kasım 2022-30 Nisan 2023 tarihleri arasında çevrimiçi olarak toplandı. Anket formları Google Forms üzerine aktarılarak öğrencilere iletilmiştir. Google Forms ile oluşturulan çevrimiçi anket içerisinde; veri toplama araçlarını tanımlayan, araştırmanın amacını ve kapsamını açıklayan, katılımcıların ölçeklere verdikleri cevapların gizli tutulacağını ve sadece bilimsel çalışmalarda kullanılacağını belirten bilgiler yer almıştır. Ayrıca, ölçeklerin nasıl yanıtlanması gerektiğine ilişkin yönergeler ve yazılı onam da katılımcılara sunulmuştur. Formların doldurulması için gerekli süre yaklaşık beş dakikadır.

Veri Analizi

Araştırmadan elde edilen bulguların değerlendirilmesinde, istatistiksel analizler için SPSS® (Statistical Package for Social Sciences 20.0) for Windows paket programları kullanılmıştır. Çalışma verileri değerlendirilirken, tanımlayıcı istatistiksel metotlardan frekans, yüzde, ortalama, standart sapma gibi ölçümler kullanılmıştır. Niceliksel verilerin karşılaştırılmasında, parametrelerin gruplar arası karşılaştırmalarında verilerin homojenlik ve normal dağılıma uygunluğu için Shapiro-Wilk testi yapılmıştır. Yapılan test sonucu verilerin normal dağılım göstermediği belirlenmiştir. Verilerin değerlendirilmesinde Mann-Whitney Testi, Kruskal-Wallis Testi, Pearson korelasyon gibi istatistiksel testler kullanılmıştır. Elde edilen sonuçlar %95 güven aralığında, anlamlılık düzeyi $p<0.05$ olarak değerlendirilmiştir.[22]

BULGULAR

Araştırma kapsamına alınan hemşirelik öğrencilerinin sosyo-demografik özellikleri incelendiğinde, yaş ortalamaları 22.89±1.90'dır ve yaş aralığı 21-35 yaş arasındadır. Öğrencilerin %78.3'ü kadın, sadece %1.7'si evli, %7.8'i sağlık meslek lisesi (SML) mezunudur. Öğrencilerin ebeveynlerinin eğitim, gelir, bağımlılık, başarı, mesleki özellikleri ile ilgili durumları Tablo 1'de sunulmuştur.

Öğrencilerin HÖASÖ'den aldıkları puan ile cinsiyet (kız öğrencilerin HÖASÖ puanları erkeklerden daha yüksek), sigara kullanımı (sigara kullanmayanların stres puanı daha yüksek), klinik yeterlilik (klinikte kendini yetersiz hissedenlerin stres puanı daha yüksek) ve kendini tanımlama (kendini sakin olarak tanımlayan öğrencilerin stres puanları daha düşük) arasında istatistiksel olarak anlamlı fark bulunmuştur ($p<0.05$). Tablo 2'de sunulan veriler, cinsiyet, sigara kullanımı ve klinik yeterlilik gibi faktörlerin HÖASÖ ve SYSSB puanları üzerindeki etkilerini göstermektedir. Katılımcıların SYSSB ölçeğinden aldıkları puan ile sosyal güvence (sosyal güvencesi olan öğ-

rencilerin daha yüksek), gelir durumu (gelir durumu yüksek öğrencilerin daha yüksek) ve klinik yeterlilik (klinikte kendini yeterli hisseden öğrencilerin daha yüksek) arasında istatistiksel olarak anlamlı fark bulunmuştur ($p<0.05$).(Tablo 2).

Tablo 1. Öğrencilerin sosyo-demografik özelliklerine göre dağılımı.

Sosyo-demografik özellikler	Sayı (n)	Yüzde (%)
Yaş ortalaması: 22.89+1.90 (21-35)		
Cinsiyet		
Kadın	141	78.3
Erkek	39	21.7
Medeni Durum		
Bekâr	177	98.3
Evli	3	1.7
Mezun olduğu okul		
Sağlık Meslek Lisesi	14	7.8
Anadolu Lisesi	166	92.2
Annenin Eğitim Durumu		
İlkokul	85	47.2
Ortaokul	31	17.2
Lise	46	25.6
Üniversite	18	10.0
Babanın Eğitim Durumu		
İlkokul	62	34.4
Ortaokul	38	21.1
Lise	44	24.4
Üniversite	36	20.0
Kaldığı Yer		
Devlet Yurdu	62	34.4
Özel yurt	24	13.3
Öğrenci evi	54	30.0
Aile Yanı	40	22.2
Sosyal güvence		
Var	143	79.4
Yok	37	20.6
Gelir Durumu		
Gelir Giderden az	75	41.7
Gelir Gidere Denk	89	49.4
Gelir giderden fazla	16	8.9
Sigara kullanma		
Evet	43	23.9
Hayır	137	76.1
Alkol kullanma		
Evet	65	36.1
Hayır	115	63.9
Başarı Durumu		
2.00-2.50 arasında	-	-
2.51-3.00 arasında	21	11.7
3.01 ve üzeri	159	88.3
Klinik yeterlilik		
Yeterli	70	38.9
Kısmen yeterli	102	56.7
Yetersiz	8	4.4
Klinik de sorun yaşama durumu		
Evet	40	22.2
Hayır	140	77.8
Hemşirelik Mesleğini Sevme durumu		
Evet	145	80.6
Hayır	35	19.4
Mezuniyet sonrası yapmak istediği		
Hastanede çalışmak	118	65.6
Hastane dışında mesleğini yapmak	22	12.2
Hemşirelik dışında bir iş yapmak	23	12.8
Diğer (çalışmama, yurt dışı v.b)	17	9.4
Genel kendini tanımlama		
Sakin/rahat biriyim	84	46.7
Stresli/gergin biriyim	86	47.8
Diğer	10	5.6
Toplam	**180**	**100.0**

Tablo 2. Öğrencilerin HÖASÖ ve SYSSB ölçeklerinden aldıkları puanların dağılımı.

Sosyo-Demografik Özellikler	HÖASÖ	Ortanca	İstatistik	SYSSB	Ortanca	İstatistik
Cinsiyet						
Kadın	71.85±24.14	76	z=-4.028	79.18±9.12	76	z=-0.916
Erkek	55.66±20.38	55	p=0.000*	76.84±3.21	76	p=0.360
Medeni durum						
Bekâr	68.52±24.40	70	z=-1.000	78.68±9.07	76	z=-0.465
Evli	57.66±10.11	63	p=0.317	78.33±8.84	77	p=0.642
Mezun olduğu okul						
Sağlık Meslek Lisesi	60.64±30.17	62	z=-1.026	79.78±7.13	78.5	z =-0.766
Anadolu Lisesi	68.99±23.69	70	p=0.305	78.58±9.20	76	p=0.444
Annenin eğitim durumu						
İlkokul	67.05±25.24	69	x^2=2.379	78.02±9.25	76	x^2=2.482
Ortaokul	64.90±24.80	64	p=0.498	78.61±7.87	76	p=0.479
Lise	73.08±19.81	74		79.28±8.62	78	
Üniversite	68.22±28.88	65		80.33±11.30	76	
Babanın eğitim durumu						
İlkokul	64.41±25.28	66		76.90±9.33	75.5	
Ortaokul	71.57±22.27	75.5	x^2=2.361	78.73±9.19	77	x^2=7.667
Lise	69.50±22.02	71.5	p=0.501	78.34±7.74	76	p=0.053
Üniversite	70.27±27.06	73		82.08±9.30	82	
Kaldığı yer						
Devlet yurdu	68.90±24.43	71.5	x^2=3.338	78.04±8.00	76	x^2=1.252
Özel yurt	76.08±17.20	74	p=0.303	78.29±8.29	76	p=0.741
Öğrenci evi	65.87±25.15	68.5		78.68±10.70	76	
Aile ile	66.17±26.14	64		79.87±8.79	76	
Sosyal güvence						
Var	68,98±24.70	71	z=-0.830	79.56±9.38	77	z=-2.534
Yok	65,86±22.63	69	p=0.406	75.24±6.72	75	p=0.011*
Gelir durumu						
Gelir giderden az	70.80±24.26	71	x^2=2.243	76.44±8.18	76	x^2=10.481
Gelir gidere denk	68.38±24.03	63.5	p=0.326	79.49±9.23	84.5	p=0.005*
Gelir giderden fazla	60.00±25.39	68		84.62±8.97	76	
Sigara kullanma						
Evet	62.93±24.78	63	z=-1.965	80.81±10.00	79	z=-1.751
Hayır	70.04±23.94	73	p=0.049*	78.00±8.66	76	p=0.080
Alkol kullanma						
Evet	66.40±21.73	66	z=-1.072	79.44±9.62	76	z=-0.660
Hayır	69.44±25.61	71	p=0.284	78.24±8.72	76	p=0.509
Başarı durumu						
2.00-2.50 arasında	-	-		-		
2.51-3.00 arasında	69.52±22.65	71	z=-0.176	80.38±10.38	78	z=-0.552
3.01 ve üzeri	68.18±24.53	69	p=0.860	78.45±8.87	76	p=0.581
Klinik yeterlilik						
Yeterli	60.87±28.08	60	x^2=9.041	80.57±9.76	77	x^2=13.260
Kısmen yeterli	72.83±19.74	72.5	p=0.011*	77.89±8.36	75.5	p=0.001*
Yetersiz	76.50±26.96	82.5		72.12±7.21	71.5	
Klinik de sorun yaşama durumu						
Evet	69.65±24.57	73.5	z=-0.592	77.17±10.18	76	z=-1.035
Hayır	67.97±24.25	69	p=0.554	79.10±8.69	76	p=0.301
Mesleğini sevme durumu						
Evet	68.94±24.76	72	z=-0.907	79.26±8.99	77	z=-1.817
Hayır	65.85±22.25	63	p=0.364	76.25±9.02	75	p=0.069
Mezuniyet sonrası yapmak istediği						
Hastanede çalışmak	70.44±24.47	71.5		79.07±9.59	76	
Hastane dışı hemşirelik	70.40±21.89	73	x^2=4.800	78.90±8.33	77.5	x^2=4.049
Hemşirelik dışı	59.21±25.27	55	p=0.187	75.91±6.92	75	p=0.256
Diğer (çalışmama, yurt dışı v.s)	63.47±22.74	66		79.35±8.60	76	
Genel kendini tanımlama						
Sakin/ rahat biriyim	61.60±22.48	60.5	x^2=19.349	78.92±9.07	76	x^2=3.542
Stresli/ gergin biriyim	76.03±23.18	80.5	p=0.000*	78.08±9.06	75	p=0.170
Diğer	58.80±29.72	73.5		81.70±8.98	80.5	

HÖASÖ: Hemşirelik Öğrencileri İçin Algılanan Stres Ölçeği, SYSSB: Sosyal Yeterlik ve Sosyal Sonuç Beklentileri Ölçeği z=Mann-Whitney Testi, x^2=Kruskal-Wallis Testi. *p<0.05

HÖASÖ ve SYSSB ölçeğinden elde edilen puanların dağılımları, Tablo 3'te ayrıntılı olarak sunulmuştur. Pearson korelasyon analizi sonuçlarına göre, iki ölçek arasında -0.163 değerinde zayıf bir negatif ilişki gözlemlenmiştir, ancak bu ilişki p>0.05 anlamlılık düzeyinde değildir.

Tablo 3. Öğrencilerin HÖASÖ ve SYSSB ölçeğinden aldıkları puan ortalamalarının dağılımı.

Ölçekler	Min-Max	Ort.	Sd
Mesleki bilgi ve beceri eksikliğinden kaynaklanan stres	0-12	6.53	3.00
Hastaya bakım verirken yaşanan stres	0-32	18.03	7.02
Ödevlerden ve iş yükünden kaynaklanan stres	0-20	13.10	4.64
Öğretim Elemanları ve hemşirelerden kaynaklanan stres	0-24	14.70	5.75
Ortamdan kaynaklanan stres	0-12	6.97	3.01
Akranlardan ve günlük yaşamdan kaynaklanan stres	0-16	8.99	4.01
Stres Toplam puan	0-116	68.34	24.26
Sosyal Yeterlik	37-65	53.56	6.87
Sosyal Sonuç Beklentisi	10-30	25.11	3.29
Sonuç toplam	56-95	78.67	9.05

HÖASÖ: Hemşirelik Öğrencileri İçin Algılanan Stres Ölçeği, SYSSB: Sosyal Yeterlik ve Sosyal Sonuç Beklentileri Ölçeği

TARTIŞMA

Hemşirelik öğrencilerinin ödev ve iş yüküne bağlı olarak yaşadıkları stres düzeyi, diğer öğrencilere göre daha yüksek bulunmuştur.[25] Özellikle, hemşirelik öğrencileri zor ders programları, riskli girişimler, dönem ödevleri ve sınavlar nedeniyle ciddi bir stres altındadır.[26] Bu çalışma, öğrencilerin algılanan stres düzeylerinin medeni durum, mezun olunan okul, ebeveynlerin eğitim durumu, kalınan yer, sosyal güvence, gelir durumu, alkol kullanımı, akademik başarı, klinikte sorun yaşama, mesleği sevme ve mezuniyet sonrası hedefler gibi birçok değişkenden etkilenmediğini göstermiştir.

Cinsiyetin algılanan stres düzeyi üzerindeki etkisi bu çalışmada önemli bir bulgu olarak ortaya çıkmıştır. Çeşitli araştırmalarda, cinsiyet ile algılanan stres düzeyi arasında farklı sonuçlar elde edilmiştir. Örneğin, Eşigül ve Önder (2017) ile Altundağ (2011) tarafından yapılan çalışmalarda, üniversite öğrencilerinin cinsiyetlerine göre algıladıkları stres düzeyleri arasında anlamlı bir fark bulunmamıştır.[27,28] Ancak, Yerlikaya (2009) ve Altunkol (2011) tarafından gerçekleştirilen araştırmalarda, kız öğrencilerin stres puanlarının erkeklerden anlamlı derecede yüksek olduğu belirlenmiştir.[29,30] Taşdelen ve Zaybak (2013)'ın hemşirelik öğrencileri üzerine yaptıkları çalışmada ise, cinsiyet ile algılanan stres puan ortalamaları arasında anlamlı bir fark tespit edilmemiştir.[8] Öte yandan, Ergin ve Çevik (2017) tarafından gerçekleştirilen bir araştırmada cinsiyet ile algılanan stres puanları arasında istatistiksel olarak anlamlı bir fark bulunmuştur; bu bulgu, kız öğrencilerin erkek öğrencilere göre daha fazla stres yaşadığını göstermektedir.[10] Singh ve arkadaşlarının (2013) çalışmasında, erkeklerin kaygılarını kız öğrencilere göre daha basit ve az ifade ettikleri belirtilmiştir.[31] Ayrıca, Ocak ve Güler'in (2013) çalışması, kadınların algılanan stres belirtilerini daha fazla bildirdiğini ortaya koymuştur.[32] Bu bulgular, cinsiyetin algılanan stres üzerindeki etkilerini anlamak açısından önem taşımaktadır.

Bu çalışmada, sigara içen üniversite öğrencilerinin algıladıkları stres düzeyinin sigara içmeyenlere göre daha düşük olduğu bulunmuştur. Karaca ve arkadaşlarının (2017) çalışmasında ise sigara içen öğrenciler arasında mesleki bilgi ve beceri eksikliğinden kaynaklanan stres alt boyutlarında yüksek puanlar elde edilmiştir.[33] Bu bulgu, sigaranın strese karşı etkili bir baş etme mekanizması olmadığını göstermektedir. Ancak, bu veriler doğrultusunda sigara tüketiminin öğrencilere geçici bir rahatlama hissi verebileceği düşünülmektedir. Ancak sigara içme ve alkol tüketimi, etkisiz başa çıkma yöntemlerinden biridir. Bu tür davranışların olumsuz bir yaşam tarzına neden olabileceği kabul edilmektedir.[34] Öğrencilerin stres düzeylerini yönetmelerine, düzenlemelerine ve olumlu baş etme stratejilerini geliştirmelerine yardımcı olacak danışmanlık programları oluşturulmalıdır. Bu tür programlar, öğrencilerin sağlıklı baş etme mekanizmalarını geliştirmelerine ve stresle daha etkili bir şekilde başa çıkmalarına yardımcı olabilir.

Bu çalışmanın sonucunda, klinik olarak kendini yeterli gören öğrencilerin algıladıkları stres düzeylerinin kendini kısmen yeterli gören öğrencilere göre daha düşük olduğu bulunmuştur. Klinik olarak kendini yeterli görmenin stres düzeyini düşürdüğü düşünülmektedir. Öğrenciler klinik ortamda çeşitli hastalarla ve hastalıklarla karşılaşır ve bu hastalara bakım sunabilmek için ileri düzeyde bilgi ve becerilere ihtiyaç duyarlar. Stresin temel kaynağı, öğrencilerin hastalara bakım verme, mesleki bilgi ve beceriler konusunda yetersiz hissetmeleri olabilir.[34] Bu nedenle, hemşirelik öğrencilerine sağlanan destek ve eğitim stresle

başa çıkmalarını ve güvenle hasta bakımı yapmalarını sağlamak için kritik öneme sahiptir.

Daha önce yürütülen çalışmaların sonuçları; öğrencileri gereksiz stresten korumak, sağlık çalışanları ile iş birlikçi ilişkiler kurmalarına yardımcı olmak ve ilk klinik uygulamaları için gerçekçi beklentiler oluşturmak amacıyla hemşirelik eğitmenlerinin klinik uygulamanın amaçlarını ve doğasını detaylı olarak açıklamaları gerektiğini göstermiştir.[33] Bu tür önlemler, öğrencilerin klinik deneyimlerini daha etkili ve olumlu bir şekilde yönetmelerine yardımcı olabilir. Bu çalışmada; kendini sakin/rahat olarak tanımlayan öğrencilerin, stresli/gergin olarak tanımlayan öğrencilere kıyasla algıladıkları stres düzeylerinin daha düşük olduğu bulunmuştur. Van Kuiken ve arkadaşları (2017) ve Patterson'un (2016) yılında yapmış oldukları çalışmaların sonucunda; hemşirelik öğrencilerinin kendilerini rahat, sakin ve odaklanmış hissetmelerini sağlayan girişimlerin (farkındalık dakikası, güncel olay tartışması, duygusal özgürlük tekniği vb.) stresi yönetmeleri üzerinde olumlu bir etkisinin olduğunu belirlenmiştir. Bu yöntemleri kullandıktan sonra ise öğrencilerin uyku düzenlerinin iyileştiği, kendilerini sakin hissettikleri, daha iyi ruh hali içinde bulundukları ve stresle daha iyi başa çıkma yeteneği kazandıkları belirlenmiştir.[35,36] Bu sonuç çalışmamızın sonuçlarını desteklemektedir. Hemşirelik öğrencileri eğitimlerinin daha ilk yıllarında mesleki yaşamlarında stresli olaylarla başa çıkmada kullanabilecekleri olumlu yolları öğrenme ve uygulamayı sağlayabilecek dersler görmektedirler. Hemşirelik öğrencilerinin yaşadıkları stresi yönetebilmeleri ve sakin kalabilmeleri için olumlu başa çıkma tekniklerini kullanmaları hem kendi hem de hizmet sunduğu hasta ve yakınları için önem taşımaktadır.

Bir insanın davranışlarını etkileyen faktörlerden biri de sonuç beklentileridir. İnsanlar, çevresel olaylarla yaşadıkları deneyimler arasındaki ilişkileri gözlemleyerek sonuçlar hakkında beklentiler oluştururlar. Bu beklentiler, kişinin çevresel etkilerden kurtulmasına ve geleceği şekillendirerek hedeflerine ulaşmasına olanak tanır.[9,11,15,16] Sağlıklı ilişkiler kurma, olumlu sosyal yaşantılar sağlama ile sosyal öz yeterlilik arasında önemli bir ilişki bulunmaktadır.[15] Hemşirelik bakımı 7 gün 24 saat kesintisiz devam eden bir nitelik göstermektedir. Bu nedenle özellikle hemşirelik öğrencilerinin sosyal yeterlilik düzeylerinin yükseltilmesi ve bu konuda desteklenmeleri önem taşımaktadır. Öğrencilerin sosyal yeterlik düzeylerinin yüksek olması, kendilerine güvenen ve kendilerini yeterli bulan bireyler olduklarını göstermektedir. Sosyal yeterlik ve sosyal sonuç beklentileri üzerine yapılan bu çalışmada, sosyal yeterlik düzeyinin yükseltilmesi ve bu konuda desteklenmenin önemi vurgulanmıştır. Öğrencilerin sosyal güvencesinin olması, gelir düzeylerinin yüksek olması ve klinikte kendilerini yeterli görmelerinin, sosyal yeterlik ve sosyal sonuç beklentileri puanlarını artırdığı gösterilmiştir. Pratik olarak kendini yeterli gören öğrenciler, hem hastalara kaliteli bakım sunabilecek hem de sosyal yeterlilik düzeylerini yükseltebileceklerdir. Hemşirelik öğrencilerinin ruh sağlıklarının korunması, akademik ve mesleki zorluklarla başa çıkabilmeleri açısından da son derece önemlidir. Bu, öğrencilerin başarılarını ve mesleki yetkinliklerini artırmalarına yardımcı olurken aynı zamanda sağlık hizmetlerinde kaliteli ve güvenilir bakım sunmalarını da sağlar. Bunun yanı sıra hemşirelik öğrencilerinin klinik stresörlerle başa çıkma deneyimlerinin araştırılması, öğrencilerin başa çıkma stratejilerine ilişkin farkındalıklarını artırır. Klinik ortamda stresle başa çıkma stratejilerini tanıyan akademik otoriteler, öğrencilere etkili başa çıkma stratejileri konusunda gerekli eğitimi sağlayabilir.[37] Hemşirelik öğrencilerinin stresle başa çıkma becerilerinin artması ve yaşadıkları ağır yük altında hastaları maksimum kalitede tedavi etmeye devam edebilmeleri için dayanıklılık düzeylerini arttırmaya çabalamak esastır.[38] Bu amaçla gereken eğitim ve danışmanlık hizmetleri verilerek psikolojik sağlamlığı olan meslek adaylarının yetiştirilmesi üzerine odaklanılabilir.

Algılanan stres düzeyi ile sosyal yeterlik ve sosyal sonuç beklentileri arasında zayıf, negatif yönde bir ilişki bulunmuştur. Diğer bir ifade ile hemşirelik fakültesi son sınıf öğrencilerinin algıladıkları stres düzeyi arttıkça sosyal yeterlik ve sosyal sonuç beklenti düzeylerinin azaldığı belirlenmiştir. Bu çalışmada elde edilen sonuç literatür ile uyumludur.[39,40] Kısa bir süre sonra iş yaşamında yer alacak olan son sınıf hemşirelik öğrencilerinin; başta hasta/yakınları ve sağlık ekibinde yer alan diğer üyeler ile etkili iletişim kurabilmeleri, etkili sosyal ilişkiler geliştirebilmeleri ve rollerini sağlıklı biçimde sergile-

yebilmeleri için sosyal öz yeterliklerinin gelişmiş olması gereklidir.

Sonuç ve Öneriler

Araştırma sonuçları, stres düzeyinin kız öğrencilerde daha yüksek olduğunu, sigara kullanan öğrencilerde ise stres düzeyinin düşük olduğunu göstermektedir. Ayrıca, klinik olarak kendini yeterli hissetme ve sakin bir yapıya sahip olmanın, stres düzeyini azalttığı belirlenmiştir. Öğrencilerin sosyal güvencelerinin varlığı, gelir durumlarının iyi olması ve klinik bilgi/uygulamalarda kendilerini yeterli bulmaları, sosyal yeterlik ve sosyal sonuç düzeylerini artırmaktadır.

Elde edilen bulgular, öğrencilerin stres düzeyinin azaltılmasında teorik bilgilerin yanı sıra bu bilgilerin uygulamaya aktarılmasında kendilerini yeterli hissetmelerinin önemini vurgulamaktadır. Bu bağlamda, teorik derslerin ardından uygulamaların öncelikle laboratuvarlarda yapılması ve öğrencilerin uygulamaları doğru bir şekilde yapabilmeleri için gerekli tekrarların sağlanması önemlidir. Laboratuvarlarda, zengin görsel materyaller, demonstrasyonlar, videolar, rol oynama ve simülasyon gibi yeni ve teknoloji tabanlı eğitim tekniklerinin kullanılması önerilmektedir. Bu sayede, öğrencilerin yeterlilikleri artırılarak klinik uygulamalarda kendilerini daha güvende hissetmeleri sağlanabilir. Araştırma, öğrencilerin stresle başa çıkmak için sigara kullanımına yöneldiğini ortaya koymuştur. Bu nedenle, öğrencilere stresle başa çıkmada etkili yöntemler hakkında bilgilendirme ve rehberlik yapılması önemlidir. Hemşirelik öğrencilerinin stresle başa çıkma becerilerinin geliştirilmesi, hasta/bireylere kaliteli tedavi ve bakım verebilmelerini ve dayanıklılık düzeylerinin artmasını sağlayacaktır. Bu amaçla öğrencilik döneminde, gereken eğitim ve danışmanlık hizmetleri verilerek, psikolojik sağlamlığı olan meslek adaylarının yetiştirilmesi üzerine odaklanılması önerilir.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Etik Kurul İzni

Bu çalışma için Ege Üniversitesi Sağlık Bilimleri Bilimsel Araştırma ve Yayın Etiği Kurulundan onay alındı (01.12.2022 tarih ve 13/07-1719 sayılı).

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: MS. Veri toplama/İşleme: MS. Veri analizi ve yorumlama: MS, ST. ZES. Literatür taraması: MS, ST. ZES. Yazım: MS, ST. ZES. Gözden geçirme ve düzeltme: MS, ST. ZES.

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Comparison of Rapid Diagnostic Test with Enzyme-Linked Immunosorbent Assay and PCR for Detection of Hepatitis B Surface Antigen

Hepatit B Yüzey Antijeninin Saptanması için Hızlı Tanı Testinin Enzime Bağlı İmmünosorbent Testi ve PCR ile Karşılaştırılması

Melek BİLGİN[1] Mehmet Hakan TAŞKIN[1] Esmeray MUTLU YILMAZ[2] Çiğdem ÇEKİÇ CİHAN[1]

ÖZ

Amaç: Hepatit B virüs (HBV) enfeksiyonu, önemli morbidite ve mortalite oranları ile küresel halk sağlığı sorunu olmaya devam etmektedir ve tanı için HBs Ag'nin tespiti çok önemlidir. İdeal olarak hızlı testlerin duyarlılığının yüksek özgüllüğününde kabul edilebilir yükseklikte olması gerekir, böylelikle yanlış pozitif ve yanlış negatif sonuçların önüne geçilebilir. Bu çalışmanın amacı, ELISA ve PCR ile doğrulanmış vakalarla hızlı tarama testlerinin performansını değerlendirmektir.
Araçlar ve Yöntem: Prospektif olarak planlanan bu çalışma Şubat 2024-Mart 2024 tarihleri arasında Samsun'da üçüncü basamak bir hastanede gerçekleştirilmiştir. HBsAg testi için mikrobiyoloji laboratuvarına çeşitli kliniklerden gönderilen toplam 160 kan örneği çalışmaya dahil edilmiştir. Tüm örnekler ELISA ve PCR yöntemi ile çalışıldıktan sonra hızlı test ile çalışılmıştır.
Bulgular: ELISA ile karşılaştırıldığında hızlı testin özgüllüğü %97.70, duyarlılığı %87.20, pozitif prediktif değeri (PPV) %57.82, negatif prediktif değeri (NPV) %99.53olarak saptanmıştır. Ayrıca HBsAg hızlı testi PCR ile karşılaştırıldığında duyarlılığı %44.50, özgüllüğü ise %47.40 olarak belirlenmiştir.
Sonuç: Çalışmamız ile hızlı testlerin ELISA ile karşılaştırıldığında yüksek özgüllük ve kabul edilebilir duyarlılığa sahip olduğu ancak PCR ile karşılaştırıldığında yeterince uyumlu olmadığı sonucuna varılmıştır.

Anahtar Kelimeler: HBsAg; hızlı test; ELISA; PCR

ABSTRACT

Purpose: Hepatitis B virus (HBV) infection is a global public health problem with significant morbidity and mortality rates and the detection of HBsAg is a very important test for diagnosis. Ideally, rapid tests should have a high sensitivity and an acceptable level of specificity, so that false positive and false negative results can be prevented. The objective of this study was to evaluate the performance of rapid screening tests with confirmed cases with ELISA and PCR.
Materials and Methods: This study was conducted as a prospective study in a tertiary hospital in Samsun between February 2024 and March 2024. A total of 160 blood samples sent to the microbiology laboratory for HBsAg testing from various departments were included in the study. All samples were studied with a rapid test after being studied with ELISA and PCR methods.
Results: Compared to ELISA, the rapid test had a specificity of 97.70%, a sensitivity of 87.20%,a positive predictive value (PPV) of 57.82% and a negative predictive value (NPV) of 99.53%. In addition, when the HBs Ag rapid test was compared with PCR, the sensitivity was 44.50% and the specificity was 47.40%.
Conclusion: Our study concluded that rapid tests have high specificity and acceptable sensitivity compared to ELISA, but they are not sufficiently consistent when compared to PCR.

Keywords: ELISA; HBsAg; PCR; rapid test

Received: 21.03.2024; Accepted: 12.12.2024

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How to cite: Bilgin M, Taşkın HT, Mutlu Yılmaz E, Çekiç Cihan Ç. Comparison of rapid diagnostic test with enzyme-linked immunosorbent assay and PCR for detection of hepatitis B surface antigen. Ahi Evran Med J. 2025;9(1):92-97. DOI: 10.46332/aemj.1454307

INTRODUCTION

Hepatitis B virus (HBV) is an important public health problem that can cause chronic hepatitis infection, liver cirrhosis and hepatocellular carcinoma.[1,2] The World Health Organization (WHO) estimates that chronic HBV infection affects approximately 350 million people worldwide and plans to eliminate this infection, which is a public health problem, by 2030.[3] If this target is not achieved, annual global deaths due to HBV are predicted to increase by 39% from 2015 to 2030.[4] Laboratory confirmation of the diagnosis is necessary because it's impossible to distinguish hepatitis B from other viruses based on clinical symptoms alone.[4] Because HBV virus often causes asymptomatic infections, accurate detection of viral markers is very important in controlling the transmission of highly infectious HBV virus.[5] HBsAg is a crucial viral antigen that serves as a superior marker for detecting the Hepatitis B virus.[5] Several methods are employed to detect HBsAg, such as enzyme-linked immunosorbent assay (ELISA), enzyme immunoassays (EIA), Nucleic Acid Amplification Test (NAT), polymerase chain reaction (PCR), and immunochromatographic tests (ICT) in patient samples.[6] Enzyme-linked immunosorbent assay, EIA, PCR, and NAT methods are expensive and require technical human support, making them suitable for well-equipped laboratories. In contrast, rapid kits are cost-effective and can be used in basic laboratories.[6] The immunochromatographic method has the advantage of being quick and can be performed by minimally laboratory technician.[6]

HBsAg rapid test is a rapid screening method used for qualitatively detecting HBsAg in whole blood samples, serum, or plasma.[7] The clinical performance of rapid tests is currently limited due to their variable sensitivity and non-quantitative results.[8] The present study evaluated the performance of rapid screening tests with already confirmed cases with ELISA.

MATERIALS and METHODS

This study was conducted in a tertiary care hospital in Samsun in compliance with the Declaration of Helsinki from February 2024 to March 2024. Approval for this study was obtained from Samsun University Non-Interventional Research Ethics Committee (dated 28.02.2024 and numbered 2024/5/18).

Serum samples of the microbiology laboratory for HBsAg testing from various departments were included in the study.

Sample procedure: One hundred and sixty blood samples were included in this study; firstly all samples were centrifuged, and serum was separated. The samples were tested for HBsAg with Elisa then rapid test and PCR. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of rapid tests were compared with ELISA and PCR.

Procedure: The HBsAg rapid test device (ABON^{Tm} Abbott ABD) is a chromatographic immunoassay that detects HBsAg in blood, plasma, or serum. The working procedure was carried out as specified in the kits; add 3 drops of serum (approximately 75 µlt) into the sample wells of the test device, wait for 15 minutes for the colored line(s) to appear, and then read the test results visually without any instrument. The sensitivity and specificity of these assays were reported (by the manufacturer) as 99.3% (95%Cl:98.3%-99.68%) and 99.84% (95% Cl:99.63%-99.95%), respectively.

The ELISA technique was used for comparative evaluation. HBsAg detection was performed using the Architect i2000SR immunoassay analyzer (Abbott Laboratories, North Chicago, USA). The HBsAg Qualitative II test is a chemiluminescent microparticle immunoassay (CMIA) for the qualitative detection of Hepatitis B surface antigen (HBsAg) in human serum or plasma. The system calculates the result for the using the ratio of the sample RLU to the cutoff RLU (S/CO) for each specimen. Results were interpreted as <1.00 nonreactive and ≥1.00 reactive.

HBV DNA quantitation was performed using the Abbott RealTime HBV PCR assay (Wiesbaden, GERMANY) using nucleic acid amplification or signal amplification technologies to detect A-H genotypes according to the manufacturer's instructions. A highly conserved Surface gene was used to detect these genotypes. The HBV DNA level detected by this test with 95% probability was 10 IU/mL for a 0.5 mL sample.

Statistical Analysis

Statistical analysis were performed using SPSS v22 for Windows (IBM, IL, USA). The data for continuous variables were shown as mean±standard deviation, and categorical variables were shown with percent differences. To compare categorical values, the chi-square test was used. Additionally, to evaluate the sensitivity and specifity of the HBs Ag rapid test we performed Receiver operating characteristic (ROC) curve analysis.

Sample size calculation was determined using the G*Power 3.1.9.7 power analysis program. As a result of the analysis, it was determined that the total sample size was at least 134. (Test family: Chi-square test, Stastical test: Variance: Difference from constant (one sample case), Type of power analysis: Apriori: Compute required sample size- given α, power and effect size).

RESULTS

A total of 160 patients aged between 20 and 82 were included in our study. The average age of these patients was found to be 57.28±14.72. Of these patients, 65 (40.63%) were female and 95 (59.38%) were male. Blood samples of these patients were tested for HbsAg using ELISA and rapid test method. PCR was performed on 129 of the 141 patients whose HBs Ag were positive with Elisa. The HbsAg results with ELISA and rapid test and HBV DNA results with PCR are presented in Table 1. The highest HbsAg positivity rate was detected in the test performed according to the PCR method. The HbsAg positivity rate detected by the ELISA method was found to be statistically higher than the rate detected by the rapid diagnostic test ($p<0.001$). Since patients whose HbsAg test was negative by the ELISA method were not tested with the PCR method, no comparison could be made between the two methods. The HbsAg positivity rate detected by the PCR method was found to be statistically higher than the rate detected by the rapid diagnostic test ($p<0.001$) (Table 1).

We compared rapid antigen tests with ELISA for the detection of HBsAg from patient serum. The comparison of rapid tests with ELISA is shown in Table 2.

Table 1. Test results obtained with 3 different methods.

Methods	Positive n (%)	Negative n (%)
ELISA n=160	141 (88.13)	19 (11.88)
PCR n=129	122 (94.57)	7 (05.43)
Rapid test n=160	117 (73.13)	43 (26.88)

ELISA: Enzyme-Linked ImmunoSorbent Assay, PCR: Polymerase Chain Reaction

Table 2. Comparison of rapid test with ELISA.

Method		ELISA		Total
	Result	Positive n	Negative n	
Rapid test	**Positive n**	117	0	117
	Negative n	24	19	43
Total		141	19	160

ELISA: Enzyme-Linked ImmunoSorbent Assay

A total of 160 serums were performed with ELISA; 141 were HBsAg positive and 19 were HBsAg negative. Among the 141 samples with HBsAg seropositivity by ELISA, 117 showed positive results and 24 (17.02%) showed negative results by HBsAg rapid test, these are evaluated as false negative group. In the HbsAg positive group by ELISA, the HbsAg values ranged from 6 s/co to 7426 s/co. HBs Ag values of 141 positive samples are shown in Table 3.

Table 3. HBs Ag values of 141 positive samples.

HBsAg values (s/co) by ELISA	Number of patients positive with ELISA	Number of patients negative with rapid test
1-100 s/co	14 (9.93%)	13 (54.17%)
101-500 s/co	26 (18.44%)	10 (41.67%)
501-1000 s/co	10 (7.1%)	1 (4.16%)
≥ 1000 s/co	91 (64.53%)	-
Total	141 (100%)	24 (100%)

Upon examination of the ELISA values of 24 samples that tested negative with the rapid test, it was found that only one sample had a value of more than 500 s/co. The receiver-operating characteristic (ROC) curve analysis was used to evaluate the performance of the rapid test (Figure1)

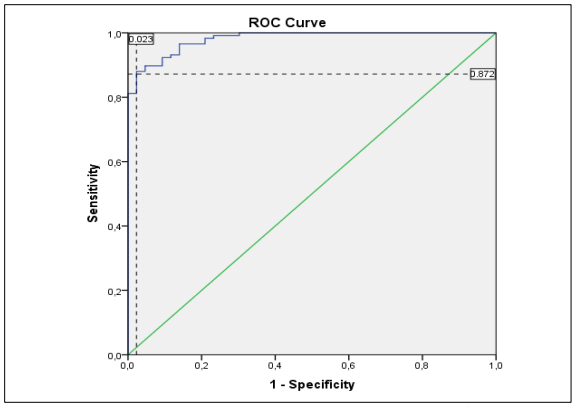

Figure 1. Receiver operating characteristic curve for HbsAg rapid test compared with ELISA.

According to the ROC analysis, the cut-off value of HbsAg positivity obtained according to the rapid test and the HbsAg test levels obtained according to the ELISA was determined to be 449.00 s/co. In addition as a result of ROC analysis, the area under the curve was found to be 0.981 (95% CI 0.966-0.997), the sensitivity was 87.20% and the specificity was 97.70%. However, the negative predictive value (NPV) of the rapid test was 99.53% (95%CI 99.27-99.70), and the positive predictive value (PPV) was 57.82% (95%CI 06.81-96.26).

Among the 141 samples with HBsAg seropositivity by ELISA, 129 were tested with PCR. PCR and rapid test results of these patients are shown in Table 4.

Table 4. Comparison of rapid test with PCR.

Method		PCR		Total
	Result	Positive n	Negative n	
Rapid test	**Positive n**	105	5	110
	Negative n	17	2	19
Total		122	7	129

PCR: Polymerase Chain Reaction

PCR was performed on 129 samples with positive Hbs Ag ELISA test. 122 were detected as positive and 7 as negative. 17 of 122 positive samples were detected as negative by rapid test. When these samples were examined, it was determined that the HBV DNA level of 15 of them were <100 IU/ml and 2 of them were between 100-200 IU/ml.

The correlation of HBV DNA level and HBsAg rapid test was evaluated using ROC analysis.

According to the ROC analysis, the cut-off value of HbsAg positivity obtained according to the rapid test and the HBV DNA levels obtained according to the PCR method was determined to be 21.50 IU/L. In addition, as a result of ROC analysis, the area under the curve was found to be 0.418 (95% CI 0.280-0.56), the sensitivity was 44.50% and the specificity was 47.40% (Figure 2).

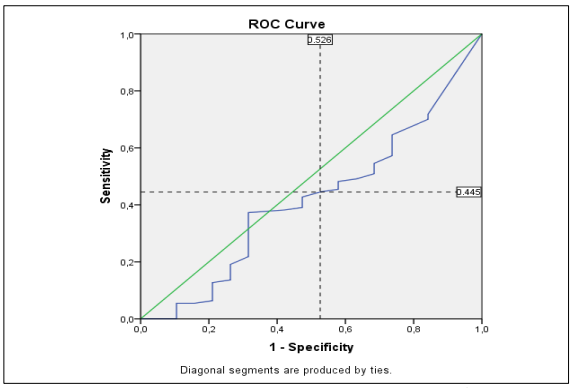

Figure 2. Receiver operating characteristic curve for HbsAg rapid test compared with PCR.

DISCUSSION

In our study, HBsAg rapid test was compared with ELISA and PCR fort the screening of HBs Ag. Since the 1990s, rapid tests have been available for the detection of anti-HIV, HBsAg, and anti-HCV.[10] The biggest problem for HBs Ag rapid test is to detect the low levels of the target antigen that are present in a relatively high proportion of asymptomatic carriers.[11] Therefore rapid tests are particularly required to have a high degree of sensitivity and acceptable level of specifity to reduce false results.

In this study, when the rapid test was compared with ELISA the sensitivity of the rapid test was 87.20% and the specificity was 97.70%. Several previous studies conducted globally have reported similar findings.[12,5] Lau et al. declared that although rapid immunochromatographic testing has several advantages EIA testing is the standard method for detecting HBsAg and HBe-Ag.[13] Similar to our study, Prabha P et al., have reported 83.4% sensitivity and 100% specificity of rapid screening test.[5] Yogendra T et al. reported that sensitivity was 95.12% and specificity was 99.82%.[14] Another study showed 96.8% sensitivity of rapid test kit with a specificity of 99.7% for HBsAg as compared to ELISA and PPV was calculated to be 98.41% and NPV was 99.56%.[15] PPV refers to the ability of an assay to accurately detect infected individuals among all those who test positive with

the kit. NPV measures the ability of an assay to accurately identify non-infected individuals who test negative with the kit being used.[16] In our study, the rapid test had a negative predictive value of 99.53% and a positive predictive value of 57.82%. Due to the high number of HBsAg-positive samples in this study, we observed a higher rate of false negatives which resulted in a lower positive predictive value (PPV) when compared to other studies. In our study, 17.02% of HBsAg-positive samples had negative results in rapid tests, and these false negatives can lead to misdiagnosis and delay in treatment, which can have serious consequences. According to ROC analysis, HBsAg positivity may not be detected by the rapid test if the HBs Ag value is less than 449 s/co with ELISA. It is important to be aware of the limitations of rapid tests and to confirm any negative results with follow-up testing to ensure accurate diagnosis and timely treatment.

Comparisons of the sensitivity and specificity of rapid tests and quantitative immunoassays to detect HBsAg have been performed by many researchers, but few comparative studies are using the quantitative PCR method as the gold standard.[6] In a study conducted by Navvabi et al., the results of two tests, the HBs-Ag rapid test, and the ELISA test were compared with the PCR test. The HBs Ag rapid test showed a sensitivity of 97% and a specificity of 91%, while the ELISA test showed a sensitivity of 78% and a specificity of 76%.[17] In a study by Mohammad Hassan Khadem Ansari et al., six commonly used rapid diagnostic tests were evaluated for their sensitivity and specificity, compared with PCR methods and they reported that immunochromatographic results must be interpreted with caution because samples with low reactivity in quantitative PCR may show negative HBsAg results.[6] In our study, we also compared the rapid test with the PCR method and the rapid test has a sensitivity of 44.50% and a specificity of 47.40%. While these figures provide some indication of the test's reliability, they also suggest that rapid tests may fail to detect of HBsAg in cases where the HBV DNA level is below 21.50 IU/L.

When we compared the results of ELISA and PCR tests, we found that out of the 141 sera that were detected positive by ELISA, 129 were retested with PCR and 7 of them were negative with PCR. Due to these results, sensitivity and specificity were lower when we compared the rapid test with PCR.

However, this study had some limitations. Firstly, due to patients being unreachable or missing hospital appointments, HBV DNA quantification was not performed on all patients, resulting in a relatively small sample size. Secondly, there was a lack of knowledge regarding the patients' treatments and follow-up.

Conclusion

Our study concluded that rapid tests have high specificity and acceptable sensitivity compared to ELISA, but are not compatible enough when compared to PCR. Although in some situations where large groups of people are being screened, false positives are often preferred over false negatives, it is crucial to conduct further studies that can demonstrate the effectiveness of rapid tests in various populations and geographic locations. Only by ensuring the reliability and accuracy of these tests can we use them confidently to diagnose medical conditions. Rapid tests are simple and rapid screening methods that offer comparable sensitivity and specificity to the ELISA. But it should not be forgotten that false negatives can lead to misdiagnosis and delay in treatment.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

Approval for this study was obtained from Samsun University Non-Interventional Research Ethics Committee (dated 28.02.2024 and numbered 2024/5/18).

Authors' Contributions

Concept/Design: MB, MHT, EMY, CÇC. Data Collection and/or Processing: MB, MHT, EMY, CÇC. Data analysis and interpretation: MB, MHT, EMY, CÇC. Literature Search: MB, CÇC. Drafting manuscript: MB, MHT. Critical revision of manuscript: CÇC, EMY.

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BİLİMSEL ARAŞTIRMA MAKALESİ

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Konuşma ve Dil Bozukluğu Olan Çocuk ve Ergenlerde Sosyodemografik, Prenatal ve Postnatal Özellikler

Sociodemographic, Prenatal and Postnatal Characteristics of Children and Adolescents with Speech and Language Disorders

İfakat Şule KORKMAZ[1] Esra HOŞOĞLU[1] Serdar KARAKULLUKÇU[2] Bahadır TURAN[1]

ÖZ

Amaç: Bu çalışmada, konuşma ve dil bozukluğu olan çocuk ve ergenlerle sağlıklı bireylerin sosyodemografik, prenatal ve postnatal özellikleri karşılaştırılarak, konuşma ve dil bozuklukları için risk faktörlerinin belirlenmesi amaçlanmaktadır.
Araçlar ve Yöntem: Çalışmada 01.01.2023-31.12.2023 tarihleri arasında tarafımıza başvuran, konuşma ve dil bozukluğu tanısı konulan 3-17 yaş arası olgular ile sağlıklı kontrollerden oluşan 1299 kişilik örneklem üzerinde gerçekleştirilmiştir. Olgu grubunda 76, kontrol grubunda 43 çocuk ve ergen çalışmaya dahil edilme kriterlerini karşılamış ve bu katılımcıların sosyodemografik, prenatal ve postnatal özelliklerini içeren veriler analiz edilmiştir.
Bulgular: Sosyodemografik veriler açısından iki grup arasında anlamlı fark bulunmadı. Prenatal faktörlerden gebelikte demir takviyesi kullanımı olgu grubunda anlamlı derecede yüksek bulundu (p=0.02). Postnatal faktörlerden ise sadece okul öncesi eğitim alma sıklığı kontrol grubunda anlamlı derecede yüksek bulundu (p=0.012).
Sonuç: Dil ve konuşma gelişimi, biyolojik ve çevresel faktörlerden etkilenen ve anne karnında başlayıp hayatın ilk yıllarda hızla devam eden bir süreçtir. Bu gelişimi olumsuz etkileyen faktörlerin erken tespiti ve önlem alınması büyük önem taşımaktadır. Çalışmamız, okul öncesi eğitimin bu gelişim için önemli olduğunu göstermektedir.

Anahtar Kelimeler: dil bozukluğu; konuşma bozukluğu; risk faktörleri; okul öncesi eğitim

ABSTRACT

Purpose: This study aims to identify risk factors for speech and language disorders by comparing the sociodemographic, prenatal, and postnatal characteristics of children and adolescents with speech and language disorders to those of healthy individuals.
Materials and Methods: Our study was conducted on a sample of 1.299 individuals aged 3-17 years, consisting of cases diagnosed with speech and language disorders and healthy controls, who applied to our clinic between 1January 2023, and 31 December 2023. In the case group, 76 children and adolescents, and in the control group, 43 children and adolescents met the inclusion criteria. The data including the sociodemographic, prenatal, and postnatal characteristics of these participants were analyzed.
Results: There was no significant difference between the two groups in terms of sociodemographic data. Prenatal factors showed a significantly higher frequency of maternal iron supplementation during pregnancy in the patient group (p=0.02). Postnatal factors showed a significantly higher frequency of preschool education attendance in the control group (p=0.012).
Conclusion: Language and speech development is a process influenced by biological and environmental factors, starting in the womb and rapidly continuing during the early years of life. Early detection and intervention of factors that negatively affect this development are crucial. Our study demonstrates that preschool education is important for this development.

Keywords: language disorders; preschool education; risk factors; speech disorder

Gönderilme tarihi: 08.08.2024; Kabul edilme tarihi: 27.12.2024

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Makaleye atıf için: Korkmaz İŞ, Hoşoğlu E, Karakullukçu S, Turan B. Konuşma ve dil bozukluğu olan çocuk ve ergenlerde sosyodemografik, prenatal ve postnatal özellikler. Ahi Evran Med J. 2025;9(1):98-107. DOI: 10.46332/aemj.1530372

GİRİŞ

Konuşma ve dil, insan deneyiminin merkezinde yer alır; bilgiler, düşünceler, duygular ve diğer içsel deneyimlerin algılanmasını ve iletilmesini sağlar. Konuşma ve dil becerilerinin kazanımı yaşamın ilk yıllarından itibaren başlar ve bu beceriler sosyal etkileşimler ve ilişkilerde yer alma yeteneğinin temellerini oluşturur. Bu becerilerle çocuk toplumda ve eğitim ortamında bilgi edinme süreçlerine aktif katılım sağlar.[1] Bu nedenle bir çocuğun sağlıklı ruhsal gelişimi için bu becerilerin zamanında kazanılması önemlidir.

Konuşma ve dil bozuklukları, bir çocuğun yaşına uygun olarak beklenen konuşma ve dil becerilerinin gelişmemesi olarak tanımlanabilir.[2,3] Konuşma ve dil alanında yaşanan sorunların türüne göre bu bozukluklar çeşitli şekillerde sınıflandırılmakta olup çocukluk çağında en sık kullanılan sınıflamalardan biri Mental Bozuklukların Tanısal ve İstatistiksel El Kitabı, Beşinci Baskıda (The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5)) yer alan sınıflamadır. Bu bozukluklar DSM 5'te "Nörogelişimsel Bozukluklar" kapsamında değerlendirilmekte olup, dili anlamada ve ifade etmede yetersizliklerle giden durumlar "Dil Bozukluğu"; kişinin yaşına, kültürüne ve içinde bulunduğu gelişim dönemine uygun sesler çıkaramaması ve ses uyumunun bozuk olması ile karakterize durumlar "Konuşma Sesi Bozukluğu"; kişinin etkili bir şekilde iletişim kurma kapasitesini engelleyen, konuşmanın istemsiz olarak kesintiye uğradığı durum ise "Çocukluk Çağı Akıcılık Bozukluğu (Kekemelik)" olarak tanımlanmaktadır.[3]

Konuşma ve dil bozuklukları çocukluk çağında en sık görülen nörogelişimsel psikiyatrik durumlardan biridir.[2] Dil bozukluklarının genel prevelansının %3-8, konuşma sesi bozukluğunun çocuklarda en az %3 ve kekemeliğinde çocuklarda %8-11 sıklıkta olduğu bildirilmektedir.[2,4,5] Konuşma ve dil bozuklukları erkeklerde kızlara oranla daha sık görülmektedir.[2] Bu bozukluklar kişide yalnız iletişimi değil, aynı zamanda konuşma ve dil becerilerine bağlı olan okuma, yazma ve ilişkili akademik becerileri de etkilemekte ve düşük benlik algısı, sosyal izolasyon ve duygusal sorunlar gibi olumsuz sonuçlara neden olabilmektedir.[1,2] Yapılan araştırmalar genel olarak tedavi alındığında, özellikle erken müdahale grubunda olmak üzere konuşma ve dil bozukluklarının iyi gidişat gösterdiğini bildirmektedir.[2] Bu nedenle bu bozuklukların erken tanı ve tedavisi önem taşımaktadır.

Konuşma ve dil bozukluklarının etiyolojisine ilişkin faktörler tam olarak aydınlatılamamış olmakla birlikte genetik ve çevresel faktörlerin bir arada rol oynadığına ilişkin kanıtlar bulunmaktadır.[2] Konuşma ve dil gelişimini çeşitli sosyokültürel, prenatal ve postnatal faktörlerin olumsuz etkilediği ve bu bozukluklar açısından risk oluşturduğu düşünülmektedir.[6-10] Sosyodemografik faktörler, bireylerin yaşadığı sosyal ve ekonomik çevre ile doğrudan ilişkilidir. Ebeveynlerin eğitim seviyesi, sosyoekonomik düzey (SED) in ve kardeş sayısının konuşma ve dil gelişimi ile ilişkili olduğu gösterilmiştir.[6-8] Prenatal dönemde fetusun beyin gelişimini etkileyebilecek olan birçok etmen ilerleyen yıllardaki bilişsel sosyal ve dil alanındaki sorunlarla ilişkili olabilmektedir.[11] Prenatal dönemde maternal stres düzeyi ve nütrisyonel özellikler konuşma ve dil bozukları ve diğer nörogelişimsel bozukluklar için risk oluşturabilmektedir.[11-13] Hayatın ilk ayları ve yılları beyin gelişiminde önemli bir yere sahiptir. Bu dönemde yaşanan sorunlar çocukların nörogelişimsel özelliklerini etkileyebilmektedir.[2,14] Prematürite, düşük doğum ağırlığı, doğum sırasında yaşanan komplikasyonlar, ekran maruziyeti, uyaranın az olması gibi postnatal faktörlerin de konuşma ve dil gelişimiyle ilişkili olabileceği gösterilmiştir.[15-17]

Bu çalışmada, konuşma ve dil bozukluğu tanısı olan çocuk ve ergenlerle sağlıklı kontrollerin sosyodemografik, prenatal ve postnatal dönem özelliklerinin karşılaştırılması amaçlanmaktadır. Böylece konuşma ve dile özgü gelişimsel bozukluklar için ayrımlaşan olası risk faktörlerinin belirlenmesi hedeflenmektedir. Risk faktörlerinin belirlenmesinin, erken tanı ve müdahale stratejilerinin geliştirilmesi açısından kritik bir öneme sahip olduğu düşünülmektedir.

ARAÇLAR ve YÖNTEM

Bu çalışma için Karadeniz Teknik Üniversitesi Tıp Fakültesi Bilimsel Araştırmalar Etik Kurulu'ndan onay alındı (06/05/2024 tarih ve 20 sayılı).

Katılımcılar

01.01.2023- 31.12.2023 tarihleri arasında, Karadeniz Teknik Üniversitesi Tıp Fakültesi Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları polikliniklerine başvuran, DSM 5'e göre konuşma ve dil bozukluğu tanısı alan 3-17 yaş aralığında 76 çocuk olgu grubu çalışmaya dahil edilmiştir. Otizm Spektrum Bozukluğu tanısı olan ve yaşadığı konuşma sorunları bilişsel gelişimde gecikme ile açıklanabilecek hastalar çalışmaya dahil edilmemiştir. Bilinen düzeltilmemiş herhangi görme ya da işitme kusuru olan hastalar, yarık damak dudak gibi anatomik bozuklukları bulunan ve bu nedenle konuşma ve dil bozuklukları gelişen hastalar da çalışma dışında tutulmuştur. Olgu grubundaki hastalara geriye yönelik olarak sistemden ICD F80.0 (Artikülasyon bozukluğu), F80.1 (Ekspressif dil bozukluğu), F80.2 (Reseptif dil bozukluğu), F80.8 (Konuşma ve dile ait diğer gelişimsel bozukluklar), F80.9 (Gelişimsel konuşma ve dil bozuklukları, tanımlanmamış) ve F98.5 (Kekemelik) tanı kodları taratılarak ulaşılmıştır.

Kontrol grubu için de aynı tarih aralıklarında ICD Z00.4 (Genel psikiyatrik muayene, başka yerde sınıflanmamış) tanı koduyla tarafımızca değerlendirilen olgular hasta grubuyla yaş ve cinsiyet açısından eşleştirilerek rastgele seçilmiş, DSM 5'e göre psikiyatrik bir tanısı ve kronik hastalığı ve görme ya da işitme kusuru olmayan olgular dahil edilmiştir.

Geriye yönelik sistem incelemesi için hastane başhekimliğinden izin alınarak hastaların dosya numaralarına bilgi işlem aracılığı ile ulaşılmıştır. Bu kapsamda toplam 3-17 yaş aralığındaki 1299 hastanın verileri geriye dönük olarak incelenmiştir. Olguların dosya kayıtları incelenerek veri formu doldurulmuştur. Her iki grupta da eksik verileri olan olgular çalışmaya dahil edilmemiştir.

Gereçler

Araştırmacı tarafından geliştirilen veri formu aracılığıyla sosyodemografik özellikler (çocuğun cinsiyeti, yaşı, anne babanın eğitim durumu, kardeş sayısı, SED gibi), prenatal (gebelikte psikososyal stres faktörü, düşük tehlikesi gibi) ve postnatal (doğum ağırlığı, doğum zamanı gibi) özelliklere ilişkin veriler kaydedilmiştir.

İstatistiksel Analiz

SPSS 23.0 kullanılarak istatistiksel analiz yapıldı. Araştırma verilerinin istatistiksel değerlendirilmesinde sürekli degişkenlerin dağılımının normal dağılıma uyup uymadığı Kolmogorov-Smirnov ve Shapiro-Wilks testleriyle değerlendirildi, normal dağılım varsayımları sağlanmadığından gruplar arası karşılaştırmalarda Mann-Whitney U testi kullanıldı. Kategorik nitelikte olan değişkenlere ait karşılaştırmalarda ise Pearson ki-kare ve Fisher'in kesin ki-kare testleri kullanıldı. İstatistiksel önemlilik $p<0.05$ olarak kabul edildi.

BULGULAR

Çalışmamızda dahil edilme kriterlerini karşılayan olgu grubu olarak 76 ve kontrol grubu olarak 43 kişinin verileri analiz edildi. Olgu grubunda yer alan çocuk ve ergenlerin %52'sinde dil bozukluğu, %30'unda kekemelik ve %17'sinde konuşma sesi bozukluğu tespit edildi. Olgu grubunun yaş ortalaması 66.12 (±33.29) ve kontrol grubunun 65.95 (±16.28) aydı ($p=0.18$). Olgu grubunun %73.7'si (n=56) erkek, %26.3'ü (n=20) kız ve kontrol grubunun %74.4'ü (n=32) erkek, %25.6'sı (n=11) kızdı ($p=0.93$). İki grubun anne ve baba yaşları, anne ve baba öğrenim durumları, aile yapısı, ekonomik durumu, kardeş sayısı ve evde yaşayan kişi sayısı karşılaştırıldığında gruplar arasında anlamlı fark bulunmadı ($p>0.05$) (Tablo1).

Prenatal faktörler değerlendirildiğinde iki grup arasında gebelikte psikososyal stresörlere maruziyet, düşük tehlikesi, herhangi bir sağlık sorunu ve multivitamin ve/veya folik asit kullanımı arasında anlamlı fark bulunmadı ($p>0.05$). Ancak gebelikte demir takviyesi kullanım oranı olgu grubunda anlamlı olarak yüksek bulundu ($p=0.02$). Prenatal özellikler ayrıntı bir şekilde Tablo 2'te yer almaktadır.

Postnatal özellikler değerlendirildiğinde ise prematüre doğum oranı, düşük doğum ağırlığı oranı, doğum sonrası kuvöz bakımı, ikter, asfiksi ve mekonyum aspirasyonu öyküsü açısından iki grup arasında anlamlı fark bulunmadı ($p>0.05$). Gelişim basamaklarında yürüme zamanı açısından iki grup arasında anlamlı fark saptanmazken, tek kelime kullanmaya başlama yaşının olgu grubunda

anlamlı olarak yüksek olduğu bulundu (p=0.001). İki grup arası ekran süresi açısından anlamlı fark bulunmadı (p>0.05). Kontrol grubunda okul öncesi eğitim alma sıklığı olgu grubuna göre anlamlı derecede yüksekti (p=0.012). Postnatal özellikler ayrıntı bir şekilde Tablo 3'te yer almaktadır.

Tablo 1. Katılımcıların ve ailelerin sosyodemografik özellikleri.

Değişkenler	**Olgu (n=76**	**Kontrol (n=43)**	**Test değeri** **P değeri**
Çocuğun yaşı (ay)	66.12 (±33.29)	65.95 (±16.28)	U=1393[ǂ] p=0.18
Cinsiyet			
Erkek	56 (%73.7)	32 (%74.4)	X2=0.008[*]
Kız	20 (26.3)	11 (%25.6)	p=0.93
Annenin yaşı (yıl)	34.33 (±5.2)	35.07 (±5.4)	U=840[ǂ] p=0.70
Babanın yaşı (yıl)	37.75 (±5.6)	38.76 (±6.7)	U=790[ǂ] p=0.73
Anne öğrenim			
İlkokul n(%)	13 (%20.0)	6 (%14.0)	X2=3.896[**]
Ortaokul n(%)	8 (%12.3)	4 (%9.3)	p=0.58
Lise n(%)	18 (%27.7)	14 (%32.6)	
Ön lisans n(%)	7 (%10.8)	6 (%14.0)	
Lisans n(%)	19(%29.2)	11 (%25.6)	
Yüksek lisans n(%)	0 (%0.0)	2 (%4.7)	
Baba öğrenim			
İlkokul n(%)	13 (%20.3)	6 (%14.0)	X2=6.987[**]
Ortaokul n(%)	8 (%12.5)	6 (%14.0)	P=0.20
Lise n(%)	20 (%31.3)	8 (%18.6)	
Ön lisans n(%)	3 (%4.7)	3 (%7)	
Lisans n(%)	20 (%31.3)	17 (%39.5)	
Yüksek lisans n(%)	0 (%0.0)	0 (%0.0)	
Aile yapısı			
Çekirdek aile ile n(%)	67 (%88.2)	39 (%90.7)	X2=5.364[**]
Geniş aile ile n(%)	3 (%3.9)	3 (%7.0)	P=0.19
Anne ile n(%)	5 (%6.6)	0 (%0.0)	
Baba ile n(%)	0 (%0.0)	0 (%0.0)	
Akraba ile n(%)	1 (%1.3)	0 (%0.0)	
Sosyoekonomik düzey			
Düşük n(%)	14 (%18.4)	4 (%9.3)	X2=2.225[*]
Orta n(%)	51 (%67.1)	34 (%79.1)	P=0.32
Yüksek n(%)	11 (%14.5)	5 (%11.6)	
Kardeş sayısı	2.18 (±0.9)	2.19 (±0.8)	U=1631[ǂ] P=0.98
Evde yaşayan kişi sayısı	4.16 (±1.0)	4.21 (±0.7)	U=1540.5[ǂ] P=0.58

[*]Pearson Chi-Square , [**]Fisher'in kesin ki-kare testi, [ǂ]Mann-Whitney U testi

Tablo 2. Olgu ve vaka gruplarının prenatal risk faktörlerinin dağılımı.

Değişkenler	**Olgu** **n:76**	**Kontrol** **N:43**	**Test değeri** **P değeri**
Gebelikte psikososyal stres faktörü	2 (%2.6)	0 (%0.0)	X^2=1.151[**] P=0.53
Düşük tehlikesi	5 (%6.6)	2 (%4.7)	X^2=0.184[**] P=1.00
Gebelikte annede sağlık sorunu	8 (%10.5)	0 (%0.0)	X^2=4.853 P=0.05
Gebelikte multivitamin/folik asit kullanımı	30 (%39.5)	16 (%37.2)	X^2=0.059[*] P=0.84
Gebelikte demir kullanımı	23 (%30.3)	5 (%11.6)	X^2=5.300[*] **P=0.021**

[*]Pearson Chi-Square , [**]Fisher'in kesin ki-kare testi

Tablo 3. Olgu ve vaka gruplarının postnatal risk faktörlerinin dağılımı.

Değişkenler	**Olgu n:76**	**Kontrol n:43**	**Test değeri P değeri**
Prematüre doğum	12 (%15.8)	6 (%13.9)	X^2=0.005* P=0.94
Düşük doğum ağırlığı	8 (%10.5)	8 (%18.6)	X^2=1.540* P=0.21
Asfiksi öyküsü	4 (%5.3)	1 (%2.3)	X^2=0.589** P=0.65
Mekonyum aspirasyonu öyküsü	1 (%1.3)	0 (%0.0)	X^2=0.571** P=1.00
Doğum sonrası kuvöz öyküsü	16 (%21.1)	9 (%20.9)	X^2=<0.001* P=0.98
İkter öyküsü	10 (13.2)	7 (%16.3)	X^2=0.218* P=0.64
Desteksiz yürüme (ay)	13.36 (± 3.95)	12.16 (± 2.39)	U=1315.5ǂ P=0.12
Tek kelime kullanımı (ay)	19.46 (± 4.45)	12.86 (± 9.04)	**U=812.5ǂ P<0.001**
Ekran süresi (dk)	177.78 (± 102.89)	170.76 (± 93.13)	U=390.5ǂ P=1.00
Okul öncesi eğitim	29 (%38.7)	27 (%67.2)	X^2=6.379* **P=0.012**

*Pearson Chi-Square ,**Fisher'in kesin ki-kare testi, ǂMann-Whitney U testi

TARTIŞMA

Çalışmamızda konuşma ve dil bozukluğu olan çocuk ve ergenlerin sosyodemografik prenatal ve postnatal özellikleri sağlıklı kontrollerle karşılaştırılmıştır. Sosyodemografik özellikler açısından anlamlı bir fark bulunamamıştır. Ancak olgu grubunda erkek cinsiyet kız cinsiyete göre daha yüksekti, kontrol grubunun toplanmasında cinsiyet açısından eşitleme yapılarak toplandığı için iki grup arasında fark bulunmamıştır. Prenatal özelliklerden demir kullanımının olgu grubunda daha fazla, postnatal özelliklerde ise okul öncesi eğitime gitme sıklığının sağlıklı kontrollerde daha fazla olduğu bulunmuştur.

Literatürdeki çalışmalar genel olarak erkek cinsiyetin konuşma ve dil gelişiminde sorunlar için risk faktörü olduğu bildirilmektedir.[6-8] Erkeklerin fizyolojik gelişimlerinin nispeten daha yavaş olması ve nörolojik hastalıklara karşı daha duyarlı olmalarının bu duruma neden olabileceği düşünülmektedir.[6] Literatürle tutarlı olarak olgu grubu popülasyonumuzda erkek çoğunluğu dikkat çekmektedir. Özellikle erkek çocukların dil ve konuşma gelişimi açısından takip edilmesi önemli görülmektedir.

Ebeveynler özellikle hayatın ilk yıllarında çocuklara gerekli uyaran ortamını sağlayarak gelişimlerini etkilerler.[18] Özellikle anneye ilişkin özelliklerin çocukların dil gelişimiyle ilgili olduğu düşünülmektedir.[7] Çalışmamızda iki grup arasında anne yaşı açısından anlamlı bir fark bulunmamıştır. Yaşça daha büyük olan annelerin çocuklarına karşı daha özgüvenli ve duyarlı olmaları ve bunun sonucunda daha iyi dil uyarımı sağlamaları nedeniyle ileri anne yaşının konuşma ve dil bozuklukları için koruyucu olabileceğini bildiren görüşler vardır.[7,9] Ancak çalışmalar bu konuda farklı sonuçlar içermektedir. Diepeveen ve ark. dil bozukluğu olan çocukların annelerinin daha genç yaşta olduğunu bildirmiştir.[9] Pan ve ark. ise anne yaşının 2 yaşındaki çocuklar dil gelişimiyle anlamlı bir ilişkisi olmadığını bildirmiştir.[19] Westerlund ve ark. genç anne yaşıyla ifade edici kelime bilgisi arasında pozitif bir ilişki olduğunu bildirmiş ve bu durumun daha genç annelerin çocuklarıyla gurur duymaya daha istekli olabilecekleri ve çocuklarında ilerleme belirtilerini daha istekleri arayabilecekleriyle ilişkili olduğunu öne sürmüşlerdir. Aynı çalışmada çocuklara kitap okuma düzeyinin dil gelişimini olumlu yönde etkilediği ve ileri yaş annelerin çocuklarına daha fazla kitap okudukları da bulunmuştur.[7] Tüm bu bulgular anne yaşıyla dil gelişimi

arasındaki ilişki çok faktörlü ve karmaşık olabileceğini düşündürtmektedir.

Ebeveynlerin eğitim düzeylerinin de dil gelişimini etkilediği düşünülmektedir. Yapılan çalışmalar genel olarak anne eğitim düzeyi ile dil gelişimi arasında pozitif bir ilişki olduğunu gösterilmiştir.[6,7] Yüksek eğitim düzeyine sahip annelerin çocuklarıyla daha fazla ilgileneceği ve onlara daha fazla uyaran sağlayacağı düşünülmektedir.[7] Ancak çalışmamızda gruplar arasında anne eğitim düzeyi açısından anlamlı bir fark tespit edilmemiştir. Çalışmamızla benzer şekilde Prathanee ve ark. dil gelişimi ile anne eğitimi arasında anlamlı bir ilişki bulamamışlar.[8] Annenin çocuğa vereceği uyaran miktarının sadece eğitim düzeyiyle ilişkili olmayabilir. Anne eğitim düzeyinin dil ve konuşma gelişimi üzerine etkisini daha kapsamlı değerlendiren çalışmalara ihtiyaç olduğu görülmektedir.

SED çocukların potansiyellerini gerçekleştirebilmeleri için uygun çevresel şartların sağlanmasında önemli bir faktör olarak düşünülmektedir. Düşük SED'in toksinlere daha çok maruz kalma, yeterli şekilde beslenememe, tıbbi bakım almadaki yetersizlikler, ebeveyn çocuk iletişiminde ortaya çıkan sorunlar (ebeveynlerin stres düzeyi çocuklarına daha az sosyal ve bilişsel uyaran vermelerine neden olabilir), anne eğitim düzeyi ve çocuğa yönelik konuşma miktarının az olması gibi sebeplerden dolayı konuşma ve dil gelişiminde geriliklerle ilişkili olabileceği öne sürülmüştür.[10] Ancak çalışmamızda iki grup arasında SED açısından anlamlı bir fark bulunmamıştır. Çalışmamızla benzer şekilde Prathanee ve ark. SED ve dil gelişimi arasında anlamlı bir ilişki tespit edememişlerdir.[8] Çalışmamızda ailelerin SED'lerine ilişkin veriler bize başvurdukları tarihlerde alınmıştır. Örneklemimizin yaş ortalamaları olgu grubu için 66.12 (±33.29) ve kontrol grubu için 65.95 (±16.28) aydı. Ailelerin mevcut SED'i çocuğun dil gelişiminde önemli bir yeri olan bebeklik ve erken çocukluk dönemindeki SED'i yansıtmayabilir. Bu durum fark tespit edilmemesine neden olmuş olabilir.

Çocuk sayısının fazla olmasının annenin çocukla birebir etkileşimini azaltabilecek olası nedeniyle dil ve konuşma gelişimini olumsuz etkileyeceği düşünülmektedir.[8] Özellikle ilk çocukların dil gelişimi açısından daha fazla uyaran almalarından dolayı ilk çocuk olmanın dil ve konuşma bozuklukları açısından koruyucu olduğu öne sürülmüştür.[7,9] Çalışmamızda kardeş sayısı açısından gruplar arası anlamlı bir fark bulunmamıştır. Katılımcıların kaçıncı çocuk oldukları çalışmamız verileri içinde bulunmamaktadır. Kardeş sayısından ziyade kaçıncı çocuk oldukları dil gelişiminde daha etkili bir faktör olabilir.

Gebelikteki stres annede hipolamohipofizer aksı etkileyerek stres hormonlarının salınmasına neden olur. Bu hormonlar plasenta aracılığı ile fetusa geçerek fetusun beyin gelişimini etkileyebilir. Gebelikte strese maruz kalan annelerin çocuklarında ilerleyen yıllarda nörogelişimsel sorunların gözlendiği gösterilmiştir.[11] Çalışmamızda annenin gebelikte psikososyal stres faktörü varlığı ve düşük riski (annede oluşturacak stres üzerinden etki edebilir) açısından gruplar arası anlamlı fark bulunamamıştır. Çalışmamızda yer alan gebelik döneminde stresör olay varlığına ilişkin veriler sözel olarak alınmış olup annelerin söz konusu stresör yaşam olaylarındaki stres düzeylerinin derecelendirilmesi için standardize bir ölçüm aracı kullanılmamıştır. Gebelikte stres düzeyini kortizol düzeyi gibi daha objektif verilerle değerlendiren çalışmalarla daha güvenilir sonuçlar elde edilebilir.

Gebelikte annenin yeterli beslenmesi gerekli mineral ve vitaminleri alması sadece gebeliğin sağlıklı sürmesi için de fetusun beyin gelişimi içinde önemlidir.[12] Dünya Sağlık Örgütü gebelikte folik asit ve demir desteğini önermektedir.[20] Folat, nükleik asit sentezi ve DNA metilasyon süreçlerinden sorumlu tek karbon metabolizmasında önemli bir yardımcı faktördür ve yetersiz folat alımı, nöral tüp defektleri gibi fetal beyin gelişimindeki anormalliklerle ilişkilidir.[21] Gebelikte folik asit takviyesinin çocukların dil gelişiminde olumlu etki ettiğini gösteren çalışmalar bulunmasına rağmen fazla folik asit kullanımının dil gelişimini olumsuz etkileyebileceği de bildirilmiştir.[12,13] Çalışmamızda gebelikte folik asit kullanımı varlığı sorulmuş olup, miktarı değerlendirilmemiştir. Anne folik asit düzeyi ve takviye miktarını da değerlendiren çalışmalarla bu konu da daha güvenilir bilgiler edinilebilir. Hamilelik sırasında, fetal plasenta ünitesinin ihtiyaçlarını karşılamak için demire olan talep artar. Bu nedenle gebelere demir takviyesi önerilir. Demir bebeğin beyin gelişimi ve bilişsel işlevleri için çok önemlidir ve serebellumda miyelinizasyon, hipokampüs gelişimi ve

nörotransmitter sentezi gibi süreçlerde kritik bir rol oynar.[22] Nörogelişimsel sorunların annedeki demir eksikliğiyle ilişkili olduğunu gösteren yayınlar mevcuttur.[23] Çalışmamızda demir kullanımı olgu grubunda daha yüksek olarak bulunmuştur. Annelerin takviye öncesi kan demir düzeylerini ve aldıkları demir takviyesi miktarlarını bilmememiz bulgularımızı yorumlamamızı zorlaştırmaktadır. Demir düzeylerinin değerlendirildiği gelecek çalışmalar daha güvenilir bilgilerin edinilmesini sağlayacaktır.

Postnatal faktörlerden doğum ve doğum sonrası özellikleri değerlendiren çalışmalar çelişkili sonuçlar içermektedir. Prathanee ve ark. düşük doğum ağırlığının dil gelişiminde en önemli prediktörlerinden biri olduğunu bildirmişlerdir.[8] Stanton-Chapman ve ark. düşük doğum ağırlığının dil gelişimini olumsuz etkilediğini, gestasyonel yaş ile dil becerileri arasında anlamlı bir ilişki olmadığını bildirmiştir.[17] Toblin ve ark. ise dil boz ile düşük doğum ağırlığı doğumun süresi, doğum ve doğum komplikasyonları arasında anlamlı bir ilişki tespit edememişlerdir.[24] Bir başka çalışmada ise perinatal ve neonatal özelliklerin dil bozukluğu için tek tek risk faktörü olmadıklarını ancak kümülatif etkiyle risk faktörü olabilecekleri bildirilmiştir.[16] Diepeveen ve ark. ise perinatal faktörlerden 5. dakikadaki APGAR skoru dışında diğer özelliklerin dil bozukluğu ile ilişkili olmadığını bulmuştur. APGAR skoru beyin olgunlaşmamışlığının veya bozukluğunun göstergelerinden biri olabileceğini bu nedenle ilerleyen zamanlarda görülen gelişimsel bozukluklar için bir prediktör kullanılmasıyla ilgili çalışmaların yapılabileceğini öner sürmüşlerdir.[15] Çalışmamızda APGAR skoru değerlendirilmemiştir. Prematüre doğum, düşük doğum ağırlığı, asfiksi, mekonyum aspirasyonu, doğum sonrası kuvöz öyküsü ve ikter öyküsü açısından ise iki grup arasında anlamlı fark bulunamamıştır. Doğum sırasında gerçekleşen olumsuz olayların çocuğun genel bilişsel gelişimini olumsuz yönde etkilediği bildirilmektedir.[24] İngiltere'de yapılan geniş kapsamlı bir epidemiyolojik çalışmada, 7 yaşındaki 11.889 çocukta prenatal ve postnatal dönemde yaşanan komplikasyonlarla (düşük doğum ağırlığı (DDA), muhtemel hipoksi-iskemik komplikasyonlar ve kronik hipoksi) mevcut nöropsikolojik işlevselliğin (akademik başarı becerileri, sözel-kavramsal yetenekler ve algısal-motor yetenekler) ilişkisi değerlendirilmiştir. Yapılan değerlendirmede, üç komplikasyon türünün de çeşitli karıştırıcılar kontrol edildikten sonra daha düşük nöropsikolojik performansla anlamlı bir şekilde ilişkili olduğu ve DDA'nın nöropsikolojik performansla en güçlü ilişkiye sahip olduğu bulunmuştur.[25] Bilişsel gelişim geriliklerinde konuşma ve dil becerilerinin de etkilendiği bilinmektedir.[14] Konuşma ve dil bozukluğu tanısı bilişsel gelişimdeki gerilikte dahil konuşma ve dildeki sorunların başka durumlarla açıklanamadığı durumlarda konulmaktadır.[3] Doğum sırasında yaşanan sorunlar sebebiyle konuşma ve dil sorunu yaşayan her çocuk konuşma ve dil bozukluğu tanısı almayabilir. Bu nedenle araştırmamızda böyle bir ilişki tespit edilmemiş olabilir. Konuşma ve dil bozukluklarının spesifik değerlendirildiği daha fazla ve geniş örneklemde yapılan çalışmalar bu konuya aydınlık getirebilir.

Dil ve konuşma bozukluğunun erken belirtilerinden biri ilk kelime kullanım zamanının gecikmesidir.[2] Çalışmamızda da ilk kelime kullanım zamanının olgu grubunda anlamlı derecede geç olduğu bulunmuştur. Desteksiz yürüme zamanında ise iki grup arasında fark bulunmamıştır. Desteksiz yürümenin gecikmesi genel olarak bilişsel gelişim gecikmesinde ortaya çıkan bir durumdur. Bu çocuklarla yukarıda da bahsedildiği gibi aynı zamanda konuşma ve dil becerileri de yaşından geri olabilmektedir.[14] Olgu grubuna bilişsel gelişim geriliğine bağlı konuşma ve dil sorunu olduğu düşünülen grubun dahil edilmemesi iki grup arasında anlamlı fark olmamasını açıklayabilir.

Ekran medyasının bilişsel etkileri hem olumlu hem de olumsuz olabilir. Ekranlar eğitim ve öğrenmeyi destekleyebilir, ancak uzun süre ekran başında kalmak ve çoklu görevler yapmak, yönetici işlevlerde bozulmalara ve düşük akademik performansa yol açabilir. Aşırı ekran kullanımı ayrıca obezite, uyku bozuklukları ve ruh sağlığı sorunları gibi sosyal ve duygusal gelişim problemlerine neden olabilir, duyguları yorumlama yeteneğini bozabilir, agresif davranışları artırabilir ve genel psikolojik sağlığı olumsuz etkileyebilir. Ekran süresi çocukların bakıcılarıyla olan etkileşimini azaltarak dil gelişimini olumsuz etkileyebilir; bu etki, birlikte izleme ve konu uygunluğu gibi faktörlere bağlıdır.[26] Çocukların ekran kullanımları ile dil gelişimi arasındaki ilişkiyi değerlendiren bir meta

analizde daha fazla ekran kullanımının (yani, günde/haftada saat başına düşen) çocuk dil becerileriyle negatif; daha kaliteli ekran kullanımının (yani, eğitim programları ve bakıcılarla birlikte izleme) ise pozitif bir ilişkisi olduğu bulunmuştur. Ekran kullanımına başlama yaşının daha geç olması, çocuklarda daha güçlü dil becerileriyle de ilişkilendirilmiştir.[27] Çalışmamızda çocukların başvuru sırasındaki günlük ekran süreleri değerlendirilmiş olup gruplar arasında anlamlı bir fark bulunamamıştır. Ekran sürelerinin ayrıntılı (kiminle, ne izleyerek vb) ve erken çocuklar dönemindeki süreye odaklanan şekilde değerlendiren değerlendirilmemesi çalışmamızın sonuçlarının etkilemiş olabilir.

Okul öncesi eğitimin çocukların bilişsel, sosyal, dil ve öğrenme alanlarını olumlu yönde etkilediği bildirilmektedir.[28] Okul öncesi eğitim, çocuklara dil becerilerini güçlendiren uyarıcı ortamlar ve etkinlikler sunarak iletişim becerilerini destekler. Bu sayede çocuklar kendilerini daha iyi ifade edebilir, özgüvenleri artar ve akademik başarıları için sağlam bir temel oluşturulur.[29,30] Okul öncesi eğitime giden ve gitmeyen birinci sınıf öğrencilerini karşılaştıran bir çalışmada dil becerilerinin okul eğitimine gitme öyküsü olan grupta daha iyi olduğu tespit edilmiştir.[30] Benzer grupta yapılan başka bir çalışmada da okulöncesi eğitim alan öğrencilerin sözcük dağarcıkları ve dili anlama ile kullanma becerilerinin, eğitim almayan öğrencilere göre daha yüksek olduğu ve bu öğrencilerin ilköğretime başlamak için daha hazır oldukları gösterilmiştir.[31] Çalışmamızda da bu bulgularla paralel biçimde sağlıklı kontrollerde okul öncesi eğitim almış olma sıklığı konuşma ve dil bozukluğu olan gruptan daha yüksek bulunmuştur. Okul öncesi eğitim çocukların dil ve konuşma becerilerini destekleyici bir etki gösterebilir. Bu bağlamda konuşma ve dil alanında sorunlar yaşayan çocukların özellikle okul öncesi eğitime yönlendirilmeleri faydalı olabilir.

Çalışmamızın çeşitli kısıtlılıkları bulunmaktadır. Araştırmamızın örneklem boyutunun küçük olması, verilerin katılımcıların ebeveynlerinden geriye dönük olarak alınması araştırmamızın kısıtlılıklarıdır. Hatırlamada yer alan biaslar olası sonuçları etkileyebilir. Sağlık kayıtları üzerinden elde edilen bilgilerle daha güvenilir sonuçlar elde edilebilir. Veriler geriye dönük olarak toplanmış olsa da, sosyodemografik, prenatal ve postnatal özelliklerin geniş bir yelpazede ele alınması, çalışmamızın güçlü yönlerinden biridir. Hem biyolojik hem de çevresel etmenlerin birlikte değerlendirildiği bu araştırma, risk faktörlerinin erken tespiti ve önlenmesi açısından büyük bir potansiyele sahiptir. Özellikle okul öncesi eğitimin dil gelişimi üzerindeki etkisini vurgulaması, erken dönemdeki müdahale stratejilerine ışık tutmaktadır. Çalışmamızda konuşma ve dil bozukluklarına ilişkin faktörler toplu olarak ele alınmış; ancak her bir bozukluğun ayrı ayrı değerlendirilmesi yapılmamıştır. Her ne kadar konuşma bozukluklarında ortak risk ve etiyolojik faktörler bulunsa da, her bir bozukluğun kendine özgü risk faktörleri ve etiyolojik unsurları da mevcuttur.[2] Bu nedenle, bu faktörlerin her bir dil bozukluğu için ayrı ayrı incelendiği çalışmalar, daha net ve anlamlı sonuçlar elde edilmesine katkıda bulunabilir.

Sonuç

Sonuç olarak, çalışmamızda konuşma ve dil bozukluğu olan çocuk ve ergenlerin sosyodemografik, prenatal ve postnatal özellikleri sağlıklı kontrollerle karşılaştırıldığında bazı önemli bulgular elde edilmiştir. Olgu grubunda erkek cinsiyetin daha yaygın olması, prenatal dönemde demir kullanımının fazla olması ve sağlıklı kontrollerde okul öncesi eğitime gitme sıklığının daha yüksek olması dikkat çekicidir. Ancak, anne yaşı, ebeveyn eğitim düzeyi, SED ve prenatal stres faktörleri gibi diğer değişkenler açısından gruplar arasında anlamlı farklar tespit edilememiştir. Çocuklarda dil ve konuşma gelişimi anne karnında başlayıp hayatın ilk yıllarında yoğun bir şekilde devam eden biyolojik değişimlerden ve çevresel faktörlerden etkilenen bir süreçtir. Bu sürecin çok dinamik olması, literatürde çok farklı sonuçlarla karşılaşmamıza neden olmaktadır. Bu nedenle, dil ve konuşma bozuklukları üzerine yapılan çalışmaların artmasıyla konuyu derinlemesine anlama kapasitemiz de artacaktır. Özellikle erken tanı ve müdahale stratejilerinin geliştirilmesi için daha geniş örneklem gruplarında ve uzun süreli takip çalışmalarının yapılmasına ihtiyaç duyulmaktadır. Elde edilen verilerin gelecekteki araştırmalar için önemli bir temel oluşturacağı ve çocukların dil ve konuşma gelişimlerine yönelik daha etkili yaklaşımların belirlenmesine katkı sağlayacağı düşünülmektedir.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Bilgilendirme

Çalışmamız 7-11 Mayıs 2024 tarihinde gerçekleşen 33. Çocuk ve Ergen Ruh Sağlığı kongresinde sözel bildiri olarak sunulmuştur

Etik Kurul İzni

Bu çalışma için Karadeniz Teknik Üniversitesi Tıp Fakültesi Bilimsel Araştırmalar Etik Kurulu'ndan onay alındı (06/05/2024 tarih ve 20 sayılı).

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: İŞK, EH, SK, BT. Veri toplama/İşleme: İŞK, SK. Veri analizi ve yorumlama: İŞK, EH, SK, BT. Literatür taraması: İŞK, EH. Yazım: İŞK, EH, SK, BT.

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ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Relationship between Preoperative Pulmonary Function Test Parameters and Postoperative Pulmonary Complications in Laparoscopic Obesity Surgery

Laparoskopik Obezite Cerrahisinde Preoperatif Solunum Fonksiyon Testi Parametreleri ile Postoperatif Pulmoner Komplikasyonlar Arasındaki İlişki

***Merve AYIK TÜRK*[1]**

ÖZ

Amaç: Laparoskopik obezite cerrahisinde preoperatif spirometrinin değeri tartışmalı bir konudur. Çalışmamızın amacı, preoperatif solunum fonksiyon testleri (SFT) ile postoperatif pulmoner komplikasyonlar arasındaki ilişkiyi araştırmaktır.
Araçlar ve Yöntem: Çalışmaya İzmir'deki bir eğitim ve araştırma hastanesinde bariatrik cerrahi öncesinde göğüs hastalıkları bölümünde değerlendirilen 73 hasta dahil edildi. Demografik veriler, SFT verileri ve postoperatif pulmoner komplikasyonlar retrospektif olarak analiz edildi.
Bulgular: On yedi hastanın (%23.3) preoperatif SFT'sinde anormal pulmoner fonksiyon paterni saptandı ve 7 hastada ise (%9.6) postoperatif pulmoner komplikasyon izlendi. Yaş, cinsiyet, cerrahi süresi ve anormal pulmoner fonksiyon paternlerinin komplikasyon gelişiminde anlamlı faktörler olduğu bulundu (sırasıyla, p=0.026, 0.047, 0.004 ve 0.024). Çok değişkenli analizde, cerrahi süresi komplikasyonlarla ilişkili bulundu (p=0.009).
Sonuç: Bu bulgular, preoperatif SFT'de anormal pulmoner fonksiyon paternine sahip hastaların postoperatif komplikasyon riskinin artabileceğini göstermektedir. Bu bağlamda, bariatrik cerrahide preoperatif SFT değerlendirmesi, özellikle komplikasyon riski daha yüksek olan hastalar için cerrahi ve postoperatif izleme kararlarını etkileyebilir.

Anahtar Kelimeler: laparoskopik bariatrik cerrah; pulmoner komplikasyonlar; preoperatif; spirometri

ABSTRACT

Purpose: The value of preoperative spirometry in laparoscopic obesity surgery is a subject of debate. The aim of our study is to investigate the relationship between preoperative pulmonary function tests (PFT) and postoperative pulmonary complications.
Materials and Methods: The study included 73 patients who were evaluated in the pulmonology department before bariatric surgery at a training and research hospital in Izmir, Turkey. Demographic data, pulmonary function, and postoperative complications were retrospectively analyzed.
Results: Seventeen patients (23.3%) had abnormal preoperative PFT results, while postoperative complications occurred in 7 patients (9.6%). Age, gender, surgery duration, and abnormal pulmonary function patterns were found to be significant factors in the development of complications (p=0.026, 0.047, 0.004, and 0.024, respectively). In multivariate analysis, surgery duration was identified as statistically significant in relation to complications (p=0.009).
Conclusion: These findings suggest that patients with abnormalities in preoperative PFT may have an increased risk of postoperative complications. In this context, preoperative PFT assessment in bariatric surgery could influence surgical and postoperative monitoring decisions, especially for patients at higher risk of complications.

Keywords: laparoscopic bariatric surgery; preoperative; pulmonary complications; spirometry

Received: 18.11.2024; Accepted: 31.12.2024

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How to cite: Ayık Türk M. Relationship between preoperative pulmonary function test parameters and postoperative pulmonary complications in laparoscopic obesity surgery. Ahi Evran Med J. 2025;9(1):108-113. DOI: 10.46332/aemj.1587224

INTRODUCTION

Obesity is a significant public health concern and is linked to an elevated risk of cardiovascular diseases, diabetes, and other chronic conditions.[1] It is estimated that 600 million people worldwide have a Body Mass Index (BMI) over 30 kg/m².[2] As the global population increases, it grows by 2.5 people every second, and one of these 2.5 individuals is projected to be overweight or obese.[3]

Extensive research has confirmed the link between obesity and cardiovascular as well as metabolic diseases.[4,5] Recently, however, there has been a heightened focus on the association between obesity and respiratory conditions, with evidence suggesting that obesity can lead to reduced lung function.[6]

Bariatric surgery is increasingly being performed, not only to control obesity but also to manage related comorbidities. In this context, bariatric surgery, while crucial in treatment, may contribute to increased mortality and morbidity in patients due to associated pulmonary function loss. The role of preoperative spirometry in laparoscopic bariatric surgery remains a subject of debate. Some studies have indicated that abnormal spirometric values may correlate with postoperative complications;[7,8] while others suggest that spirometry findings are linked to complications predominantly in patients with obstructive sleep apnea syndrome (OSAS).[9]

Thus, the preoperative preparation of these patients should be approached with a multidisciplinary plan to anticipate potential complications. The goal of our study is to explore the relationship between respiratory function tests in preoperative preparation and their role in predicting postoperative mortality and complication risk.

MATERIALS and METHODS

Study Population

Approval for this study was obtained from the Health Research Ethics Committee of S. B. Ü. İzmir Bozyaka Training and Research Hospital (dated 03.04.2024 and numbered 2024/09). All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study included consecutive patients who underwent a preoperative screening program for bariatric surgery at a training and research hospital in Izmir, Turkey, between July 2021 and June 2024. Prior to surgery, all patients scheduled for bariatric surgery were referred to the pulmonology department. Patients who underwent a pulmonary function test within 30 days before surgery were included, whereas those with incomplete clinical data or invalid spirometry results were excluded.

Clinical records were retrospectively reviewed at a single center, analyzing demographic characteristics such as age, gender, and BMI; smoking history; chronic diseases; respiratory symptoms; preoperative pulse oximetry values, ARISCAT risk score, spirometry results (FEV1, FVC, and FEV1/FVC); and postoperative complications and in-hospital mortality.

Height and weight were measured with light clothing and without shoes. BMI was calculated by dividing weight (in kilograms) by height (in meters squared).[10]

Spirometry was conducted for all patients by a certified spirometry technician in the pulmonology clinic. The results were interpreted according to the American Thoracic Society criteria as follows:[11] an FEV1/FVC ratio of less than 70% of the predicted value was classified as an obstructive pattern. A restrictive pattern was defined as an FVC of less than 80% of the predicted value with a normal FEV1/FVC ratio, and a mixed pattern was defined as the combination of both. The impact of spirometry abnormalities on the development of postoperative pulmonary complications was subsequently evaluated.

The ARISCAT Score for postoperative pulmonary complications was calculated using age, preoperative saturation, respiratory infection in the last month, preoperative anemia (Hgb ≤10 g/dL), surgical incision, duration of surgery, and emergency procedure.[12]

In our seven cases with complications, major and minor complications were classified as follows: prolonged

oxygen requirement (n=2) and post-operative atelectasis (n=2) were classified as minor complications, while respiratory failure requiring non-invasive (n=1) or invasive mechanical ventilation (n=2) and cases requiring intensive care unit admission were defined as major complications.

All patients were monitored for complications throughout their hospital stay, upon discharge, and at the postoperative follow-up visit 30 days after surgery.

Statistical Analysis

Statistical analysis was conducted based on variable scaling using IBM SPSS® Statistics version 23.0 (Chicago, IL) and MedCalc version 22.018. G-power analysis estimated a minimum sample size of 58 with a power of 0.90, a margin of error of 0.10, and an effect size of 0.45 in the G-Power 3.1.9.2. program. The Kolmogorov-Smirnov test was used to assess the normality of continuous data. Patient characteristics were presented as mean (SD), median (IQR), or as counts and percentages of the total. Multiple logistic regression analysis was used to assess the relationship between factors and the postoperative complications. The relationship between spirometry variables (%FEV1, FVC, and FEV1/FVC) and complications was investigated using ROC analysis, with the optimal cut-off value determined by the Youden index. Area under the ROC curve (AUC) values for the curves that were statistically different from the null line were then compared. A p-value of ≤0.05 (5%) was considered significant for a two-tailed comparison (type I error). A 95% confidence interval (CI) was calculated for all odds ratios.

RESULTS

A total of 73 patients who underwent bariatric surgery were analyzed. The mean age of the patients was 42±10.55 years, and the majority were female (n=56, 76.7%). The median duration of surgery for the patients was 129 [29] minutes. The majority of patients had at least one comorbid disease (n=54, 74%). In six patients (8.2%), the accompanying disease was OSAS. In the evaluation of respiratory function tests, 17 patients (23.3%) displayed abnormalities in preoperative testing. Specifically, an obstructive pattern was observed in 5 patients (6.8%), a restrictive pattern in 8 patients (11%), and a mixed pattern in 4 patients (5.5%). Complications were noted in 7 patients (9.6%), including 3 (4.1%) classified as major and 4 (5.5%) as minor. In-hospital mortality was reported in 2 patients (2.7%).

In univariate analysis, age, gender, duration of surgery, and the presence of an abnormal respiratory function pattern (obstructive, restrictive, or mixed) were found to be associated with complications (p=0.026, 0.047, 0.004, and 0.024, respectively). The characteristics of the patients and their association with complications are summarized in Table 1.

The relationship between spirometry parameters and complications was examined using ROC analysis, yielding AUC (95% CI) values as follows: %FEV1, 0.69 (0.57-0.79); %FVC, 0.70 (0.58-0.80); FEV1/FVC, 0.55 (0.43-0.67); and duration of surgery, 0.83 (0.72-0.91) (Figure 1).

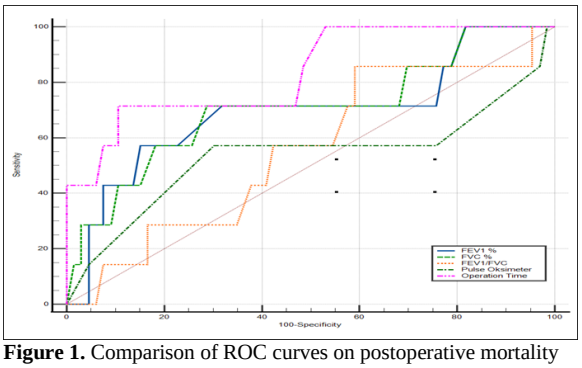

Figure 1. Comparison of ROC curves on postoperative mortality

Variables identified as statistically significant in univariate analysis were further assessed in multivariate analysis. When examining the relationship between age, duration of surgery, spirometry, and complications, only the duration of surgery remained statistically significant in multivariate analysis (p=0.92, 0.009, and 0.092, respectively) (Table 1).

Table 1. Characteristics of patients and association with complications by univariate and multivariate analysis.

Characteristic		Univariate analysis p value	Multivariate analysis HR(CI)	p value
Age	42 ±10.55	0.026	0.99 (0.90-1.09)	0.93
Gender				
Female	56 (76.7)	0.047		
Smoking History				
Current smoker	33 (45.2)	0.54		
Never smoked	28 (38.4)			
Former smoker	12 (16.4)			
Smoking (pack/year)	7.5 [5]	0.94		
Comorbidity				
Yes	54 (74)	0.59		
OSAS	6 (8.2)	0.099		
Respiratory Function Test				
Normal	56 (76.7)	0.024	6.39 (0.73- 55.36)	0.092
Obstructive	5 (6.8)			
Restrictive	8 (11)			
Mixed	4 (5.5)			
Pulse Oximeter (%)	97 [3]	0.75		
ARISCAT Risk Score	31 [0]	0.093		
FVC (L)	2.99 [1.08]	0.64		
FVC (%)	90 [15]	0.076		
FEV1 (L)	2.63 (0.70)	0.40		
FEV1 (%)	88 [17]	0.095		
FEV1/FVC	84 [7.5]	0.63		
Duration of Surgery	129 [29]	0.004	0.94 (0.91-0.98)	0.009
Complication	7 (9.6)			
Major	3 (4.1)			
Minor	4 (5.5)			
In-hospital mortality	2 (2.7)			

*If the data show a normal distribution, they are presented as mean (SD); if not, as median [25-75]. Categorical variables are presented as counts (percentage of the total).
*OSAS: obstructive sleep apnea syndrome, FVC: forced vital capacity, FEV1: Forced Expiratory Volume in 1 second.

DISCUSSION

This study indicates that abnormalities in pulmonary function tests (PFT) may be linked to a higher risk of postoperative complications in morbidly obese patients undergoing laparoscopic bariatric surgery. Although our findings weren't confirmed in multivariate analysis due to the limited sample size, there is a potential association between preoperative PFT abnormalities and postoperative complications.

Obesity is closely connected to various respiratory issues, including effort dyspnea, OSAS, obesity hypoventilation syndrome, chronic obstructive pulmonary disease (COPD), asthma, pulmonary embolism, and aspiration pneumonia.[13] These conditions increase the likelihood of pulmonary complications after surgery, such as atelectasis, pneumonia, and acute respiratory failure.[14] While bariatric surgery remains the most effective long-term treatment for severe obesity, obesity's link with respiratory diseases can lead to serious complications. Accurately predicting postoperative pulmonary risks would enable high-risk patients to receive specialized monitoring and care. For this reason, it's essential to identify predictors of pulmonary complications.

During the era of open bariatric surgery, pulmonary function tests were valuable in predicting postoperative complications. Various studies have shown that values such as FEV1 < 80% and FEV1/FVC < 70% may increase the risk of postoperative complications.[8,9,15] However, the American College of Physicians guidelines do not recommend the routine use of preoperative spirometry.[16] Although studies on preoperative spirometry have yielded varied results, the accessibility of spirometry as a test and the strong association observed between abnormal spirometry results and pulmonary complications suggest that spirometry could serve as a predictor for pulmonary complications. More comprehensive reviews and meta-analyses are needed to confirm spirometry's predictive value.

In open bariatric surgeries, the connection between preoperative spirometry and postoperative complications is more evident, while its necessity in laparoscopic procedures remains uncertain. This study explores this question. Although our study population is limited, it provides indications regarding the potential use of spirometry in assessing postoperative risk. Moreover, evidence suggests that individuals with abnormal spirometry test

results have a threefold increased risk of complications following laparoscopic bariatric surgery.[7] Knowing that a patient is at high risk before surgery may influence the surgeon's choice of procedure (open/laparoscopic) or decision to extubate the patient and may also serve as a prompt to extend monitoring time in the intensive care unit.[8]

In our study, the postoperative complication rate was 9.6%, which is relatively high compared to other studies reporting rates between 1.35% and 4.6%.[17-19] Of the three patients with major complications, two required intubations for respiratory failure, while one was managed with non-invasive ventilation. In comparison with the literature, the postoperative complication rate in our study appears relatively high, which may be attributed to the small sample size. In a large multicenter study involving bariatric surgery, no distinction was made between laparoscopic and open surgical techniques, and pneumonia and respiratory failure were observed in 18.6% of the cases during the postoperative period[20]. In another study investigating laparoscopic surgery, the rate of postoperative pulmonary complications was reported as 5.4%.[21] Postoperative pulmonary complication rates vary significantly across study populations. Notably, one study reported that postoperative pulmonary complications in bariatric surgery were associated with a 50-fold increase in 30-day mortality (OR 47.1; 95% CI, 38.6–57.5; $p<0.0001$).[22] Therefore, accurately predicting pulmonary complications in the preoperative period is crucial for preventing adverse outcomes and reducing both morbidity and mortality. Given that PFTs are easily accessible and straightforward to perform, their use in preoperative evaluation may represent a cost-effective strategy.

Several factors have been identified as being associated with respiratory failure, including congestive heart failure, open surgical technique, chronic kidney failure, gastric bypass, peripheral vascular disease, male gender, age >50, history of alcohol abuse, chronic lung disease, diabetes mellitus, and smoking.[19] These factors play a significant role in determining postoperative outcomes and may contribute to an increased risk of pulmonary complications, particularly in patients undergoing bariatric surgery. Additionally, the duration of surgery was independently associated with complications in our analysis. However, while age and impairment in PFT were found to be statistically significant in univariate analysis in relation to post-operative pulmonary complications, this relationship was not detected in multivariate analysis. Nonetheless, the presence of obstruction, restriction, or mixed impairment in PFT showed a p-value close to 0.05 in the multivariate analysis. This suggests that if the sample size is increased, this difference might also reach statistical significance in multivariate analysis. Therefore, it is thought that future multicenter studies could more clearly reveal this difference.

Our study has certain limitations. First, the single-center and retrospective design was a primary limitation. The retrospective nature may introduce selection bias and limit the ability to establish causality. Second, due to the small sample size, the results cannot be generalized to the entire population. Additionally, the low number of pulmonary complications in our study did not allow for specific subgroup comparisons. To address these limitations, prospective, multicenter studies are needed to validate our findings and provide more robust evidence. We hypothesize that increasing the sample size would more definitively elucidate the relationship between PFT and post-operative pulmonary complications.

In conclusion, our study highlights the potential role of preoperative pulmonary function tests in assessing the risk of postoperative pulmonary complications in patients undergoing laparoscopic bariatric surgery. Despite the limited sample size, our findings suggest that abnormal preoperative spirometry results may be associated with a higher risk of postoperative complications. The study underscores the importance of a multidisciplinary approach in managing patients with respiratory risk factors, emphasizing that personalized surgical planning and extended monitoring may help mitigate these risks. Future large-scale studies are essential to establish spirometry as a routine predictive tool, optimizing patient outcomes and enhancing safety in bariatric procedures.

Conflict of Interest

The author declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

Approval for this study was obtained from the Health Research Ethics Committee of S. B. Ü. İzmir Bozyaka Training and Research Hospital (dated 03.04.2024 and numbered 2024/09).

Authors' Contributions

Concept/Design: MAT. Data Collection and/or Processing: MAT. Data analysis and interpretation: MAT. Literature Search: MAT. Drafting manuscript: MAT. Critical revision of manuscript: MAT. Supervisor: MAT.

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REVİEW

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

The Psychological Impact of War on Immigrants: Public Health Strategies for Support

Savaşın Göçmenler Üzerindeki Psikolojik Etkisi: Destek için Halk Sağlığı Stratejileri

***Gülcan DEMİR*[1]**

ÖZ

Silahlı çatışma, buna maruz kalan göçmenler üzerinde önemli psikolojik etkiler yaratmaktadır. Bu bireyler, depresyon, anksiyete ve travma sonrası stres bozukluğu (TSSB) gibi ruhsal sağlık sorunlarıyla karşılaşmakta olup, sosyal izolasyon, ayrımcılık ve dil engelleri gibi faktörlerle bu sorunlar daha da kötüleşmektedir. Uzun süreli şiddet ve askeri faaliyetler, bu psikolojik sorunların riskini daha da artırmaktadır. Bu çalışma, savaşın göçmenler üzerindeki psikolojik etkilerini incelemeyi ve ruh sağlığı desteği sağlamak için etkili stratejiler geliştirmeyi amaçlamaktadır. Çalışma, travma, ayrımcılık ve sosyal faktörlerin, göçmen nüfusları arasında depresyon, anksiyete ve TSSB gibi durumlara nasıl katkıda bulunduğuna odaklanmaktadır. Savaş mültecileri arasında depresyon ve anksiyete gibi ruhsal sağlık sorunlarının yaygınlığını değerlendirmek için mevcut literatür gözden geçirilmiştir. Savaş travması, ayrımcılık ve ekonomik zorluklar ile sosyal izolasyon gibi diğer katkı sağlayan faktörler arasındaki ilişki incelenerek, daha geniş psikolojik sonuçların anlaşılmasına yönelik bir analiz yapılmıştır. Savaş travması ve ayrımcılığa maruz kalmak, anksiyeteyi ve TSSB geliştirme olasılığını önemli ölçüde artırmaktadır, bu da bir bireyin uzun vadeli işlevselliğini ciddi şekilde etkileyebilir. Derleme, özellikle sosyal ve ekonomik zorluklarla karşılaşıldığında, göçmenlerin ruh sağlığını desteklemek için hedeflenmiş müdahalelere duyulan ihtiyacı vurgulamaktadır. Sosyal desteğin, savaşın olumsuz psikolojik etkilerini azaltmada etkili olduğu gösterilmiştir. Kültürel uyum, dini inançlar ve finansal güvenlik gibi faktörler, göçmenlerin ruh sağlığını iyileştirmek için de önemlidir. Bu alanda daha fazla araştırma yapılması, göçmenlerin savaş sonrası psikolojik ihtiyaçlarını karşılamak için etkili müdahale ve politikaların geliştirilmesi gerektiğini ortaya koymaktadır.

Anahtar Kelimeler: anksiyete; depresyon; halk sağlığı; ruh sağlığı; TSSB

ABSTRACT

Armed conflict has significant psychological effects on migrants exposed to it. They often face mental health challenges such as depression, anxiety, and post-traumatic stress disorder (PTSD), which are worsened by factors like social isolation, discrimination, and language barriers. Prolonged violence and military activities further increase the risk of these psychological issues. This study aims to explore the psychological impact of war on migrants and identify effective strategies for providing mental health support. It focuses on how trauma, discrimination, and social factors contribute to conditions like depression, anxiety, and PTSD among migrant populations. A review of existing literature was conducted to assess the prevalence of mental health issues, such as depression and anxiety, among war refugees. The relationship between war trauma, discrimination, and other contributing factors like economic hardship and social isolation was analyzed to better understand the broader psychological consequences. Exposure to war trauma and discrimination significantly heightens anxiety and the likelihood of developing PTSD, which can severely affect an individual's long-term functioning. The review highlights the need for targeted interventions to support migrants' mental health, especially in the face of social and economic challenges. Social support has been shown to reduce the negative psychological effects of war. Factors such as cultural adaptation, religious beliefs, and financial stability are also crucial for improving migrants' mental well-being. Further research is needed to develop effective interventions and policies that address the mental health needs of migrants in conflict-affected areas.

Keywords: anxiety; depression; mental health; PTSD; public health

Received: 08.01.2025; Accepted: 27.02.2025

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How to cite: Demir G. The psychological impact of war on immigrants: public health strategies for support. Ahi Evran Med J. 2025;9(1):114-121. DOI: 10.46332/aemj.1615445

INTRODUCTION

In recent years, the increasing wars and conflicts around the world have led to a rapid rise in the number of migrants and refugees. Major conflicts such as the Syrian civil war, the war in Ukraine, and Israel's occupation of Gaza have displaced millions of people and caused a major humanitarian crisis. Turkey, hosting 3.1 million Syrian refugees, has become the country with the largest number of refugees in the World.[1] Additionally, as a result of the conflict in Ukraine, the UN Refugee Agency assistance reached 4.32 million people in 2022 and 2.63 million people in 2023.[2] Refugees living in urban areas in Turkey face many barriers, such as language barriers, lack of information, stigma, security concerns, and financial difficulties.[3] Despite this, studies show that the majority of refugees do not seek the psychological help they need.[4]

The existing literature provides indirect evidence of large-scale population movements resulting from conflicts and crises. For instance, Goniewicz suggests that the refugee crisis triggered by Russia's aggression against Ukraine may lead to significant population movements to Poland and other EU countries, driven by factors including war, famine, and climate change.[5] Korkmaz asserts that, according to the Middle East Council of Churches, 150.000 Christians were forcibly displaced in Iraq between 1960 and 2000 as a result of war and state-sponsored persecution.[6] These data highlight the impact of war on displaced populations, demonstrating that such conflicts can result in significant migration patterns. These references underscore the necessity of comprehensive data to understand migratory movements caused by armed conflict and to assess the scale of these movements.

The psychological effects of war and trauma are evident among migrants from areas affected by armed conflict. Migrants may experience mental health issues, including anxiety, depression, and post-traumatic stress disorder (PTSD), as a result of exposure to war trauma and settlement stress. Furthermore, social isolation, discrimination, and language barriers experienced by immigrants may also serve to exacerbate existing mental health difficulties.[7]

The migration process is replete with complex stressors that can give rise to long-term mental health issues for refugees and migrants alike.[8] The trauma associated with exposure to war violence can lead to persistent mental and emotional challenges for migrants, further impacting their well-being. The legal status of migrants is also a significant determinant of mental health outcomes. Legal insecurity has been linked to increased stress, anxiety, depression, and trauma.[9] Factors such as exposure to violence, family loss, and long-term stress can precipitate the development of serious mental health conditions, including PTSD in individuals who have been affected by war.[10] The mental health of refugee and migrant families may be compromised by the adversities associated with war, displacement, and other stressors.[11] A number of studies have demonstrated that experiences related to war continue to have an impact on the mental health of refugees and internally displaced persons. Moreover, the transmission of intergenerational trauma within migrant families represents a crucial area of investigation with regard to the long-term effects observed at various stages of the migration process.

This review aims to assess the psychological effects of war and trauma on migrants from a public health perspective, focusing on how these experiences affect mental health, considering variations based on different factors. It also identifies areas needing further investigation. The review explores the prevalence, symptoms, and lasting effects of psychological conditions such as depression, anxiety, and PTSD, while examining the role of social support, economic hardship, cultural adaptation, and environmental factors. Ultimately, the goal is to inform the development of effective interventions to improve migrant mental health through evidence-based public health policies and practices.

Psychological Impacts of War and Trauma

Depression

Individuals who have been exposed to war and other forms of conflict face numerous stressors, including violence, prolonged stress, and physical assault. These experiences often lead to adverse health and mental health outcomes, particularly anxiety, depression, and

trauma-related symptoms.[10] Research has shown that the accumulation of traumatic experiences during migration is a significant factor contributing to the prevalence of anxiety and depression among migrants.[12] Additionally, perceived discrimination in the host country is associated with worse mental health outcomes, including depressive symptoms.[13] Stringent immigration policies and the stressors linked to the pandemic further increase the prevalence of depression among certain migrant groups, such as Latino immigrant parents.[14] Social support is also recognized as an important protective factor, mitigating the negative effects of accumulated stress on depression.[15]

The risk of developing depression and anxiety is also notably high among individuals exposed to civil war violence, emphasizing the long-term psychological consequences of conflict. Studies investigating various migrant groups, such as refugees, undocumented migrants, and internally displaced persons, have provided valuable insights into the prevalence of depressive symptoms among war refugees. For instance, Verhülsdonk et al. found that traumatic experiences, especially torture, contribute significantly to the development of depression among refugees and migrants.[16] Similarly, Þórðardóttir et al. documented a heightened risk of psychiatric illness among those who have experienced war and displacement.[17] Other studies, such as those by Voglino et al., have observed high rates of anxiety and depression among African immigrants.[18] Adhikary et al. found a strong link between low income and depression among both non-migrants and return migrants in Nepal.[19] Furthermore, Poudel et al. highlighted the increased depressive and anxiety symptoms among migrant workers during the pre-movement phase.[20] These findings underscore the elevated risk of depression in individuals displaced by conflict and the compounded effects of trauma and migration stress.

Moreover, depression significantly impacts migrants' daily lives, adaptation processes, family dynamics, and overall well-being. It is crucial to understand how depression affects migrants to create effective interventions. For instance, Alvarez advocates for trauma-focused, culturally tailored programs to address the depressive and anxiety symptoms of Latina immigrant women.[21] Sharma suggests that immigrant mothers are especially prone to depression due to post-migration adjustment difficulties, cultural losses, and challenges in finding employment.[22] Calzada and Sales observed higher depression rates among immigrants who arrived in the U.S. at a young age, highlighting the complexity of the relationship between migration experiences and mental health.[23] Additionally, Metcalf notes that undocumented immigrants face significant stress adapting to new communities, particularly regarding economic, health, and social issues tied to their legal status.[24] Lee also reported that as immigrants remain in the host country for longer periods, they experience higher rates of depressive symptoms compared to the local population, suggesting a link between cultural adaptation and mental health outcomes.[25]

Finally, studies on Syrian refugees in Turkey show the prevalence of mental health issues such as PTSD and depression. A study of 420 adult Syrians in Ankara revealed a PTSD rate of 36.5% and a depression rate of 47.7%. Female sex, physical illness, and a greater number of traumatic events were found to predict both PTSD and depression. PTSD was also predicted by a history of psychiatric illness, while depression was linked to lower economic status. Notably, lower economic status predicted depression in men but not in women.[26]

The occurrence of childhood traumas (e.g., war experience) has been demonstrated to exert a long-term influence on mental health, thereby enhancing the probability of a depression diagnosis.[27] Migrant women, especially during the reproductive period, are at higher risk for depression, with symptoms being more prevalent during pregnancy and postpartum.[28] Research indicates that when migrants are satisfied with their resettlement decisions, depression prevalence decreases. For example, African immigrant women in Canada are particularly vulnerable to postpartum depression and anxiety, highlighting the need for targeted interventions.[29]

Depression has a profound impact on migrants' daily lives, adjustment processes, family dynamics, cultural adaptation, employment status, and social integration. It is of the utmost importance to gain an understanding of

the challenges posed by depression in migrants in order to develop targeted interventions and support mechanisms that address their mental health needs. Further research and the implementation of adapted interventions are required in order to enhance the well-being of migrants and facilitate their resilience.

Anxiety

It is well documented that exposure to war and other forms of conflict is a significant risk factor for the development of anxiety disorders among migrants. It can be reasonably deduced that these stress factors related to war may serve to increase the prevalence of anxiety disorders among migrants. Furthermore, anti-migrant policies have been linked to increased anxiety in children, precipitating fears of separation from their parents.[30] This indicates that the socio-political environment and experiences of discrimination may exacerbate anxiety in migrants, particularly among children. Pfeiffer underscores the observation that trauma-related mental disorders, including anxiety, tend to manifest with greater prevalence in communities that have been affected by war.[31] Hinchey et al. highlight that exposure to war trauma can result in an increase in anxiety symptoms over time, underscoring the long-term effects of this situation.[32] The results of these studies indicate that trauma and discrimination-related stressors are associated with elevated anxiety levels among migrants. In light of these findings, it is imperative to gain a deeper understanding of the impact of war and trauma on anxiety, in order to inform the development of effective interventions and support systems that address the mental health needs of migrants.

The presentation of anxiety disorders in migrants may vary according to a number of factors, including the individual's migration experiences, cultural background, and socio-political context. Acharya et al. discovered that the advent of the SARS-CoV-2 pandemic precipitated an increase in anxiety disorders among immigrants aged 25 years and older in South Korea. Such disorders may present with symptoms including excessive worry, fear, and restlessness.[33] Lindegaard et al. reported high levels of anxiety among Arabic-speaking immigrants in Sweden.[34] Flores et al. highlighted the existence of a robust correlation between the accumulation of trauma related to the migration process and the emergence of heightened anxiety symptoms among undocumented Latino immigrants.[35] St-Pierre et al. underscored the prevalence of generalized anxiety and panic disorders among individuals with an immigrant background who have been subjected to ethnic discrimination.[36] Haro-Ramos and Rodríguez indicate that Latino day laborers in the United States exhibit heightened anxiety symptoms as a consequence of the precarity associated with immigration policy.[37]

The symptoms of anxiety disorders include worry, fear, restlessness, and physical symptoms. It is of the utmost importance to comprehend and address these symptoms in order to facilitate the implementation of suitable interventions that will bolster the mental well-being of migrant communities.

Anxiety can have a significant impact on migrants' social cohesion and integration processes, which in turn affects their lives and well-being. As Weiss posits, the process of navigating immigration laws can serve to further complicate integration processes, thereby increasing the risk of social isolation and stigmatization.[38] Lemon posits that discriminatory immigration policies based on structural racism create barriers to social cohesion by increasing anxiety and depression in Latino families.[13] Gillespie et al.[39] investigated the influence of adverse experiences during childhood on the mental health of immigrants by examining the relationship between social adjustment skills and mental health variables.[40] To comprehend the significant influence of anxiety on migrants' social adaptation and integration processes, it is essential to establish suitable support systems that facilitate migrants' adjustment to their new communities.

Post-Traumatic Stress Disorder

PTSD is a common occurrence among migrants, frequently resulting from traumatic experiences, conflict, and displacement. It is postulated that war-related traumas and conflict-induced stress may contribute to the development of PTSD symptoms in migrants. The effects of war and trauma serve to increase the risk of PTSD in migrants, thereby underscoring the necessity of addressing mental health concerns and providing support for

migrants. It has been documented that individuals who experience forced displacement due to migration frequently manifest symptoms of PTSD, indicating a significant challenge in coping with the traumatic effects of war and displacement.[26]

Fel et al. reported that the presence of children was associated with an increased risk of more severe PTSD among civilians involved in the conflict in Ukraine.[41] Anjum et al. observed that women in Ukraine were more susceptible to developing PTSD and other mental health issues in contexts of conflict.[42] Amone-P'Olak et al. demonstrated that traumatic events may precipitate an exacerbation of PTSD symptoms in war survivors.[43] Tinsae conducted a systematic review and meta-analysis, which indicated that the prevalence of PTSD is high among the Ethiopian population who have experienced the impact of war.[44] Hussein et al. found that exposure to war trauma in Baghdad had a detrimental impact on academic performance among adolescents, increasing the risk of developing PTSD in this age group.[45] Ainamani et al. reported that women residing in a war zone exhibited heightened PTSD symptoms as a consequence of exposure to traumatic events.[46] Vignaud et al. asserted that PTSD and major depressive disorder are prevalent among migrants, indicating a substantial prevalence of PTSD symptoms in individuals who have experienced trauma and displacement.[47]

The long-term effects of PTSD can have a significant impact on individuals' mental health, general well-being, and daily functioning. Crosta et al. identified three primary predictors of elevated PTSD symptomatology: low perceived economic stability, high neuroticism, and fear of contagion. Prolonged untreated PTSD can result in significant impairments in social and occupational functioning.[48] Falasi et al. investigated the long-term psychological consequences of the pandemic on healthcare professionals, underscoring the necessity of comprehending and addressing these effects.[49] Levi and Moss demonstrated that the prevalence of PTSD and depression remained elevated five years after the Flint, Michigan water crisis. This indicates that environmental catastrophes have a sustained influence on mental health, resulting in the development of psychiatric disorders.[50]

These studies underscore the significance of the long-term consequences of PTSD and highlight the imperative for the development of efficacious strategies for the identification, assessment, and management of these posttraumatic effects.

Limitations

It should be noted that this review is subject to several limitations. First and foremost, the reviewed studies employed disparate methodological approaches and utilized varying sample groups, which may restrict the generalizability of the findings. Moreover, the paucity of studies concentrating on particular regions and populations renders a comprehensive evaluation of the psychological consequences of war and trauma on migrants challenging. These limitations may result in an incomplete understanding of the results and the omission of pertinent variables. For instance, the considerable heterogeneity of migrants from diverse cultural and socioeconomic backgrounds may not have been sufficiently addressed. Future studies may overcome these limitations by employing more homogeneous sample groups and longitudinal research designs. Moreover, an expansion in the number of studies on migrants from disparate regions and cultural backgrounds may facilitate the attainment of more comprehensive and generalizable results.

Conclusion

This review highlights the significant psychological consequences of war and trauma on migrants, with higher rates of depression, anxiety, and PTSD observed within this population. The experiences of violence, displacement, and forced migration contribute to these mental health challenges, with social support, economic hardship, cultural adaptation, and environmental factors further influencing the severity of these effects.

To address these challenges, it is crucial for public health policies to incorporate strategies aimed at supporting migrants' mental health. Key strategies include increasing access to mental health services, strengthening social integration, meeting basic needs, and enhancing social support systems. Additionally, public health initiatives must ensure that migrants have increased access to cultu-

rally appropriate, trauma-informed care and community-based resources.

It may also be beneficial for future research to explore the potential role of artificial intelligence and machine learning in improving the accessibility and effectiveness of mental health interventions for migrants. These technologies could be utilized to develop predictive models for early intervention and improve the personalization of care for migrant populations.

Future research should focus on specific areas, including the mental health of migrant children, second-generation migrants, and the long-term effects of anti-migrant policies. For example, research could investigate the impact of different forms of social support on the mental health of migrant children. Studies examining the challenges and protective factors for second-generation migrants could provide insight into their unique mental health needs. Longitudinal research on the intergenerational transmission of trauma would also enhance understanding of the long-term psychological effects of migration on families, supporting the development of targeted interventions for both parents and children.

Artificial intelligence-supported tools, including ChatGPT 3.5, have been used in the translation, grammatical correc-tions, and editing process of this study.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Ethics Committee Permission

Since the study is a compilation, ethics committee permission is not required.

Authors' Contributions

Concept/Design: GD. Data Collection and/or Processing: GD. Data analysis and interpretation: GD. Literature Search: GD. Drafting manuscript: GD. Critical revision of manuscript: GD.

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AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Geç Yaşta Tanı Alan Yaygın Değişken İmmün Yetmezlik Olgusu

A Late-Diagnosed Case of Common Variable Immunodeficiency

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ÖZ

Yaygın Değişken İmmün Yetmezlik (YDİY) primer immün yetmezliklerin (PIY) en yaygın formudur. YDİY azalmış serum immünoglobulin seviyeleri, azalmış antikor üretimi veya spesifik antikor üretiminin olmaması ve normal veya düşük B-lenfosit sayımları ile karakterizedir. Sık tekrarlayan enfeksiyonlar ve otoimmünite, gastrointestinal inflamatuar hastalık, karaciğer hastalığı, lenfoid hiperplazi, granülomatöz hastalık, sitopeniler, ilerleyici akciğer hastalığı ve kanser gibi enfeksiyöz olmayan komplikasyonlar dahil olmak üzere geniş bir klinik sunum yelpazesine sahiptir. Temel tedavileri antibiyotik profilaksisi ve immünoglobulin replasman tedavisidir. Bu olgu sunumunda 62 yaşında; ayrıntılı immunoloji sorgulamasında son beş senedir en az altı kere tekrarlamış olan biri yatış gerektiren pnömoni hikayesi, pulmoner tromboemboli öyküsü ile 10 gün yoğun bakım ünitesinde yatışı, lenfoproliferasyonu olan ve ileri tetkikler sonucunda YDİY tanısı alan bir olgu sunulmuştur.

Anahtar Kelimeler: hipogamaglobulünemi; immünglobulin eksikliği; immün sistem hastalıkları; primer immünyetmezlik; tekrarlayan pnömoni

ABSTRACT

Common Variable Immunodeficiency (CVID) is the most common form of primary immunodeficiency (PID). CVID is characterized by decreased serum immunoglobulin levels, decreased or absent antibody production, and normal or low B-lymphocyte counts. It has a wide variety of clinical presentations, including recurring infections, inflammatory diseases, gastrointestinal diseases, lymphoid hyperplasia, granulomatous diseases, cytopenias, progressive lung diseases, and non-communicable diseases such as cancer. The main treatments are antibiotic prophylaxis and immunoglobulin replacement therapy. In this case report, a 62-year-old patient with a medical history of pneumonia that had recurred at least six times in the last five years, one of which required hospitalization, a history of pulmonary thromboembolism, and a 10-day intensive care unite stay, lymphoproliferation, and a diagnosis of CVID as a result of further examinations is presented.

Keywords: hypogammaglobulinemia; ımmunoglobulin deficiency; ımmune system diseases; primary immunodeficiency; recurrent pneumonia

Gönderilme tarihi: 06.10.2024; Kabul edilme tarihi: 28.01.2025

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Makaleye atıf için: Doğan C, Kasap N, Örçen C. Geç yaşta tanı alan bir yaygın değişken immün yetmezlik olgusu. Ahi Evran Med J. 2025;9(1):122-127. DOI: 10.46332/aemj.1562436

GİRİŞ

Yaygın Değişken İmmün Yetersizlik (YDİY), Primer antikor eksikliği ve antikor cevap yokluğu ile karakterizedir. En sık görülen primer immün yetersizlik (PİY) durumudur. Hipogamaglobulüneminin birçok sekonder nedeni vardır (Tablo 1). YDIY tanısı enfeksiyonlara duyarlılık, otoimmünite, granülomatöz hastalık, poliklonal lenfoproliferasyon ve etkilenmiş bir aile bireyinin olmasından; en az birinin bulunması ve serum IgG, IgA ve/veya IgM düşüklüğü ve düşük antikor cevabı veya düşük B hücre seviyeleri ve T hücre eksikliğinin olmaması ile tanı konmaktadır.[1]

Tablo 1. Hipogamaglobulinemi nedenleri*.

İlaçlara bağlı YDİY
- Antimalaryal ajanlar
- Kaptopril
- Karbamazepin
- Glukokortikoidler
- Fenklofenak
- Altın tuzları
- Penisilamin
- Fenitoin
- Sülfasalazin
- Rituksimab

Genetik defektler (Tek gen)
- Ataksi telenjiektazi
- SCID'nin otozomal resesif formları / diğer combine immün yetmezlik formları
- Hiper-IgM sendromları
- Transkobalamin II eksikliği ve hipogammaglobulinemi
- X'e bağlı agammaglobulinemi
- X'e bağlı lenfoproliferatif bozukluk (EBV ile ilişkili)
- X'e bağlı SCID
- Bazı metabolik bozukluklar

Kromozom Anomalileri
- Kromozom 18q sendromu
- Monozomi 22
- Trizomi 8
- Trizomi 21

Enfeksiyon Hastalıkları
- HIV
- Kızamıkçık virüsü ile konjenital enfeksiyon
- Sitomegalovirüs ile konjenital enfeksiyon
- Toxoplasma gondii ile konjenital enfeksiyon
- EBV

Malign Hastalıklar
- Kronik lenfositik lösemi
- Timoma ile immün yetmezlik
- Hodgkin olmayan lenfoma
- Monoklonal gamopati (Mutipl miyelom, Waldenstrom makroglobulinemisi)

Diğer Sistemik Hastalıklar
- Aşırı immünoglobulin kaybının neden olduğu immün yetmezlik (nefroz, ciddi yanıklar, lenfanjiektazi, protein kaybettiren enteropati)

YDİY: Yaygın değişken immün yetmezlik, EBV: Ebstein Bar Virüsü, HIV: Human Immunodeficiency Virus, SCID: Şiddetli kombine immünyetmezlik
*1 Numaralı kaynaktan adapte edilmiştir

Klinik olarak sadece tekrarlayan enfeksiyonlar ile seyredebileceği gibi (infection-only phenotype), olgularda otoimmün, granülomatöz, gastro-intestinal sistem (GİS) hastalıkları, lenfoma gibi hematolojik maligniteler, lenfoid hiperplazi, kronik akciğer hastalığı da eşlik edebilmektedir.[2-3]

Bu yazıda tekrarlayan pnömoni atakları ve mükerrer hastane yatışları olmasına rağmen ileri yaşta tanı alan, bir YDİY olgusu literatür eşliğinde sunulmuştur.

OLGU SUNUMU

Altmış iki yaşında erkek olgu göğüs hastalıkları polikliniğine ateş, öksürük, balgam çıkarma şikayetleri ile başvurdu. Çekilen posterio-anterior (PA) akciğer grafisinde (AG) bilateral alt zonlarda non-homojen opasite izlenen olgu bilgilendirilmiş onam formu alınarak pnömoni ön tanısı ile ileri tetkik ve tedavi amacı ile hastaneye yatırıldı (Resim 1). Toraks bilgisayarlı tomografide (BT) sağ üst lob posterior, orta lob ve alt lob'da sol alt lob'da konsolide alanlar izlendi (Resim 2). Olgunun anamnezinde sık tekrarlayan pnömoni nedeni ile çok kez, farklı sağlık

kurumlarında hastane yatışı ve tedavi öyküsü olduğu (Son 5 yılda 6 kez tekrarlayan pnömoni öyküsü), bir kez ampiyem nedeni ile Göğüs Cerrahisi kliniğinde operasyon öyküsü olduğu öğrenildi. Olgunun laboratuvar tetkikleri tablo 2'de sunulmuştur. Gönderilen balgam kültüründe *Haemophilus influenza* üremesi olan olguya intravenöz seftriakson+oral klaritromisin tedavisi başlandı. Tam kan sayımında dikkat çekici olarak nötropeni ve lenfopenisi olan olgunun çok sık enfeksiyon geçirme ve hastane yatışlarının olmasından dolayı immünoloji ve alerji hastalıkları bilim dalına danışıldı.

Tablo 2. Olgunun laboratuvar değerleri.

Parametre	Sonuç	ND	Parameter	Sonuç	ND
WBC (10^3Ul)	**2.9**	4.00-10.00	CRP (µg/L)	**122.28**	0-5
Nötrofil sayısı (10^3Ul)	**1.87**	2.00-7.00	Prokalsitonin (mg/dL)	0.035	<0,5
Nötrofil (%)	**65.1**	40.00-80.00	IgG (mg/dlL)	**33 / 37**	913-1884
Lenfosit sayısı (10^3Ul)	**0.7**	0.80-4.00	IgA (mg/dL)	**1 / 3**	139-378
Lenfosit (%)	28.2	10.00-50.00	IgM (mg/dL)	**13 / 16**	88-322
Hemoglobin (g/dL)	**10.3**	13-17	IgG-1 (mg/L)	**<9.4**	366-1196
Hematokrit (%)	**32**	40.00-54.00	IgG-2 (mg/dL)	**<39**	236-605
Üre (g/dL)	26	16.6-48.5	IgG-3 (mg/dL)	**5.4**	24-282
Kreatinin (mg/dL)	0.6	0.7-1.2	CMV PCR (Iu/mL)	**790**	20-190000
ALT (U/L)	12	0-40	EBV DNA IgG (U/mL)	1.65	Negative
AST (U/L)	7	0-41	EBV DNA IgM (U/mL)	0.004	Negative
LDH (U/L)	141	135-225	Galaktomannan Antijeni	0.163	0.5-15
Sedim. mm/saat	14	0-15			

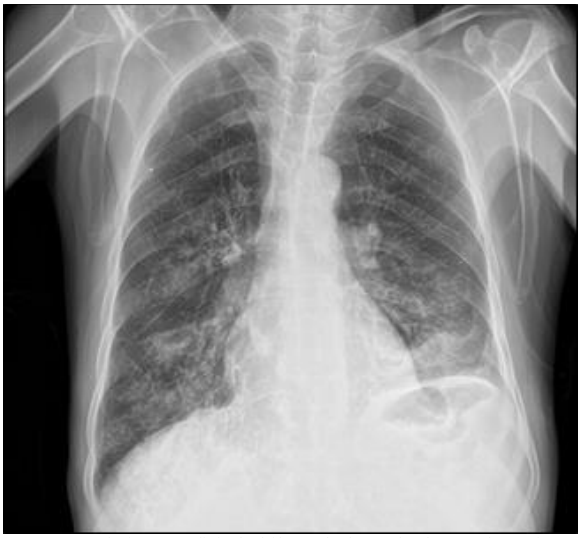
ALT: Alanin aminotransferaz, AST: Aspartat aminotransferaz, CRP: Serum Reaktif Protein, EBV: Ebstein Bar Virüsü, mm: Milimetre, Ig: İmmün globulin, Sedim: Sedimantasyon, WBC: Lökosit, LDH: Laktat Dehidrogenaz

Ayrıntılı immünoloji sorgulamasında son beş senedir en az altı kere tekrarlamış olan biri yatış gerektiren pnömoni hikayesi, pulmoner tromboemboli öyküsü ile 10 gün yoğun bakım ünitesi (YBÜ) yatışı, lenfoproliferasyonu olan (hepatosplenomegali, multiple lenfadenopati öyküsü) hastanın, özgeçmişinde bilinen ishal, egzema, abse, pamukçuk, molluscum, otit, sinüzit yok. Soy geçmiş sorgulamasında 4. derece akraba evliliği mevcut, ailede PİY öyküsü, kanser öyküsü, kemik iliği transplant öyküsü yoktu. Fizik muayenesinde splenomegali, hepatomegali, bilateral servikal, aksiller ve inguinal multiple lenfadenopatileri var. Cildi doğal. İmmünoloji önerisi ile IgG alt tipleri, CMV PCR, EBV DNA, tüm aşı yanıtları, Galaktomannan antijeni, detaylı immün fenotipleme, olası lenfoproliferatif hastalık açısından Pozitron Emisyon Tomografi (PET-BT) ile hematoloji takibi ve periferik LAP örneklenmesi ayrıca belirgin hipogamaglobulinemi nedenli 0.5gr/kg/3 hafta intravenöz immünoglobulin (İVİG), 4 saatte infüzyon şeklinde başlanması önerildi. Bakılan hemogramlarında belirgin lenfopeni, nötropeni, anemi mevcuttu. Kesin tanı için tekrarı gönderilen IgG, IgA, IgM değerleri hipogamaglobulinemi (IgG: 37 mg/dL (913-), IgM: 16 mg/dL (88-), IgA: 3 mg/dL (108-)) yaşa göre bakılan referans değerlerine göre yine belirgin düşük geldi (Tablo 1). CMV PCR pozitifliği tespit edildi. Detaylı lenfosit alt grup analizinde $CD3^+$T, $CD4^+$T ve $CD8^+$ T lenfosit sayıları normal, ancak $CD4^+/8^+$T oranı ters dönmüştü. Double negatif T hücreleri normal sınırlardaydı. $CD16^+56^+$ NK hücreleri ile $CD4^+$T ve $CD8^+$ T hücre alt grupları, $CD4^+$T CD45 RA^+/RO^+ hücrelerin oranları normaldi. $CD8^+$T CD45 RO^+ T (hafıza $CD8^+$ T) hücreleri belirgin yükselmişti, geçirilmiş sık enfeksiyonlara bağlandı. Timustan ilk çıkış gösteren T hücreleri (Recent timik hücre) normal sınırlardaydı. $CD19^+$B hücreleri normal sınırlarda ancak alt grupları olan sınıf çevrimi yapmış B hücreleri (CSB) %0 olarak hiç gözlemlenmedi ve sınıf çevrimine uğramamış B hücreleri (UCSB) %2.6 olarak yaşa göre belirgin düşüktü. Otoimüniteyi gösteren otoreaktif B hücreleri anlamlı olarak yüksekti (Resim 3). Öykü, klinik ve laboratuvar bulguları YDİY tanı kriterlerini sağlayan hastaya immünoloji tarafından YDİY tanısı konuldu. Hastaya azitromisin profilaksisi ve rutin IVIG tedavisi ile immünoloji poliklinik takibi önerildi. YDİY monogenik bir PİY'dir. Bu hastalarda malignite dahil birçok komplikasyon gelişme olasılığı olduğu için hastaların prognozunu belirleyebilerek, ileri takip ve hedefe yönelik tedavileri için genetik tanı koyabilmek hayati öneme sahiptir. Hastadan klinik ekzom sekanslama olarak genetik analiz istendi, sonuç beklenmektedir.

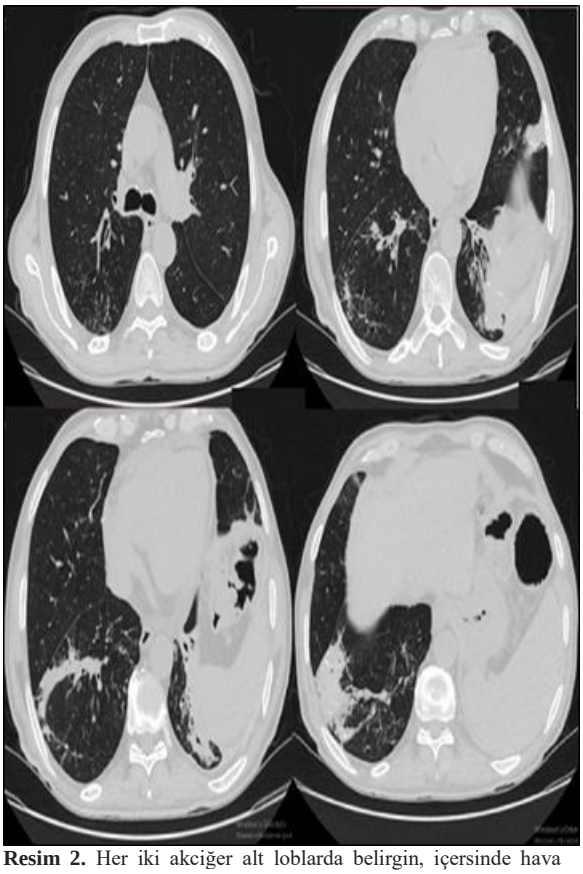
Olguya Hematoloji önerisi ile; Periferik yayma, tüm batın Ultrasonografisi (USG), boyun ve yüzeysel doku USG, Hemoglobin elektroforezi istendi. Batın USG'de hepatosplenomegali raporlanan olgunun periferik yaymada atipik hücre izlenmedi. Protein elektroforezi: hipogamag-

lobulinemi gözlenen hastanın serum protein elektroforezinde M-protein piki gözlenmedi şeklinde raporlandı. Boyun ve yüzeysel doku USG'de her iki servikal zincirde en büyüğü 11x6 mm, her iki aksiller bölgede en büyüğü 10x5 mm, her iki inguinal bölgede en büyüğü 19x6mm multipl lenfadenopatileri (LAP) olan olguda YDİY'e eşlik edebilecek granülomatöz, otoimmün, lenfoproliferatif ve malign hastalıklar açısından hematoloji, önerisi ile PET/CT çekildi, olası gastrointestinal sistem maligniteleri ekarte etmek için gastroenteroloji önerisi ile gastroskopi ve kolonoskopi yapıldı sonuçlarında malignite düşündürücü bulguya rastlanmadı. PET/BT'si bilateral servikal zincirde, paraaortik, interaortakaval, parakaval alanlarda, bilateral common iliak, internal ve eksternal iliak lojda, bilateral inguinal, mediastinal, hiler, supra-infra diyafragmatik, aksiller ve inguinal alanlarda en büyüğü 12 mm ve SUDmax: 3.9 olan yaygın lenfadenopatiler şeklinde raporlandı (Resim 4). Sol aksiller LAP eksizyonel biyopsisi; Germinal merkez organizasyonu gösteren sekonder lenfoid foliküller, malignite düşündürür bulguya rastlanmadı şeklinde raporlandı.

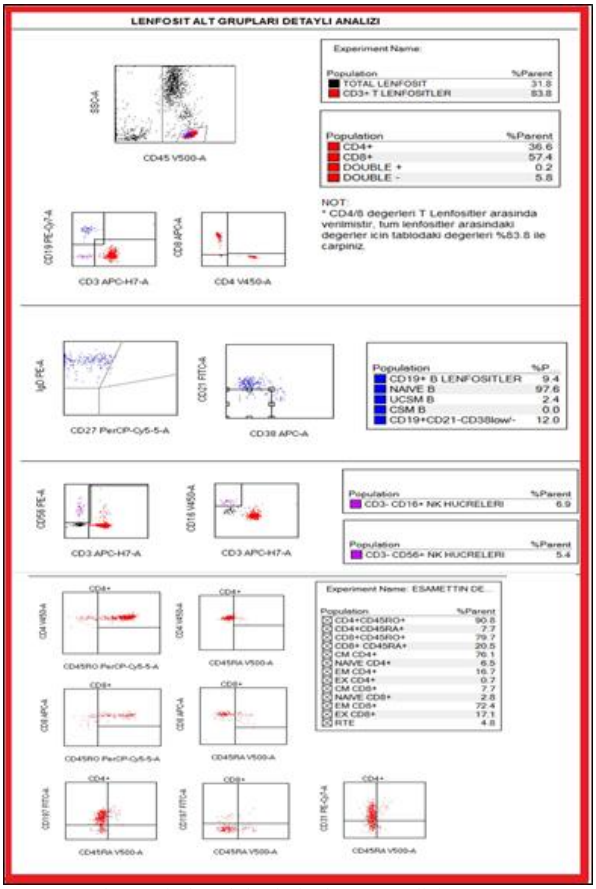
Olgu YDİY tanısı ile immünoloji polikliniğinden takip edilmesi planlanarak taburcu edildi. Olgunun 6.ay kontrollerinde klinik, radyolojik ve laboratuvar değerlerinde belirgin düzelme gözlendi. Kontrol AG belirgin regresyon gözlendi (Resim 5). Kontrol tam kan sayımında WBC:7,9 10^3/uL, Nötrofil: 5,71 10^3/uL, Nötrofil %77, Lenfosit: 1,4 10^3/uL, Lenfosit %:18.6, Ig G: 692 mg/dL, IgA: 4 mg/dL, IgM: 42 mg/dL saptandı.



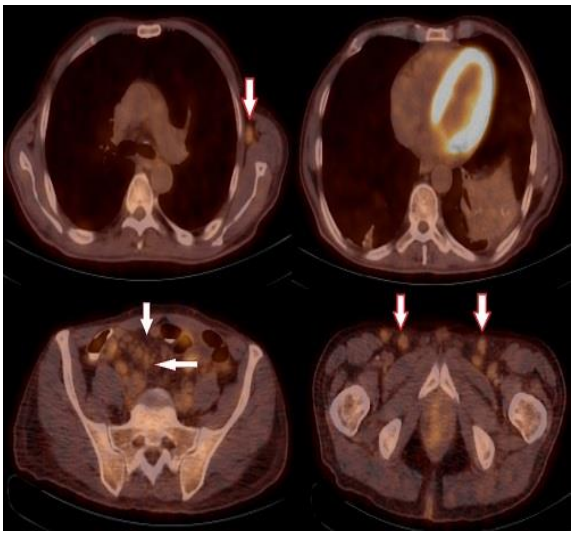
Resim 1. Akciğer grafisinde bilateral alt zonlarda non homojen opasite artışı, sol diyafragma elevasyonu.



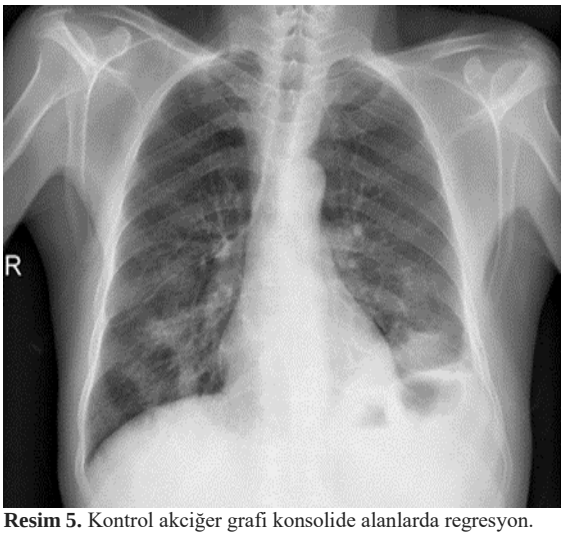
Resim 2. Her iki akciğer alt loblarda belirgin, içersinde hava bronkogramları da izlenen konsolide alanlar.



Resim 3. Olguya ait detaylı lenfosit alt grup analizi raporu



Resim 4. PET-BT'de aksiller bölgede, inguinal bölgede ve batında lenfadenoptiler (Kırmızı ok ile işaretlenmiştir).



Resim 5. Kontrol akciğer grafi konsolide alanlarda regresyon.

TARTIŞMA

Altmış iki yaşında, ateş öksürük balgam yakınması ile polikliniğimize başvuran, öyküsünde tekrarlayan pnömoni ve çok kez hastane yatış olan ve ileri incelemeler sonucu hipogamaglobulinemi ile karakterize edilen bir primer antikor yetmezliği sendromunu olan YDİY tanısı alan olgu ileri tetkik ve tedavilerde anamnezin önemine dikkat çekilmek için sunulmuştur.

Hipogamaglobulinemiye sebep olan çok fazla neden olduğu için ve YDİY tanısı da bir ekartasyon tanısı olduğu için hastalığın tanısı erken çocukluktan yaşlılığa kadar her yaşta koyulabilmektedir. Olguların büyük çoğunluğu genellikle 20-40 yaş arasında tanı almaktadır. Bizim olgumuzda olduğu gibi YDİY'in ileri yaşlarda tanı alması nadir bir durumdur. Resnick ES ve ark[2] 40 yıl boyunca takip ettikleri 473 YDİY olgusu ile yaptıkları çalışmalarda tanı anında olguların %28'nin 21 yaşının altında olduğunu ve ortalama tanı yaşını 33.5 olduğunu bildirmişlerdir. Dahl C ve ark[4] 128 YDİY olgusundan oluşan çalışmalarında >60 yaş olgu oranını %25.8 olarak bildirmişlerdir.

Hipogamaglobulinemi (IgG ve IgA ve/veya IgM düşüklüğü) YDİY tanı kriterleri arasındadır. Bunun dışında zayıflamış aşı yanıtı ve/veya memory B Lenfosit sayısında azalma tanımlanmış diğer kriterlerdir. IgG serum seviyelerinin normal aralığı farklı yaş gruplarında ve farklı ırk veya etnik kökene göre de değişiklik gösterir. YDİY'in kesin tanısı için düşük IgG düzeyine ek olarak IgA ve/veya IgM düzeyinin de düşük olması ve en az 3 hafta arayla tekrarlanan ölçümlerde de düşüklüğün devam etmesi tanı için önemli bir kriterdir.[5] Bizim olgumuzda da literatür ile uyumlu olarak başlangıç ve kontrol IgG, A, M düşüklüğü mevcuttu.

Klinik olarak YDİY'in prezantasyonu enfeksiyonların şiddetinin veya sıklığının arttığı enfeksiyöz tip, immün disregülasyon benzeri semptomlar ile seyreden otoimmün-otoenflamatuar hastalıkların (otoimmün hemolitik anemi, otoimmün trombositopeni, otoimmün tiroidit ve inflamatuar bağırsak hastalığı) eşlik ettiği tip ve malignitelerin eşlik ettiği tip olarak üç ana sınıfa ayrılabilir. Kesin nedeni tam olarak bilinmese de otoimmün-granülomatöz hastalık ve maligniteler de genel popülasyonla karşılaştırıldığında YDİY hastalarında daha yüksek prevalansta görülmektedir.[6] Çoğu zaman tekrarlayan enfeksiyonlar sonucu tanı koyulan enfeksiyöz tip YDİY'de antikor üretimi her zaman bozulmuştur. Bu genellikle B ve T hücresi fonksiyon bozukluğundan, T hücresi fonksiyonunun bozulması ve antikor üretimi için yeterli yardımın olmamasından da kaynaklanabilir. YDİY olgularında etken genellikle solunum yollarındaki kapsüllü hücre dışı bakterilerdir.[7-8] Yapılan çalışmalarda en sık görülen enfeksiyonun pnömoni olduğunu bildirilmektedir. Bizim olgumuzun da kliniğimize başvuru durumu ve daha önceki yatış nedenleri pnömoniydi. Esmaeilzadeh ve ark[9] 383 YDİY olgusunda en sık görülen enfeksiyonun %36.8 olguda pnömoni olduğunu, Zainaldain ve ark[10] tarafından yapılan sistematik bir incelemede, YDİY'li olguların üçte ikisinden fazlasının pnömoni ile başvurdu-

ğunu bildirmişlerdir. Olgumuz eşlik eden granülomatöz, otoimmün hastalık ve maligniteler açısından multidisipliner olarak değerlendirilmiş ve patoloji saptanmamıştır. Balgam kültüründe *Haemophilus influenza* üremiş ve pnömoni tedavisi almıştır.

Tedavide bugün için en etkili yöntem immünoglobulin replasman tedavisidir. Özellikle tekrarlayan enfeksiyonlar ve bunlara bağlı gelişen komplikasyonların önlenmesinde dramatik yanıt sağlar. İmmunoglobulin replasman tedavisinde standart doz 0.4 ila 0.5 g/kg'dır ve düzenli aralıklarla Ig G düzeyleri kontrol edilir.[11] Olgumuzda da 0.5 gr/kg dozunda intravenöz immunoglobulin tedavisi başlanmış ve klinik fayda sağlanmıştır.

Sonuç olarak sık tekrarlayan enfeksiyon nedeni ile başvuran erişkin yaştaki olgularda YDİY'in akılda tutulması, hastalığın sadece tekrarlayan enfeksiyonlarla değil aynı zamanda eşlik edebilecek otoimmün durumlar ve malignitelerin de olabileceği göz önünde tutulmalı, mümkün ise olguların tanı, tarama ve tedavi süreçleri multidisipliner yürütülmelidir.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Etik Kurul İzni

Hastadan yazılı ve sözlü onamı alınmıştır.

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: CD. Veri toplama/İşleme: NK. Veri analizi ve yorumlama: CO. Literatür taraması: NK. Yazım: CD. Gözden geçirme ve düzeltme: CO. Danışmanlık: CD, NK

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