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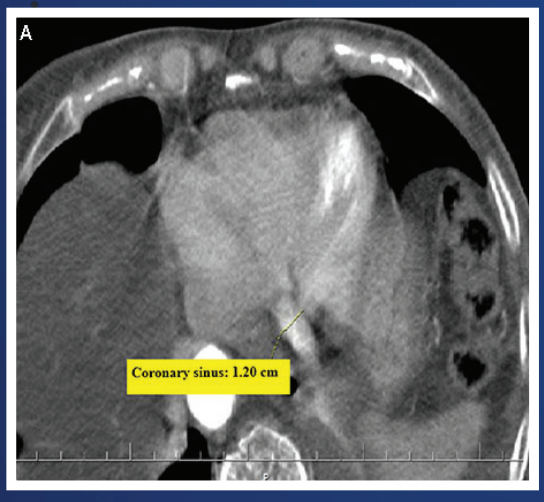

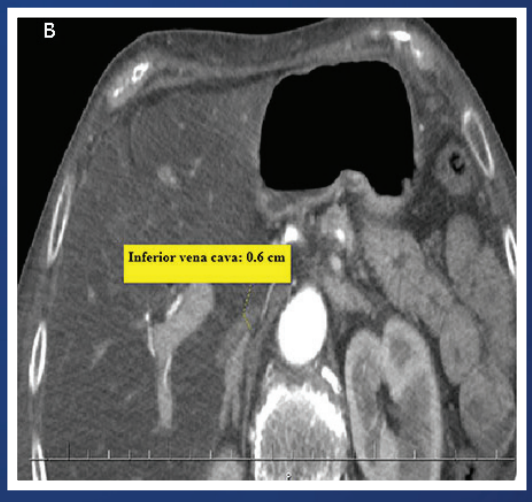

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Publisher Contact
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REVIEW / DERLEME

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Tinnitus Models in Experimental Animals

Deney Hayvanlarında Tinnitus Modelleri

Berfin Eylül Aydemir[1], Ayşe Arzu Yiğit[2]

[1]Başkent University Faculty of Health Sciences, Department of Audiology, Ankara, Turkey
[2]Başkent University Faculty of Medicine, Department of Physiology, Ankara, Turkey

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Abstract

Tinnitus can be defined as an imaginary sound perception in silence without any acoustic sound source in the external environment. Despite many years of human and experimental animal studies, its mechanism, pathophysiology and etiology are still debated. The perception of tinnitus differs between individuals in terms of intensity, frequency, temporal characteristics, and localization in the head or ear. Although it is easier to detect the presence and characterize tinnitus in humans in clinical practice and research, the use of experimental animal models is inevitable to determine the physiology of tinnitus, which significantly reduces the quality of life, and to study possible treatment methods. Although tinnitus can be induced in experimental animals by using salicylate or exposing them to noise, different techniques and methods have been used to determine the presence of tinnitus and its physiological characteristics. In this review article, it is aimed to present the tinnitus inducing methods in experimental animals used in the literature together with behavioral and electrophysiological methods used to determine the presence of tinnitus.

Keywords: Experimental animal, behavioral model, tinnitus

Öz

Tinnitus dış ortamda herhangi bir akustik ses kaynağı olmaksızın sessizlikte algılanan hayali ses algısı olarak tanımlanabilmektedir. Uzun yıllardır yapılan insan ve deney hayvanı çalışmalarına rağmen oluşum mekanizması, patofizyolojisi ve etiyolojisi hala tartışılmaktadır. Tinnitus algısı sesin şiddeti, frekansı, zamansal özellikleri, kafa ya da kulakta lokalize olması ile bireyler arasında farklılık göstermektedir. Klinikte ve araştırmalarda insanlardaki tinnitus varlığını saptamak ve karakteristik özelliklerini belirlemek daha kolay olsa da, insan yaşam kalitesini önemli ölçüde azaltan tinnitus fizyolojisinin belirlenmesi ve olası tedavi yöntemleri üzerinde çalışılabilmesi için deney hayvanı modellerinin kullanımı kaçınılmazdır. Deney hayvanların salisilat kullanılarak ya da gürültüye maruz bırakılarak tinnitus oluşturulabilse de, oluşan tinnitus varlığının ve tinnitusun fizyolojik özelliklerinin belirlenmesi için günümüze kadar farklı teknik ve yöntemler ile çalışılmıştır. Bu derleme makalesinde literatürde kullanılan deney hayvanlarında tinnitus indükleyici yöntemler ile tinnitus varlığının belirlenmesinde kullanılan davranışsal ve elektrofizyolojik yöntemlerinin bir arada sunulması amaçlanmıştır.

Anahtar Kelimeler: Deney hayvanı, davranışsal model, tinnitus

Introduction

Tinnitus can be defined as an imaginary perception of sound originating from the peripheral or central auditory system. It usually feels in silence without an acoustic sound source from the external environment and its symptoms effect an average of 10-15% of the population. The perceived sound is caused by an abnormality in the auditory system rather than a disease. The perception of tinnitus is distinguished by its intensity, frequency, temporal characteristics, localization to the head or ear and which differ between individuals and its mechanism is still unsolved exactly[1].

Address for Correspondence/Yazışma Adresi: Prof. MD., Ayşe Arzu Yiğit, Başkent University Faculty of Medicine, Department of Physiology, Ankara, Turkey
E-mail: aarzuyigit@baskent.edu.tr
ORCID ID: orcid.org/0000-0001-5837-6877

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Although there are many different classifications of tinnitus, the most common classification is objective and subjective tinnitus. Objective tinnitus is the perception of mechanically generated acoustic vibrational activity. It can also be heard by another person. It may be of vascular, muscular, skeletal or respiratory origin. It is usually caused by a mechanical cause related to the regular contraction of the middle ear muscles or is defined as pulsatile tinnitus synchronized with the pulse with the sensation of blood flow in the body[1]. Subjective tinnitus the most common type of tinnitus and heard only by individuals. Although there is no common opinion about its origin, it is thought that the corrective responses given by the central auditory system and limbic system to neural, cellular or functional impairments in the peripheral auditory system cause subjective tinnitus perception[1,2].

The main risk factors for tinnitus are hearing loss, aging, occupational or recreational noise exposure and drug use. Possible risk factors such as auditory system diseases, obesity, diet, smoking and alcohol consumption, head trauma, hypertension, hyper/hypothyroidism, genetic factors and viral infections have also been reported in the literature[3-5]. Tinnitus can be treated by eliminating or reducing the effects of potential risk factors. However, in some cases, tinnitus does not completely disappear and this condition, which negatively affects quality of life, is alleviated with long-term treatment strategies.

Although there are different opinions about tinnitus from prevalence to etiology, diagnosis and treatment/coping strategies, the subject of tinnitus remains up-to-date in the literature with both human and animal studies. Especially in recent years, experimental animal studies have helped to reveal details about tinnitus[6-8]. In this article, which was prepared to review tinnitus modeling methods in experimental animals, the substances used in tinnitus induction and behavioral and electrophysiological methods used in the evaluation of the presence of tinnitus are mentioned in the current literature.

Experimental Animal Models of Tinnitus

Studies designed to determine the presence of tinnitus, to determine its characteristic features and to examine the changes occurring in the auditory system by behavioral and electrophysiological methods in humans are more easily organized than animal models. However, it is inevitable to use animal models to conduct experimental studies on tinnitus physiology and possible treatment methods. However, in this method, it is not as easy to determine the perceptual and neural characteristics of tinnitus in animals as in humans.

Rats (Long-Evans, the Sprague Dawley, Norway rat, the Wistar, the Fisher 344), mice, guinea pigs and cats were the experimental animals of choice in the literature for the induction and subsequent evaluation of tinnitus[9]. In a review prepared by Domarecka et al.[8], 36 studies evaluating the electrophysiologic testing method in experimental animals modeled for tinnitus were reviewed and it was reported that approximately 50% of the studies conducted in the last decade used male Spraque-Dawley rats. Despite all the studies, tinnitus induced by animal models is not exactly the same as tinnitus occurring in humans and therefore the use of animal models to understand the causes and treatments of tinnitus in humans is limited. Nevertheless, animal models are an important tool to investigate the mechanisms and treatments of tinnitus. There are different methods used to induce tinnitus in animals. In these methods, ototoxic (ear-damaging) compounds are used as tinnitus inducers such as salicylates, some antibiotics (e.g., gentamicin), chemotherapy drugs (e.g., cisplatin), painkillers (e.g., ibuprofen) and noise exposure, which can damage cells in the ear and cause hearing loss[10].

Methods Used to Induce Tinnitus

Salicylate

Salicylate is an active ingredient of aspirin. It's modest amounts has analgesic, antipyretic and anti-inflammatory effects[11]. However, excessive amounts can cause temporary moderate hearing loss, and a high-pitched perception of tinnitus in humans and animals[12]. Although the exact mechanism is not fully understood, it is thought that salicylates may cause hearing loss and tinnitus by accumulating in the fluid inside the ear or by disrupting the mitochondria in the cells of the auditory system[11]. Although it varies individually, it has been reported that salicylate-induced tinnitus in animals, as in humans, is usually in the high frequency range of 10-16 kHz or 7-9 kHz[10,13]. Furthermore, tinnitus associated with salicylates usually resolves spontaneously within a few days of stopping the medication[12].

In the study by Jastreboff et al.[14] was showed that intraperitoneal administration of sodium salicylate at a dose of 350 mg/kg cause to hearing loss and tinnitus development in rats. In addition, another study reported that the concentration of sodium salicylate in the blood reaches the highest value 2-4 hours after intraperitoneal

injection and the drug completes its half-life 8-15 hours after injection[15]. In recent studies conducted for the same purpose, intraperitoneal sodium salicylate was used at different doses such as 400 mg/kg per day for 7 consecutive days[16], single dose 350 mg/kg[17], 5 days a week for 3 weeks and 200 mg/kg per day[18].

Noise

Noise exposure is one of the main factors affecting hearing health in living organisms. The duration, intensity and type of exposure may vary with the damage to the auditory system. Noise exposure in the form of sudden acoustic trauma causes sudden and relatively permanent hearing loss and tinnitus, while prolonged and gradual exposure causes progressive hearing loss and tinnitus. This difference in the relationship between exposure and outcome has led to differences in noise-induced tinnitus models in the literature.

Domarecka et al.[8] reported that noise was used as a tinnitus inducer in 19 of 39 animal tinnitus modeling studies published in the literature in the last 10 years. The characteristics of the noise stimulus used vary as unilateral or bilateral, prolonged or sudden stimulation with different frequencies in the range of 8-16 kHz and different sound intensities in the range of 80-194 dB SPL[19-21]. The type of noise stimulus to be used should be determined according to the characteristics of the damage to be caused.

Models Used to Determine the Presence of Tinnitus

Behavioral Models

As mentioned above, although the use of experimental animal models is inevitable in determining the mechanism of tinnitus formation and treatment alternatives and protocols, whether determining the tinnitus in these models and some measurements are more difficult than the methods used in humans. Behavioral models are the primary method used to assess whether tinnitus occurs in experimental animals after exposure to tinnitus-inducing substances. The basis of behavioral models is the first models created by Jastreboff et al.[22] and Bauer et al.[23] and many new methods have been developed and introduced to the literature until today.

Jastreboff's Conditioned Suppression Model

It is the first behavioral test used to evaluate tinnitus in experimental animals. Basically, it teaches the relationship between sound and drinking behavior after prolonged thirst and conditions the animal to drink water when it hears a sound. In this way, the animal is taught the difference between sound and silence. The method consists of 3 stages; 2-3 days of initial training, 4-5 days of Pavlov's conditioned suppression training, behavioral test 2 hours after salicylate administration. Before the initial training, the experimental animal keep under normal housing conditions for 18 hours without water, with 10 kHz 60 dB pure tone played in the background. The first phase of training lasted for 28 minutes with sound and 4 silent intervals of 30 seconds each for a total of 30 minutes. The training, which is applied for half an hour a day, continues for 3 consecutive days. In the second stage, which is Pavlov's conditioned suppression training, in addition to the first stage, conditioning is performed by giving a foot shock to prevent the animal's drinking behavior in the silent condition and water drinking behavior is taught only during the time it hears sound. The second phase continues for 4-5 days with periods of 30 minutes per day. In the last phase, the behavioral test phase, foot shock is not used and the behavior of the animal is recorded in sound and silent conditions (Figure 1). The number of water drinks in the sound and silent condition during the training process is proportioned and compared with the results of the third phase, the behavioral test phase, after the training. For learning, the suppression rate of drinking should be <0.5. If the water drinking behavior is greater than 0.5 in the test phase, it means that tinnitus has occurred[14,22,24].

Bauer and Brazoski's Conditioned Avoidance Model

The method is based on Jastreboff's conditioned suppression method, which is based on the principle of teaching the difference between sound and silence. In this method, the experimental animal is taught to press the pedal for food in 60 dB SPL broadband background noise after prolonged fasting. In order to prevent the pedal pressing behavior in silence, a foot shock is applied randomly in 60 seconds of silence embed in the background noise during training process. The experimental animal is considered to be conditioned when there is a 25% decrease in pedal pressing

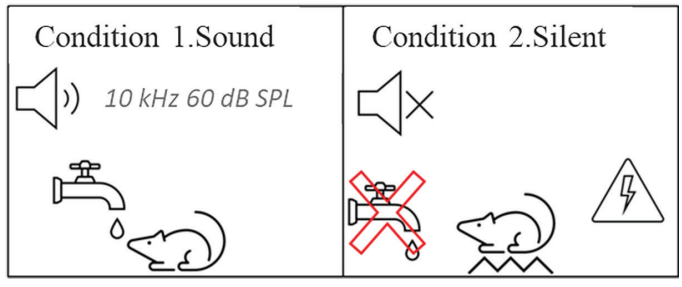

Figure 1. Jastreboff's conditioned suppression model

behavior during the training process. In the test phase, the foot shock is not applied and the evaluation is made on the basis of the fact that the experimental animal continues to press the pedal in silence if tinnitus occurs[23].

Guitton's Conditioned Avoidance Model

Guitton et al.[25] developed a method that teaches experimental animals to avoid a 3.7 mA foot shock delivered from the cage floor in the presence of 10 kHz 50 dB SPL pure sound for 3 min by first performing a conditioning experiment. In previously developed methods, the foot shock given in silence is used in the audible condition in this method. Experimental animals are conditioned to climb a ladder positioned at the corner of the cage in the audible condition. Afterwards, as a result of 10 trials lasting 10 minutes, the experimental animal is considered to have learned the training when it avoids 80% of the foot shocks given with sound. When tinnitus is induced, the experimental animal is expected to spend more time on the ladder and avoid the cage floor due to the constant sound (Figure 2).

Turner's Method for Suppressing the Startle Reflex

The startle reflex suppression method of Turner et al.[26] was designed on the basis of keeping cognitive and motivational variables under control, unlike other behavioral models that require training of the experimental animal. In this method, the experimental animal is not pre-trained for tinnitus assessment. It is basically depend on evaluation of the startle reflex to sudden sound. In the evaluation process, the experimental animal in a cage with a piezoelectric transducer at the base is randomly given 50 ms silent intervals in a continuously played 60 dB SPL narrowband sound and the pressure value of the startle pressure value is measured by giving 20 ms 115 dB SPL broadband sound during the silent interval. This startle pressure value is expected to decrease in animals with tinnitus.

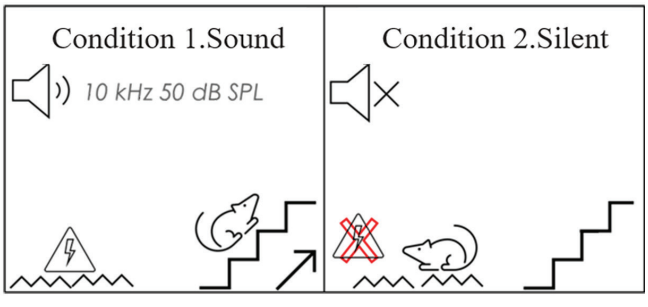

Figure 2. Guitton's conditioned avoidance model

Guitton's T Water Maze Model

The water maze method is based on the principle that the experimental animal chooses between two options. Unlike other methods, it has some advantageous such as no deprivation or foot shock is applied. The method developed by Guitton and Dudai[27] uses a T-shaped pool into which a portable escape platform can be placed. The experimental animal is released from the starting arm into 21 degrees celsius water, and by positioning the exit platform in the pool to the right while it was sound and to the left while it was silence, they are taught the arm they should turn to in a sound and silent environment. The training continues for 3 days with a total of 12 condition sessions in the order of 3 audible and 3 silent conditions, 1 session per day. Researchers recommend the use of 6 or 10 kHz 45 dB SPL pure tone for the audible condition (Figure 3). During training, the average time to reach the platform in 12 trials and the percentage of correct decisions are used as learning criteria. Afterwards, the animals, which are thought to be induced by chemical or noise induced tinnitus, are left in the starting arm of the pool where there is no platform in any arm without background sound, and they are evaluated according to which arm they spend time in and where they look for the platform. The expected performance of the tinnitus-induced animal is that it behaves as if the background sound is given during training and spends more time in the right arm due to the tinnitus it hears.

Rüttiger's Conditioned Avoidance Model

In this method, Rüttiger et al.[28] use a commercial conditioning cabinet designed for the purpose of their study. The base of the booth consists of bars suitable for foot shock application and a platform with a mechanical sensor on one side that serves as a resting place. The booth is divided into two short corridors by a wall in the center and contain a liquid feeder. And it has a photo sensor at

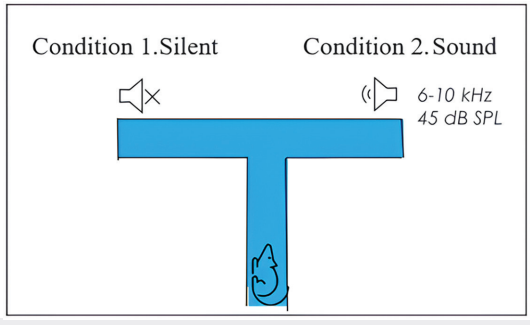

Figure 3. Guitton's T water maze model

the end of the corridors for monitoring animal movements. Reward is water containing 3% sucrose in the liquid feeder. In this method, training lasts 30-60 minutes a day, five days a week, depending on the activity of the experimental animal. During the training period, 70 dB SPL white noise with a bandwidth of 0.01-50 kHz plays continuously from a central loudspeaker and 200 ms long, 8 kHz, 70 dB SPL pure tone is presented at random times along with the noise. In this method, like the other methods, the animal taught the difference between quiet and noise. It is aimed that when the animal hears sound, suppress the water drinking behavior by foot shock application. The expected performance of the tinnitus-induced animal is the continuation of water drinking behavior even in the silent.

Lobarinas' Method to Avoid Planned Constructed Polydipsia

In the automatic avoidance technique developed by Lobarinas et al.[29], tinnitus assessment can continue for a long time because behavioral response is not dampened. In the model, polydypsia was induced in food-restricted experimental animals by giving small amounts of food at regular intervals and triggering high water drinking behavior. In the training of drinking behavior with sound, either 30 seconds 40 dB SPL narrowband stimulus or silence condition is randomly applied for 6 trials. In one of the 6 trials, when drinking behavior in the sound condition, the animal is tought to drink water in silence by applying a foot shock. Since the tinnitus-induced experimental animal hears an imaginary sound in the silent interval, it is expected to suppress the drinking behavior as in training.

Heffner's Sound Localization Method

It was developed to evaluate the presence of tinnitus in experimental animals in which unilateral tinnitus was induced by unilateral noise exposure. Firstly, the experimental animals are conditioned to noise coming from different directions, from the right and left sides of the experimental animal at a 90-degree angle in the cage. The experimental animal is continuously exposed to broadband 35 dB SPL background noise and presented with pure tones 20-30 dB above the hearing threshold at different frequencies. The animal is trained to drink water from a drinking bowl located in the direction of the presented pure tones. Turning to the drinking bowl in the direction of the stimulus is the correct response to the stimulus, while turning to the wrong side is prevented by foot shock as a negative reinforcer. In the experimental phase, although there was no sound in the environment, the experimental animal was expected to perform the auditory condition behaviors on the side of the tinnitus-induced ear[30].

Physiological Model

Physiological models are based on the measurement of neural activity changes thought to be linked with tinnitus. These measurements are obtained electrophysiologically by recording changes in neural activity directly from the auditory centers of animals exposed to agents that cause tinnitus[31]. In these days, activity changes have been measured by neuroimaging procedures like microPET, fMRI, SPECT, DTI[32,33]. Comparison of data obtained before and after exposure to the substance causing tinnitus, or comparison of results from experimental and control groups, may indicate changes in neural activity. As tinnitus is the perception of sound without external stimulus, the aim of the physiological model is that tinnitus produces normal activities that appear only when there is a sound. The most valid and observable activity is automatic neural firing activity by itself that imitates sound evoked activity. The advantages of the this model that it able to show the characteristics of changes in this activity and its location in the auditory system. On the other hand, the inability to directly prove that animals have tinnitus is the most important negative aspect of this method. Therefore, before using the physiological model, a two-stage evaluation of tinnitus in the animal with a behavioral model can keep the researcher with reliable results[34].

In the physiologic model, tinnitus assessment methods can also be diversified from an audiologic perspective. There are specific electrophysiologic testing methods used in the peripheric and central evaluation of the auditory system. These include the recording of otoacoustic emissions from the outer hair cells, auditory evoked brainstem responses, which allow evaluation of the auditory pathways at the level of the auditory nerve and brainstem, and auditory evoked potentials, which allow evaluation of hearing centers at higher levels near the level of the cortex.

Conclusion

In conclusion, tinnitus is a symptom whose cause is not fully understood and reduces people's quality of life, and there is no definitive treatment protocol. Although it appears to be a benign symptom, the discomfort caused by the presence of a constant sound in the ears or head can lead to serious psychological problems. The compose of animal models of tinnitus to develop treatment alternatives will continue to be a hope for people suffering from this symptom.

Ethics

Footnotes

Authorship Contributions

Concept: A.A.Y., Design: A.A.Y., Literature Search: B.E.A., A.A.Y., Writing: B.E.A., A.A.Y.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Retrospective Analysis of Acute Promyelocytic Leukemia; A Single-center Experience

Akut Promiyelositik Löseminin Retrospektif Analizi; Tek Merkez Deneyimi

Hale Bülbül[1], Alper Togay[2]

[1]University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Hematology, İzmir, Turkey
[2]University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Medical Microbiology, İzmir, Turkey

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Abstract

Objective: Acute myeloid leukemia (AML) is an uncommon illness in and of itself. Approximately 10% of AML cases have acute promyelocytic leukemia (APL), a particularly severe form of the disease. There is a dearth of information on Turkish patients with APL. Thus, our goal was to determine the clinical, laboratory, and survival characteristics of patients with APL diagnosed within the previous 5 years at our facility.

Methods: A retrospective analysis was performed on 15 individuals who received an APL diagnosis between 2017 and 2022. IBM SPSS Statistics 25.0 was used to conduct the statistical analysis. Kaplan-Meier analysis was used for survival analysis.

Results: With a median age of 61 years, the mean age was 56.5±15.7 years. The ratio of men to women was 1.5:1. Hypergranular variation was seen in 73.3% of our cases. Based on the risk classification, 93.3% of cases were low-risk diseases. In 40% of patients, bleeding occurred, and in 13.3%, thrombosis occurred. In total, 5 patients (33.3%) passed away and 10 patients (66.6%) survived. There was a 20% early death rate. There was a 100% rate of total remission. The medians for overall survival (OS) and event-free survival were not met; instead, they were 34.1 and 37 months, respectively. The OS rate after 1 year was 66.7%.

Conclusion: The majority of patients in our group were elderly females with low-risk illnesses. According to our research, the biggest cause of treatment failure for this normally treatable type of leukemia is early mortality.

Keywords: Acute promyelocytic leukemia, early mortality, highly curable

Öz

Amaç: Akut miyeloid lösemi (AML) kendi başına nadir görülen bir hastalıktır. Akut promyelositik lösemi (APL), AML'nin özellikle agresif bir alt tipidir ve AML olgularının yaklaşık %10'unu oluşturur. Türkiye'den APL hastalarına ilişkin veriler sınırlıdır. Bu nedenle, merkezimizde son 5 yılda tanı konulan APL hastalarının klinik, laboratuvar özelliklerini ve sağkalım sonuçlarını belirlemeyi amaçladık.

Yöntem: 2017-2022 yılları arasında APL tanısı alan 15 hasta retrospektif olarak incelendi. İstatistiksel analiz, IBM SPSS Statistics 25.0 kullanılarak yapıldı. Sağkalım analizi, Kaplan-Meier analizi kullanılarak yapıldı.

Bulgular: Yaş ortalaması 56,5±15,7 olup, medyan 61'dir. Kadın-erkek oranı 1,5:1 idi. Hastalarımızın çoğunda (%73,3) hipergranüler varyant mevcuttu. Risk sınıflandırması, düşük riskli hastalığın baskın olduğunu (%93,3) ortaya koydu. Hastaların sırasıyla %40 ve %13,3'ünde kanama ve tromboz meydana geldi. Toplamda 10 (%66,6) hasta hayatta kaldı ve 5 hasta (%33,3) öldü. Erken ölüm oranı %20 idi. Tam remisyon oranı %100 idi. Ortanca olaysız sağkalım ve genel sağkalıma (OS) ulaşılamazken, ortanca değerleri sırasıyla 34,1 ve 37 aydı. Bir yıllık OS oranı %66,7 idi.

Sonuç: Kohortumuzun çoğu ileri yaş ve düşük riskli hastalığı olan kadın hastalardan oluşuyordu. Çalışmamız, kür sağlanabilen bu lösemi formu için tedavi başarısızlığındaki en büyük faktörün erken mortalite olduğunu gösterdi.

Anahtar Kelimeler: Akut promiyelositik lösemi, erken ölüm, yüksek oranda tedavi edilebilir

Address for Correspondence/Yazışma Adresi: Hale Bülbül MD, University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Hematology, İzmir, Turkey
E-mail: halebulbul95@yahoo.com
ORCID ID: orcid.org/0000-0001-5333-8679

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Introduction

A malignant condition of the bone marrow known as acute myeloid leukemia (AML) is characterized by a maturational arrest in blood cell progenitors, which prevents normal hematopoiesis. Approximately 10% of AML cases are acute promyelocytic leukemia (APL), a subtype of AML with an aggressive clinical course that is different from other forms of AML. APL was once categorized as AML-M3 in the French-American-British classification system. Presently, it is classified as t(15;17) (q24.1;q21.2); PML-RARA by the World Health Organization (WHO)[1,2]. Two morphological variations of APL have been found; the hypergranular variety is the most prevalent. APL's more aggressive microgranular type of APL, which accounts for 25% of cases, is linked to an increased risk of hemorrhagic mortality at an early stage[3]. Upon diagnosis, individuals with APL were separated into two groups solely on the basis of their white blood cell (WBC) count (≤10,000 or >10,000/μL)[4]. APL cells typically exhibit some immunophenotypic characteristics in common with their typical promyelocytic counterparts. The hypergranular variations express bright cytoplasmic myeloperoxidase, CD13, and CD33; they have a significant side scatter; they are partially, weakly, or negatively expressed for CD34; and they either do not express CD11b or express it very poorly. Compared with typical promyelocyte, APL cells display low CD15 levels and unusually moderate CD117 levels. Similar in phenotype, the microgranular variety of APL frequently co-expresses CD2 and occasionally expresses CD34, in addition to having comparatively bright myeloperoxidase expression. In addition, some cases may have CD56, which has been linked to a worse prognosis[4]. HLA-DR negative, CD33 positive, CD13 positive, CD117 moderate, occasionally CD2 positive, CD56 positive, CD11b negative, CD15 weak or negative, and CD34 negative/partially or weakly positive are the phenotypes associated with APL, with the aforementioned caveats[5]. Patients with APL present with non-specific symptoms such as weakness, infections, and hemorrhagic signs, similar to any other acute leukemia subtype. Because of its potentially lethal coagulopathy, APL has a unique shape and clinical presentation that may be linked to a high early fatality rate. The intricate process of coagulopathy involves both primary hyperfibrinolysis and disseminated intravascular coagulation (DIC), which can occur either before or immediately after cytotoxic treatment is starte[6].

Data on APL patients from Turkey are limited. The medical records of individuals diagnosed within the last 5 years at our center were examined. Demographic information, anatomical characteristics, risk assessment, clinical characteristics like bleeding and thrombosis, results from laboratory and flow cytometry testing, mutations in FLT3 (fms-like tyrosine kinase 3), treatment, response rate, overall survival (OS), event-free survival (EFS), and causes of death in patients with APL are all presented here.

Materials and Methods

The study was approved by the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (date: 15/04/2022, no: 2022/04-22). This study was conducted in the Hematology Department of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital. The study included 15 patients with APL who were over the age of 18, screened between 2017 and 2022, and had sufficient laboratory data, flow cytometry, bone marrow aspirates, and the presence of t(15;17)/PML-RARA by fluorescence *in situ* hybridization (FISH) studies and/or conventional cytogenetics. Excluded from consideration were cases that tested negative for t(15;17)/PML-RARA or for which cytogenetics/FISH results were not available. Demographic data, morphologic features, risk stratification, clinical features such as bleeding and thrombosis, laboratory and flow cytometry findings, FLT3 mutation, treatment, response rate, OS, EFS, and causes of death were recorded. Early mortality was defined as death from any cause within the first month after diagnosis. OS was computed from the diagnostic date to the day of any cause of death. The amount of time a patient remains free of illness or complications associated with the disease (EFS) following the conclusion of primary treatment for APL.

Response criteria: Morphologic complete remission (CR) was defined as the presence of normal bone marrow cellularity without leukemic promyelocyte, with an absolute neutrophil count (ANC) and platelet count >$1x10^9$/L and >$100x10^9$/L that became independent of red blood cell transfusions. Molecular CR was defined as negativity in RT-PCR analysis for the *PML-RARA* hybrid gene.

Statistical Analysis

Statistical analysis was performed using the program IBM SPSS (Statistical Package for the Social Sciences) Statistics 25.0. Data are expressed as mean ± standard deviation or median (min-max) for continuous variables and as number n (%) for categorical variables. Survival analysis was performed using Kaplan-Meier analysis.

Results

Demographics: The average age was 61 years, and the mean age was 56.5±15.7 years (range 29-83 years). The female-to-male ratio was 1.5:1. Nine (60%) of them were female and six (40%) were male.

Risk stratification: According to risk stratification, 14 (93.3%) patients belonged to the low-risk group and 1 (6.7%) to the high-risk group.

Morphological characteristics: Judging by morphology, 11 (73.3%) patients had hypergranular variants, whereas 4 (26.7%) patients had microgranular variants.

Clinical features: Bleeding occurred in 6/15 (40%) patients. Two/15 (13.3%) patients died because of early hemorrhagic complications with DIC. Thrombosis was seen in 2/15 (13.3%) patients (1 patient had pulmonary embolism and the other had multiple thromboses in coronary and cerebral vessels).

Laboratory findings: Mean hemoglobin was 8.4±1.7 (range 6.2-11.9) g/dL with a mean hematocrit of 23.3±4.9% (range 17.6-33.5). WBC count was 3.07±3.66 x10^9/L (range 0.3-13.9); ANC was 1.12±3.05x10^9/L (range 0.05-11.7), lymphocytes 0.69±0.54x10^9/L (range 0.1-2), monocytes 1.26±1.92 x10^9/L (range 0-6.7), and platelets 52±42.79x10^9/L (range 9-162). The mean value of activated partial thromboplastin time was 25.4±4.6 seconds (range 20.1-37.9); prothrombin time was 14.7±1.9 seconds (range 11.5-17.6); international normalized ratio was 1.2±0.2 (range 0.93-1.56); D-dimer was 14096.7±8110.1 µg/L (range 5000-35000); and fibrinogen was 183.4±99.4 (range 66-369) mg/dL.

Flow cytometry: CD13, CD33, CD45, and CD117 expressions were found to be positive in all patients. CD64, CD34, and CD2 were positive in 12, 4, and 3 patients, respectively. HLA-DR, CD14, CD16, and CD19 were not detected in any sample. CD34-positive samples were microgranular variants.

FLT3 mutation: The FLT3 mutation status was known in eight patients. FLT3-ITD (internal tandem duplication) mutation was found in two patients and FLT3-TKD (tyrosine kinase domain) mutation was found in three patients. No FLT 3 mutation was observed in 3 of 8 patients. One of two (50%) patients who had FLT3-ITD and 1 of 3 (33.3%) patients who had FLT3-TKD mutations died.

Treatment: Three patients (20%) died within 2 days after diagnosis. Five (33.3%), one (6.6%), and six (40%) patients were treated with all-trans retinoic acid + arsenic trioxide (ATRA+ATO), ATRA + idarubicin, and 7+3 regimens + ATRA, respectively.

Response rate: All 12 patients achieved morphologic and molecular CR after the induction regimen. The CR rate was 100%.

Survival: Median EFS and OS were not reached. The mean EFS was 34.1 months (21.2-47.1). The mean OS was 37 months (24.2-49.9). In post-remission follow-up, non-APL AML was observed in 1 patient. The 1-year survival rate was 66.7%. OS and EFS are shown in Figure 1 and 2, respectively. The clinical and laboratory features of all patients are shown in Table 1.

Death: A total of 10 (66.6%) patients survived and 5 patients (33.3%) died. Four of the five patients who died were female. The mean age was 65 years (range, 49-83 years). The hypergranular variant occurred in two (40%) patients, whereas three (60%) patients had the microgranular variant. One patient had FLT3-ITD and one patient had FLT3-TKD mutations. Three patients died within 2 days of diagnosis, and the early mortality rate was 20%. Two of them died of early hemorrhagic complications with DIC and one of them died of to thrombotic complications. One of two patients who achieved CR died on day 36 because of sudden cardiac arrest attributable to ATO cardiotoxicity, and the other died on day 40 because of cytokine release syndrome. The characteristics of the deceased patients are shown in Table 2.

Table 1. Clinical and laboratory features of all patients

	All patients (n=15)
Age, year	56.5±15.7
Gender	
-Male, n (%)	6 (40)
-Female, n (%)	9 (60)
Risk rating	
-High, n (%)	1 (6.7)
-Low, n (%)	14 (93.3)
Morphological variants	
Hypergranular, n (%)	11 (73.3)
Microgranular, n (%)	4 (26.7)
Clinical features	
Bleeding, n (%)	6 (40)
Thrombosis, n (%)	2 (13.3)

Table 1. Continued

	All patients (n=15)
Blood tests on admission	
WBC, (/μL)×10^9	3.07±3.66 (0.3-13.9)
Neutrophils, (/μL)×10^9	1.12±3.05 (0.05-11.7)
Lymphocytes, (/μL)×10^9	0.69±0.54 (0.1-2)
Monocytes, (/μL)×10^9	1.26±1.92 (0-6.7)
Hemoglobin, g/dL	8.4±1.7 (6.2-11.9)
Hematocrit (%)	23.3±4.9 (17.6-33.5)
Platelets (/μL)×10^9	52±42.79 (9-162)
aPTT (sec)	25.4±4.6 (20.1-37.9)
PT (sec)	14.7±1.9 (11.5-17.6)
INR	1.2±0.2 (0.93-1.56)
D-dimer (μg/L)	14096.7±8110.1 (5000-35000)
Fibrinogen (mg/dL)	183.4±99.4 (66-369)
Flow cytometry	
CD2, n (%)	3 (20)
CD13, n (%)	15 (100)
CD14, n (%)	0 (0)
CD16, n (%)	0 (0)
CD19, n (%)	0 (0)
CD33, n (%)	15 (100)
CD34, n (%)	4 (26.7)
CD45, n (%)	15 (100)
CD64, n (%)	12 (80)
CD117, n (%)	15 (100)
HLA-DR, n (%)	0 (0)
FLT 3 mutation	
-FLT3 ITD n (%)	2 (13.3)
-FLT3 TKD n (%)	3 (20)
-None n (%)	3 (20)
-N/A n (%)	7 (46.7)
Treatment (remission-induction)	
-ATRA + ATO n (%)	5 (33.3)
-ATRA + idarubicin n (%)	1 (6.6)
-7+3 regimen + ATRA n (%)	6 (40)
-Any treatment n (%)	3 (20)
(Death within 2 days of diagnosis)	

Data are shown as number of means ± SD (minimum-maximum). WBC: White blood cells, aPTT: Activated partial thromboplastin time, PT: Prothrombin time, INR: International normalized ratio, ATRA: All-trans retinoic acid, ATO: Arsenic trioxide, FLT3: Fms-like tyrosine kinase 3, TKD: Tyrosine kinase domain, ITD: Internal tandem duplication, N/A: Not assessed, SD: Standard deviation

Discussion

AML is a rare disease in and of itself. Approximately 10% of adult AML cases are APL instances. According to the WHO classification system, PML-RARA is categorized as APL with t(15;17) (q24.1;q21.1); PML-RARA. With a poor median OS of 1 month, APL is the most aggressive subtype of AML in the absence of therapy. It is anticipated that a large number of patients with APL will pass away before seeing a hematologist[7-9]. Data on APL patients from Turkey are limited. We have examined the information from 15 APL patients who were previously diagnosed at our hospital. The age distribution of individuals with APL differs from that of those with other types of AML. The illness is usually diagnosed in patients between the ages of 20 and 50, and after 60, it becomes less common[10]. The median age is between 33 and 40 years, according to large research[11,12]. However, in this study, the median age was 61 years, which is high compared with previous results for APL.

The incidence did not vary by gender[13]. A predominance of female gender was observed in this study, which was also found in a large cohort of 1400 patients from the United States[14]. Similarly, in Malaysian and Pakistani patients with APL, the disease was prominent in the female gender[15,16].

Patients with APL were classified into two groups according to their WBC count at diagnosis (low risk ≤10,000 or high risk >10,000/μL)[4]. Risk stratification revealed that low-risk disease was prevalent in our center. In this study, most patients had the hypergranular variant (n=11, 73.3%), whereas 26.6% (n=4) patients had the microgranular variant. Our study showed similar results to previous studies from Spain and Italy, which revealed 28%, 29%, and 20% microgranular variants, respectively[17-19].

The mechanism underlying the coagulopathy is complex and includes both primary hyperfibrinolysis and DIC, which can occur in the absence of chemotherapy or soon after the initiation of cytotoxic chemotherapy. This complication is a medical emergency because, if left untreated, it can lead to pulmonary or cerebral hemorrhage in up to 40% of patients and early hemorrhagic death in 10 to 20%[6,20]. Bleeding was observed in 40% of our patients. 13.3% of patients died of of early hemorrhagic complications with DIC. Our results were similar to previous findings. In previous studies, thrombotic complications of APL were reported with a frequency of 2-10%[21,22]. In this study, thrombotic complications were observed in 13.5% of patients, which was slightly higher than that reported in the literature.

Table 2. Characteristic features of the deceased patients

	Age	Gender	Morphologically variants	FLT3 mutation	Bleeding or thrombosis	Early death	Death after treatment	Causes of death
Patient 1	65	Female	Hypergranular	FLT3 TKD	Bleeding	Yes	No	Early hemorrhagic complications (DIC)
Patient 2	83	Female	Microgranular	N/A	Bleeding	Yes	No	Early hemorrhagic complications (DIC)
Patient 3	49	Male	Microgranular	None	Thrombosis	Yes	No	Multiple thromboses in coronary and cerebral vessels
Patient 4	67	Female	Microgranular	FLT3 ITD	Bleeding	No	Yes (on day 40)	Cytokine release syndrome
Patient 5	61	Female	Hypergranular	N/A	None	No	Yes (on day 36)	Sudden cardiac arrest (ATO induced cardiotoxicity?)

FLT3: Fms-like tyrosine kinase 3, TKD: Tyrosine kinase domain, ITD: Internal tandem duplication, DIC: Disseminated intravascular coagulation, ATO: Arsenic trioxide, N/A: Not assessed

Although FLT3-ITD is associated with higher WBC count and lower fibrinogen levels, there are limited data showing an association between the FLT3-ITD mutation and decreased OS. On the other hand, a higher FLT3-TKD mutation burden was associated with lower OS and EFS. In conclusion, the clinical significance of FLT3 mutations in patients with APL remains controversial, suggesting that further studies are needed to clarify the clinical significance of this mutation. Conversely, FLT3-TKD mutation has not been associated with the hematologic features of APL, and studies have shown no correlation between FLT3-TKD mutation and disease outcome[23-26]. FLT3 inhibitors are not recommended for FLT3-positive APL[27]. In this study, FLT3 mutation status was known in eight patients. FLT3- ITD and FLT3-TKD mutations were found in two and three patients, respectively. FLT3 inhibitors were not administered for FLT3-positivity. CR was observed in all patients who received standard therapy for APL. Relapse was not observed in this group. One of two (50%) patients who had FLT3-ITD and 1 of 3 (33.3%) patients who had FLT3-TKD mutations died. Further studies with a larger number of patients are needed to confirm the abovementioned findings.

APL represents a medical emergency with a high early mortality rate. This is evidenced by the fact that the early mortality rate in patients participating in clinical trials is less than 10%[28-30], whereas the early mortality rate in the general population is still more than 15%[31-33]. On the other hand, data from the surveillance, epidemiology, and end results registry revealed an average 30-day mortality rate of 20% between 1977 and 2007[31]. The addition of ATRA to the treatment of this subtype improved survival outcomes for patients with APL. The ability of ATRA to induce terminal differentiation of leukemic promyelocyte can improve coagulopathy, which is the major cause of mortality. Treatment should be initiated immediately when the diagnosis is suspected based on morphology and before confirmation of definitive diagnosis by cytogenetic or immunological criteria.

Similarly, we found an early mortality rate of 20%, and the main cause of mortality was considered to be coagulopathy due to late consultation with an experienced hematologist. APL is the most curable subtype of AML[9]. In this study, the high molecular CR rate was found to be independent of remission induction therapy for APL. In real-world data, OS reached approximately 92% when ATRA plus ATO was used as the first-line treatment. However, in previous studies, OS was reported between 54.6% and 68%[17,31,34-36]. Likewise, we discovered that the OS rate at 1 year was 66.7%. The median EFS and OS did not meet expectations, although they were 34.1 and 37 months, respectively.

Study Limitations

The limitation of our study could be elaborated as a single-center retrospective study that was conducted with a small number of patients.

Conclusion

In conclusion, for this usually treatable form of leukemia, early mortality is now the main cause of treatment failure. The bulk of the patients in our group were elderly females with low-risk illnesses. It is crucial to keep in mind that even in situations where clinical studies indicate low odds of early death, early mortality may actually be greater.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (date: 15/04/2022, no: 2022/04-22). This study was conducted in the Hematology Department of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Evaluation of the Responses to the Tilt Table Test of Young Male Adolescents Who Dominantly Isometric and Isotonic Sports

İzometrik ve İzotonik Sporları Ağırlıklı Olarak Yapan Genç Erkek Adölesanların Tilt Table Testine Verdikleri Yanıtların Değerlendirilmesi

Cemaliye Başaran[1], Selda Bereket Yücel[2], Şenol Coşkun[3]

[1]University Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Pediatrics, Division of Nephrology, İzmir, Turkey
[2]Marmara University Faculty of Physical Education and Sports, Department of Kinesiology and Training, İstanbul, Turkey
[3]Manisa Celal Bayar University Faculty of Medicine, Department of Pediatrics, Division of Pediatrics Cardiology, Manisa, Turkey

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Abstract

Objective: The autonomic nervous system is an issue that needs to be examined due to the symptoms that develop due to orthostatic intolerance when a person stands up. Nowadays, it is recommended to do sports regularly from childhood. In addition, there are many different ideas about which muscle groups work and how they work, and which sport is more beneficial. In our study, we aimed to examine the responses of the autonomic nervous systems to position changes in children who do regular and different sports.

Methods: The most commonly used head-up tilt test to detect orthostatic intolerance. Fifteen male wrestlers who dominantly do isometric sports, 15 male basketball players who dominantly do isotonic sports, and 15 children of similar age and gender who do not do regular sports participated in our study. After the children were placed on a tilt table and rested for 15 minutes, the table was turned to 70 degrees and their pulse and blood pressure were measured for 50 minutes, 65 minutes in total.

Results: In our study, basal cardiac pulse values were found to be lower in the athlete groups than in the control group, more clearly in the wrestler group doing isometric sports. There was an increase in cardiac pulses upon standing up in all groups. During the test, systolic blood pressure values were found to be higher in the wrestlers than in the control group, while basal diastolic blood pressure values were found to be significantly lower in the athlete groups.

Conclusion: The fact that there is a greater increase in diastolic blood pressure upon standing up in those who dominantly isometric sports compared to those who dominantly isotonic sports suggests the need to do dominantly isometric movements to prevent orthostatic intolerance which is the most common cause of vasovagal syncope.

Keywords: Exercise, head-up tilt test, orthostatic intolerance

Address for Correspondence/Yazışma Adresi: Cemaliye Başaran MD, University Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Pediatrics, Division of Nephrology, İzmir, Turkey
E-mail: cemaliyebasaran@gmail.com
ORCID ID: orcid.org/0000-0002-6422-7998

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Öz

Amaç: İnsan ayağa kalktığında ortostatik intoleransa bağlı gelişen semptomlar nedeniyle otonom sinir sistemi irdelenmesi gereken bir konudur. Günümüzde sporun çocukluk çağlarından itibaren düzenli bir şekilde yapılması önerilmektedir. Ayrıca yapılan egzersizlerde hangi kas gruplarının nasıl çalıştığı dolayısı ile hangi sporun daha yararlı olduğuna dair çok çeşitli fikirler bulunmaktadır. Çalışmamızda düzenli ve farklı spor yapan çocukların pozisyon değişikliklerine otonom sinir sistemlerinin verdiği yanıtları incelemeyi amaçladık.

Yöntem: Ortostatik intoleransın saptanmasında en yaygın kullanılan head-up tilt testidir. Çalışmamıza izometrik ağırlıklı spor yapan 15 erkek güreşçi, izotonik ağırlıklı spor yapan 15 erkek basketbolcu ve yaş ve cinsiyet benzer, düzenli spor yapmayan 15 çocuk alınmıştır. Tilt masasına yatırılan çocuklara 15 dakika dinlenmeyi takiben masa 70 derece konuma getirilerek 50 dakika, toplamda 65 dakika boyunca nabız ve kan basıncı ölçümü yapılmıştır.

Bulgular: Çalışmamızda izometrik ağırlıklı spor yapan güreşçi grubunda daha belirgin olmak üzere bazal kardiyak nabız değerleri sporcu gruplarda kontrol grubuna göre düşük saptanmıştır. Tüm gruplarda ayağa kalkma ile beraber kardiyak nabızlarında artma olmuştur. Test boyunca sistolik tansiyon değerleri güreşçilerde kontrol grubuna göre yüksek saptanırken bazal diyastolik tansiyon değerleri sporcu gruplarda anlamlı şekilde düşük saptanmıştır.

Sonuç: İzometrik ağırlıklı spor yapanlarda ayağa kalkma ile beraber diyastolik kan basıncında izotonik ağırlıklı spor yapanlara göre daha fazla artışın olması vasovagal senkopun en sık görülen nedeni olan ortostatik intoleransın önlenmesinde izometrik ağırlıklı hareketlerin daha fazla yapılması gereğini düşündürmektedir.

Anahtar Kelimeler: Egzersiz, head-up tilt testi, ortostatik intolerans

Introduction

Changes in the cardiovascular system due to changes in the position of the human body have been a subject of constant interest and curiosity. Factors that are effective in regulating blood flow during body position changes; gravity, autonomic nervous system, cardiovascular system, central nervous system and endocrine system[1].

The response of the autonomic nervous system varies the most in a healthy person. Therefore, the autonomic nervous system response in people who experience symptoms with changes in body position is a subject that is widely evaluated. Nowadays, it is recommended to perform sports regularly starting from childhood for the cardiovascular system to function healthily. In addition, various ideas have been put forward about which sport is more beneficial due to the type of sport and which muscle groups work in which way in the exercises. The most important problem in position changes is orthostatic intolerance, which develops because of the displacement of blood in the body[2]. Although various methods are used to detect orthostatic intolerance, the head-up tilt test is currently the most used for this purpose[3-6].

Because the contraction patterns of various muscle groups in our body differ during our movements, their effects on the cardiovascular system are also different[7]. Isometric muscle contraction is a type of contraction in which the muscle tone increases while its length remains constant. This is also called static muscle contraction. In isotonic muscle contraction, the muscle length shortens (concentric) or lengthens (eccentric). Also called dynamic muscle contraction. In both types of contractions, the heart rate increases. This increase in heart rate is largely dependent on decreased vagal tone, although increased cardiac sympathetic nerve discharge also plays a role. During isometric muscle contraction, systolic and diastolic blood pressures rise sharply. Stroke volume changes relatively less, and blood flow to the constantly contracting muscles decreases because of their pressure on the blood vessels. Unlike isotonic contraction, there was a significant increase in stroke volume in this table. In addition, there was a clear decrease peripheral resistance due to vasodilation in the exercising muscles. As a result, systolic blood pressure increased moderately, whereas diastolic blood pressure generally remained unchanged or decreased. Mean arterial pressure increases because cardiac output increases because of the decrease in total peripheral pressure[8,9]. The exercises that people perform in their daily lives also include a combination of dynamic and static exercises.

In this study, we aimed to examine the responses of the autonomic nervous system to position changes in children who play sports regularly and with different characteristics and to determine which of the results is the desired response to position changes.

Materials and Methods

The study included 15 male athletes who have been actively working for at least 3 years in the sport of wrestling, where isometric muscle contraction is used more intensely, and in the sport of basketball, where isotonic muscle contraction is used more frequently (training for at least 2 h for 4 days a week and participating in domestic and international competitions). The control group was selected from individuals of similar age and gender who were not actively

involved in any sports. Ethical approval for the study was obtained (Manisa Celal Bayar University Faculty of Medicine, 2005/0001).

Tilt Table Test Protocol

All subjects tested had fasted the night before or had eaten at least 2-3 hours before monitoring, if the test was performed early in the morning. After the subjects were informed about follow-up, a written consent form was signed. The subjects were monitored after being connected to the tilt table. All subjects were allowed to rest in the supine position for approximately 15 min before the start of the test to stabilize their heart rate and blood pressure. Then, the tilt table was tilted to 70° and the subjects were allowed to stand for 50 min, which was the test period. Cardiac rhythm, heart rate, and blood pressure were monitored with at least 3-lead ECG recording with a continuous monitor at 3-min intervals. Pharmacological provocation was not used. The test was performed under the supervision of a pediatrician to avoid potential complications. The test results were evaluated by making double comparisons within each group, between groups, and triple comparisons between three groups. In addition, the test duration was compared in three different periods for each group.

1-First 15 min: To obtain basal values in the supine position,

2-Between the 15th and 45th minutes: To obtain the response in the early period of standing,

3-Between the 45th and 65th minutes: To obtain the response in the late period of standing.

Statistical Analysis

The data obtained were provided using SPSS for Windows 11.0. Kruskal-Wallis and Mann-Whitney U tests were used for comparisons between the groups. A p-value 0.05 was considered significant.

Results

Fifteen basketball players, 15 wrestler children, and 15 healthy children of similar age and gender who do not play sports regularly were included in the study. The children were all boys. The average age of those involved in wrestling sports was 15.40±0.73, the average age of those involved in basketball sports was 12.26±0.79, and the average age of the control group was 13.26±1.43. None of the participating children had a history of syncope in themselves or in their families. When all three groups were compared separately as the basal rest period in the first 15 min, the early period of standing between the 15th and 40th min, and the late period of standing between the 40th and 65th min, cardiac pulse values throughout the entire test period were lowest in wrestlers and slightly higher in basketball players. It was found to be higher and statistically significantly higher in the control group than in the other two athlete groups. No significant difference was detected in terms of systolic and diastolic blood pressure (Table 1).

When the control, basketball player, and wrestler groups were compared separately in the first 15 min, between 15 and 40 min, and between 40 and 65 min, the cardiac pulse values during the basal rest period were significantly lower than the values in the early and late periods of the standing period. Additionally, there was no significant difference between cardiac pulse values in the standing position.

When the control, basketball player, and wrestler groups are compared in terms of systolic blood pressure values during the basal rest period and the early and late periods of the standing period, the difference between them is not significant.

There was no difference in the control group in terms of diastolic blood pressure values during the basal rest period and the early and late periods of the standing period.

When the basketball player and wrestler groups were compared in terms of the parts of the test, the diastolic blood pressure values measured during the basal rest period were found to be significantly lower than those measured during both the 2nd and 3rd parts of the test. However, the difference between the second and third parts of the test was not statistically significant.

When the control group and the basketball player group were compared separately in terms of cardiac pulse values during the basal rest period, the early period of standing, and the late period of standing, there was no statistically significant difference in the basal rest period and the early period of standing. However, during the late period of standing, pulse values in the control group were significantly higher than those playing basketball (p=0.01).

When the control group and the basketball player group were compared separately in terms of systolic and diastolic blood pressure values during the basal rest period, the early period of standing, and the late period of standing, it was observed that there was no significant difference between them.

Table 1. Comparison of the groups in all three test sections

		n=15 (each group)	Median ± SD	p
0-15th minute	Cardiac pulse values	Control	86.4±6.7	0.015*
		Basketball players	84.0±9.3	
		Wrestlers	76.7±10.4	
	Systolic BP	Control	108.2±6.5	0.07
		Basketball players	110.7±6.7	
		Wrestlers	114.0±2.0	
	Diastolic BP	Control	66.5±4.6	0.07
		Basketball players	64.8±4.5	
		Wrestlers	62.0±5.7	
15-40th minute	Cardiac pulse values	Control	93.1±2.0	0.005*
		Basketball players	90.0±5.5	
		Wrestlers	83.8±10.2	
	Systolic BP	Control	109.8±6.2	0.45
		Basketball players	110.9±5.3	
		Wrestlers	113.0±2.6	
	Diastolic BP	Control	67.1±3.6	0.18
		Basketball players	68.1±3.6	
		Wrestlers	66.6±5.8	
40-60th minute	Cardiac pulse values	Control	93.4±2.4	0.00*
		Basketball players	88.8±7.2	
		Wrestlers	84.8±7.7	
	Systolic BP	Control	110.0±5.7	0.06
		Basketball players	111.5±4.0	
		Wrestlers	113.6±2.3	
	Diastolic BP	Control	66.9±1.9	0.12
		Basketball players	68.1±2.8	
		Wrestlers	66.3±3.4	

SD: Standard deviation, BP: Blood pressure; *Kruskal-Wallis and Mann-Whitney U tests were used to compare all three groups. A p-value 0.05 was considered significant

When the control group and the wrestler group were compared separately in terms of cardiac pulse values during the basal rest period, the early period of standing, and the late period of standing, the cardiac pulse values of the wrestlers were found to be significantly lower than those of the control group during the entire test period (p=0.002, 0.0005, 0.00 respectively).

When the control group and the wrestler group were compared separately in the first 15 minutes, 15th-40th minutes and 40th-65th minutes, the systolic blood pressure values of the wrestlers were found to be significantly higher than the control group during the basal rest period and in the late period of standing (p=0.01, 0.018 respectively). However, there was no significant difference between the 15th and 40th minutes between the two groups.

When the control and wrestler groups were compared separately during the three periods of the test, the diastolic blood pressure values of the wrestlers were found to be significantly lower than those of the control group during the basal rest period (p=0.03). However, there was no significant difference in the standing period.

When the basketball player group and the wrestler group were compared in terms of cardiac pulse throughout the entire test period, the wrestlers' cardiac pulse was found to be significantly lower than that of the basketball player

group throughout the entire test (p=0.02, 0.02 and 0.04, respectively).

When the basketball player and wrestler groups were compared, there was no significant difference between the groups in terms of systolic and diastolic blood pressure values during the three periods of the test.

Discussion

The head-up tilt test was used to compare the responses of children performing isometric and isotonic sports to orthostatic position change. During the entire test, the wrestlers' pulse rates were lower. Simultaneously, during the basal rest period at the beginning of the test, the wrestlers' systolic blood pressure values were found to be high and their diastolic blood pressure values were low, and at the end of the test, systolic blood pressure remained high.

The tilt table test is used as a very effective test in the evaluation of patients with vasovagal syncope triggered by orthostatic change[10]. It is an effective technique for direct diagnosis in the sensitive evaluation of vasovagal syncope[11]. The most important problem in position changes is orthostatic intolerance, which develops because of the autonomic characteristics of bipedal creatures when they become upright. Orthostatic intolerance refers to the development of symptoms (temporary loss of consciousness and/or postural tone) when moving from a lying position to a standing position[1,10,11]. When we stand up, the veins below the heart level fill with blood, the return to the heart decreases, and cerebral perfusion decreases because of the hydrostatic pressure in the blood[11]. When we stand up, the rapid decrease in the amount of blood flowing to the brain due to the pooling of blood in the large veins due to the position of the brain above the cardiac point and the gravity below it causes cerebral ischemia and loss of consciousness[12]. In response to blood pooling in the lower extremities, the muscles act as pumps and return the blood to the heart. During orthostatic changes, reflex compensatory mechanisms cause changes in heart rate and vasoconstriction[13]. In later stages, defense against cerebral hypoperfusion can be established through the release of renin-angiotensin-aldosterone, the release of epinephrine and norepinephrine, and the initiation of the central effect.

The exercises that people perform in their daily lives include a combination of dynamic and static exercises. The systemic cardiovascular response depends on whether muscle contractions are primarily isometric or isotonic. The heart rate increases with isometric muscle contraction. This increase in heart rate is largely dependent on decreased vagal tone, although increased cardiac sympathetic nerve discharge also plays a role. During isometric muscle contraction, systolic and diastolic blood pressures rise sharply. Stroke volume changes relatively less, and blood flow to the constantly contracting muscles decreases because of their pressure on the blood vessels. The response to exercise involving isotonic muscle contraction is similar to the situation described above in that there is a sudden increase in heart rate, but unlike these, there is also a significant increase in stroke volume. In addition, there was a clear decrease peripheral resistance due to vasodilation in the exercising muscles. As a result, systolic blood pressure increased moderately, whereas diastolic blood pressure generally remained unchanged or decreased. Mean arterial pressure increases because cardiac output increases because of the decrease in total peripheral pressure[9].

In the head-up tilt test, the response to normal heart rate and blood pressure is an increase in heart rate by 10-20 beats per minute. The increase in systolic blood pressure was not very significant. Diastolic pressure and mean arterial pressure increase to some extent, thus reducing the pulse pressure. These changes occur because of the rapid displacement of blood to the lower extremities and are a normal response. Most studies recommended that the angle be 60-70 degrees and found the specificity to be 90% and the sensitivity to be 67-83% in the absence of pharmacological agents[14,15]. In studies conducted by Fitzpatrick et al.[16], it was suggested that the tilt duration should be 45 min. They found the average time for syncope to occur to be 24 min. They point out that the 40-min tilt duration is more useful in detecting syncopal attacks than the 30-min tilt test, but extending the test further and continuing up to 60 min increases the sensitivity only slightly[17]. In our study, following the 15-min basal period, the tilt table was turned to 70° and the test duration was determined as 65 min. Pharmacological provocation was not applied because of its negative effect on test specificity.

Because of the study, when the three groups were compared, it was observed that the cardiac pulse values of the wrestlers were lower than those of the basketball players, and the cardiac pulse values of the basketball players were lower than those of the control group throughout the entire test. These basal values can be explained by the fact that the heart rate in athletes is lower than that in those who do not participate in sports. In addition, the fact that the heart rate

in wrestlers, that is, people who do dominantly isometric exercise, is lower than that in both basketball players and the control group can be attributed to the increase in total peripheral resistance in isometric exercise and the lower amount of blood returning to the heart due to the effect of the muscles contracting on the blood vessels.When the control group, basketball player group, and wrestler group were compared among themselves, a statistically significant increase was observed in the cardiac pulse values in the first 15 min after removing the tilt table. This increase was 7.75% in the control group, 7.1% in the basketball player group, and 9.2% in the wrestler group. This is the normal response of the head-up tilt test. This is an expected response that occurs due to the change in the amount of blood pooled in the lower extremities returning to the heart upon standing up.

In a study by Mallat et al.[18], it was pointed out that this early increase in heart rate in the tilt test is an important harbinger of the test being positive, whereas Newby et al.[19] stated that their own observations were not in this direction. Another study on the subject supports the predictive importance of the early increase in heart rate on the positivity of the test. In other words, while the test results in vasovagal syncope in people who have an increase in heart rate in the early stages of standing up, there are also researchers who found the opposite of this view in their studies[18-20].

In our study, the heart rate increased upon standing in all groups. This situation, which has been evaluated in favor of a positive test in various studies, was also encountered in our study, but the test did not result in a positive result in the control, basketball player, and wrestler groups included in the study. When the control and basketball player groups were compared, a significant decrease in pulse values was observed in the basketball player group toward the end of the test period. However, when the basketball player group was compared among themselves, pulse values were found to be low only in the first 15 min. Therefore, it would be wrong to talk about a decrease in the heart rate of basketball players toward the end of the test period.

In pairwise comparisons between the groups, while there was no significant difference between the basketball player group and the control and wrestler groups, when the control group and the wrestlers were compared, it was determined that the systolic blood pressure values in the wrestler group were significantly higher than those in the control group, both during the basal rest period and during the remaining test period. This was a response consistent with high systolic blood pressure during predominantly isometric exercise. In the head-up tilt test, an increase in systolic blood pressure upon standing up was expected. However, such an increase or decrease was not observed in any group in our study.

When a comparison was made between the groups in terms of diastolic blood pressure values, diastolic blood pressure values were found to be significantly lower in the basketball player and wrestler groups during the first 15 min compared with the subsequent test period. However, there was no significant difference between the diastolic blood pressure values of the control, basketball, and wrestler groups when compared separately and together. While the basal diastolic blood pressure increased by 5.0% upon standing in the basketball player group, this value was 7.4% in the wrestler group. This increase is compatible with the response to the displacement of blood in the body upon standing up.

There are important differences between dynamic and static muscle contractions. One of the most important of these relates to blood supply to the muscles. In static muscle contractions, blood vessels work under great pressure because of the continuous contraction effect in the muscles. This causes less and less blood to be sent to the muscles. In dynamic contraction, there is a positive effect on blood circulation as muscle movement contract and relax rhythmically. During contraction, blood reaches the ends of the capillaries that feed the muscle fibers, allowing 10-20 times more blood to reach these places. Therefore, during dynamic muscle contraction, the muscle receives plenty of glucose and oxygen, and wastes can be eliminated immediately. During strong static muscle contraction, neither glucose nor oxygen reaches the muscle. In addition, waste accumulates and is not eliminated from the muscle. Therefore, it is very difficult to withstand long-term static muscle contraction. Because the feeling of pain occurs because of these wastes. If a suitable rhythm is provided for dynamic muscle contraction, it can be continued for a long-time without any wear and tear (for example, heart muscles). During static muscle contraction, blood transport decreases inversely proportional to contraction. When the applied muscle force reaches 60% of the maximum muscle force, blood flow is completely cut-off. In lower muscle force applications, because there is less pressure on the blood vessels, some blood circulation can be achieved. During a muscle contraction of 15-20% compared with maximum loading, blood flow to the muscle is normal. While a muscle contraction of 20% can be sustained for a long time, a muscle contraction of 50% or more can be sustained for at

most 1 min. Therefore, activities that result in continuous static muscle contraction are not desirable.In a study conducted by Croci et al.[21], who investigated the effect of isometric hand gripping movement in preventing vasovagal syncope during daily life, based on the fact that isometric hand grasping movement increases blood pressure in the initial phase of vasovagal syncope, patients were made to perform hand gripping or arm stretching movements when they experienced the symptoms in the initial phase of syncope. This effect is caused by mechanical compression of the venous vascular bed in the abdomen and legs and by increased vascular resistance and sympathetic discharge during maneuvers. Therefore, it is recommended as the first treatment option in the initial stages[21].

Isotonic exercise (treadmill and bicycle) is often used to determine tolerance to exercise. However, static exercise occurs more during daily activities, and therefore, it is necessary to compare the two. In a study conducted for this purpose to determine the cardiovascular responses to static and dynamic exercise in patients with non-valvular atrial fibrillation, the exercise tolerance of the patients was investigated. The patients were given treadmill exercise as a dynamic (isotonic) exercise and hand grasping exercise as a static (isometric) exercise. When the heart rate values at the first, second, and third minutes of the exercise were compared, it was found to be significantly higher on the treadmill than in manual gripping. When the systolic and diastolic blood pressures at the 1st minute were compared, higher values were obtained on the treadmill. As a result, it was observed that the heart rate response of the patients to static exercise was lower and the patients tolerated the static exercise better[22].

In some people, orthostatic intolerance to body position changes is a major problem. Because of our study, there was a greater increase in diastolic blood pressure upon standing up in those who performed isometric-based wrestling compared with those who performed isotonic-based sports. This suggests that isometric weighted movements should be performed more frequently to prevent orthostatic intolerance, which is the most common cause of vasovagal syncope.

Study Limitations

The strength of our study is that it will contribute to the limited literature by evaluating the responses of young male athletes who perform isometric and isotonic sports to the tilt table test. Its limitations are that it was performed only on male athletes, no pharmacological provocation was used, and the number of participants was relatively small.

Conclusion

As a result, although the effects of dynamic exercise on the cardiovascular system are more positive, studies have shown that isometric muscle movements are beneficial, especially in the initial stage of vasovagal syncope. However, the effect of isometric and isotonic contraction on the cardiovascular system and orthostatic position changes in people is worth investigating.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained (Manisa Celal Bayar University Faculty of Medicine, 2005/0001).

Informed Consent: After the subjects were informed about follow-up, a written consent form was signed.

Footnotes

Authorship Contributions

Concept: C.B., S.B.Y., Ş.C., Design: C.B., S.B.Y., Ş.C., Data Collection or Processing: C.B., S.B.Y., Ş.C., Analysis or Interpretation: C.B., S.B.Y., Literature Search: C.B., S.B.Y., Writing: C.B., S.B.Y., Ş.C.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Evaluation of Occupational Hygiene Measurement Results of Chemical Risks in Hospitals: A Cross-sectional Study

Hastanelerde Kimyasal Risklerin İş Hijyeni Ölçüm Sonuçlarının Değerlendirilmesi: Kesitsel Bir Çalışma

Ayşe Coşkun Beyan[1], Berke Manoğlu[2], Emrah Beyan[3]

[1]Dokuz Eylül University Faculty of Medicine, Department of Occupational Medicine, İzmir, Turkey
[2]Dokuz Eylül University Faculty of Medicine, Department of General Surgery, İzmir, Turkey
[3]Private Medifema Hospital, Clinic of Obstetrics and Gynecology, İzmir, Turkey

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Abstract

Objective: According to the characteristics of the tasks in hospitals -cleaning works, laboratory services, polyclinic services- chemicals with high evaporation potential at room temperature and that named volatile organic compounds are used. Healthcare workers are defined as one of the worker groups that are most exposed to chemical risks in the literature. To protect the health of healthcare workers, it is necessary to evaluate the chemical risks in terms of possible negative health and safety effects for health workers and to measure their levels.

Methods: In this cross-sectional study, the measurement of chemical risks in hospitals will be discussed over two years of data from an accredited occupational hygiene laboratory to measure chemical risks.

Results: To 2.328 occupational hygiene measurements performed in 26 hospitals, 341 (14.6%) were related to chemical risks. Of the chemical risk measurement results, 19 (5.5%) exceeded the permissible limit value. Although different occupational risks were measured in 4 hospitals, chemical risks were not measured.

Conclusion: Although the activities and legal legislation offered through risk assessment in our country are sufficient in terms of quality, there are situations that need to be improved in quantity. It has been observed that national standards on the measurement of chemical risks do not adequately define the parameters to be measured, where and how they will be measured.

Keywords: Healthcare workers, hospital, chemical risks, occupational hygiene

Öz

Amaç: Hastanelerde yapılan işin özelliklerine göre-temizlik işleri, laboratuvar hizmetleri, poliklinik hizmetleri gibi- birimlerde oda sıcaklığında buharlaşma potansiyeli yüksek olan ve uçucu organik bileşikler adını verdiğimiz kimyasallar kullanılmaktadır. Sağlık çalışanları literatürde kimyasal risklere en yoğun maruz kalan çalışan gruplarından biri olarak tanımlanmaktadır. Sağlık çalışanının sağlığını koruyabilmek için kimyasal risklerin sağlık çalışanları için olası olumsuz sağlık ve güvenlik etkileri açısından değerlendirilmesi ve çalışma ortamlarındaki düzeylerinin ölçülmesi gereklidir.

Yöntem: Kesitsel olarak yürütülen bu çalışmada kimyasal riskleri ölçmek üzere akredite bir iş hijyeni laboratuvarın iki yıllık verileri üzerinden hastanelerdeki kimyasal risklerin ölçümü konusu ilgili ulusal mevzuat ile birlikte tartışılacaktır.

Address for Correspondence/Yazışma Adresi: Assoc. Prof. Ayşe Coşkun Beyan, Dokuz Eylül University Faculty of Medicine, Department of Occupational Medicine, İzmir, Turkey
E-mail: dr.aysecoskun@hotmail.com
ORCID ID: orcid.org/0000-0002-3731-2978

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Öz

Bulgular: Yirmi altı hastanede yapılan toplam 2,328 iş hijyeni ölçümünden 341'i (%14,6) kimyasal riskler ile ilgili idi. Kimyasal riskler ölçüm sonuçlarından 19'u (%5,5) izin verilen sınır değeri aşmıştı. Dört hastanede diğer iş hijyeni risklerinin ölçümü yapılsa da kimyasal riskler ölçülmemişti.

Sonuç: Ülkemizde risk değerlendirme ile sunulan faaliyetler ve yasal mevzuat nitelik olarak yeterli olsa da nicelik olarak geliştirilmesi gereken durumlar bulunmaktadır. Kimyasal risklerin ölçümü ile ilgili ulusal standartların ölçülecek parametreleri, nerede ve nasıl ölçüleceğini konusunda rehberlere ihtiyaç bulunmaktadır.

Anahtar Kelimeler: Sağlık çalışanı, hastane, kimyasal riskler, iş hijyeni

Introduction

Healthcare workers are exposed to numerous different risks considering the diversity of tasks and chemicals used in hospitals. The National Institute for Occupational Safety and Health in America has indicated that there are 25 different chemical hazards and risks in hospitals[1,2]; disinfectants, sterilizers, anesthesia gasesgasses laboratory work, and cleaning materials are the main sources of chemical risk in the hospital environment. Chemical risks are classified into volatile, semi-volatile, and persistent chemical substances based on their evaporation potentials at room temperature. Volatile organic compounds (VOCs), which continuously evaporate into the ambient air due to their high evaporation level, are usually colorless and odorless. We not only inhale these chemicals present in high concentrations in the ambient air but also absorb them through other routes such as dermal and mucosal pathways[3,4]. Isopropyl alcohol, ethanols used in disinfection and cleaning tasks, fluoranes found in anesthesia gases; (enflurane, isoflurane, desflurane, and sevoflurane), nitric oxide, ether; acetone, glutaraldehyde, formaldehyde, toluene, xylene, and ammonia commonly encountered in pathology laboratories are examples of VOCs[5]. Chemicals have acute or chronic, direct or indirect toxic effects on worker health. Toxicity varies depending on the exposure route, duration and frequency of exposure, dose of the chemical substance exposed and polymorphic features in genes and enzymes playing a role in the toxicokinetics of the toxic substance[6]. Acute effects usually arise due to intense exposures because of spills or scatterings. Respiratory or dermal irritation symptoms that start immediately after the incident are prominent. However, in chronic exposure cases, there is usually low dose and long-term exposure; they can cause toxicities such as liver and kidney damage, permanent damage on the central nervous system, asthma and respiratory diseases, congenital anomalies, and cancer[7-10]. Measuring exposure to chemicals directly or indirectly, risk control studies in the workplace, causality assessments in occupational health relations, and selection of appropriate personal protective equipment for workers are among the most important steps in planning occupational health and safety (OHS) activities[11]. Therefore, it is recommended to measure chemical risks at regular intervals using occupational hygiene methods in both national legislation and international regulations. However, there are vague issues in legal regulations about which risk will be measured where, how much, and how. There are insufficient data regarding the measurement of chemical risks in hospitals in Turkey. This study aimed to obtain data on occupational hygiene measurements and chemical risks in hospitals through occupational hygiene laboratory measurement reports and compile the relevant legal regulations in Turkey.

Materials and Methods

The study is a cross-sectional type of research. In Turkey, the authority to perform occupational hygiene measurements is given to occupational hygiene laboratories that have received accreditation certificates from Republic of Turkey Turkish Accreditation Agency by the relevant legal regulations. Accordingly, there are 10 occupational hygiene laboratories in the province of İzmir. Three of them currently appear active and have adequate laboratory status (https://www.isgum.gov.tr/labyetki.aspx). The three laboratories were contacted by phone and asked to share their data, but only one laboratory volunteered to share its data. In this study, occupational hygiene measurement result reports carried out in hospitals by a private laboratory, which is an accredited institution, between 2021 and 23 were evaluated. Occupational hygiene measurements were performed by the same experimental staff using the same methods, and the collected samples were measured by the same devices according to the Turkish Standards Instution ISO 16200-1 standard[12]. The regulation of OHS activities related to chemical risks in hospitals, occupational hygiene measurements, and protective measures were searched on the national legislation website https://www.mevzuat.

gov.tr/ with the keywords "chemical risk", "occupational hygiene", "occupational health", "occupational safety", "risk assessment", "measurement of risks", "volatile organic compounds", "carcinogen and mutagen", "hospital", "dental technician", "medical laboratory".

Data collection and data anonymization: The measurement results consist of an introductory part presenting the experimenter who performed the measurement, the date of measurement, the name of the hospital where the measurement was made, the number of workers, and the list of measured parameters, followed by sections where the tables providing risk measurement results are presented and where the measured values are compared with permitted limit values. Identifying data of hospitals were anonymized by the laboratory manager and shared with the responsible researcher.

The study was conducted in compliance with research and publication ethics. The study was approved by the Non-Interventional Ethics Committee of Dokuz Eylül University, İzmir (decision no: 45269, date: 04.09.2021).

Statistical Analysis

Descriptive findings are given with mean and standard deviation, minimum-maximum values for numerical measurement values, and percentage for categorical values. The analysis was performed using the SPSS 21.0 package program.

Results

In this study, the occupational hygiene measurement data of an accredited occupational hygiene laboratory for the years 2021-2022 were evaluated. Of the total 108 measurement activities carried out by the laboratory during the specified period, 24% (26) were conducted in hospitals. Accordingly, the average number of workers in 21 hospitals with worker data was 1081.5 and the median number of workers was 490. The least number of workers was found in a dental technician laboratory with 2 workers while the highest number of workers was observed in a secondary level state hospital with 4.500 workers. The average number of all occupational hygiene risk measurements conducted in 26 hospitals was 93.1 parameters, and the median value was 44 parameters. The hospital with the least number of occupational hygiene measurements measured 1 parameter, and the hospital with the most measured 496 parameters. Among these measurements, the average number of VOC measurements was 13.2, median 7, the hospital that did the most had conducted 74 VOC parameter measurements, and the hospital that did the least had not conducted any VOC measurements. Although different occupational hygiene measurements were made in 4 hospitals, no VOC measurements were made. The number of measurements exceeding the permitted limit value among VOC measurements was 19 out of 327 measurements (5.8%). Of the 19 measurements, 10 were measured in the pathology laboratory in the same hospital. Generally, it has been observed that VOCs are most frequently measured in pathology laboratories and dental technician laboratories. It was observed that an OHS professional participated in occupational hygiene measurements in 13 measurements, while they did not participate in the rest. Data regarding the number of workers in hospitals and occupational hygiene measurements are presented in Table 1.

In organizing OHS activities related to chemical risks in hospitals, access to 254 legal regulations was achieved in the search made with the keywords given in the method part of the compilation studies related to occupational hygiene measurements. The 14 regulations related to chemical risks in hospitals are presented in Table 2. Accordingly, it is observed that besides the general OHS legal regulations related to chemical risks in hospitals, regulations related to quality systems in health are quite comprehensive.

Discussion

In this study, occupational hygiene measurement results performed in 26 different hospitals over two years were evaluated. It was observed that hospitals mainly focused on quantitatively measuring VOCs in their occupational hygiene measurements, however, significant qualitative differences were observed. It is noteworthy that the number of VOC measurement results exceeding the permissible limit value is low in all measurements. In the national legislation, it was seen that the regulations that might be related to the measurement of chemical risks in hospitals were collected under two headings, regulations related to OHS and regulations related to quality in health.

Different results can be encountered in studies regarding the measurement of chemical risks in hospitals. In their study, Bessonneau et al.[13] reported that they measured more than 40 VOCs in 6 different units of a hospital, but almost all were below the permissible limit value. LeBouff et al.[14] stated that they measured 14 different VOCs in 14 health workers in 5 hospitals and that the worker groups had a wide variety of VOC exposures. Therefore, they emphasized the importance

of determining the substances to be measured using a good job analysis[14]. Rautiainen et al.[15] mentioned the importance of planning the measurements according to the worker groups, in addition to technical features such as the size of the room, whether the place of measurement is closer to the ceiling or the floor among the parameters considered while making measurements in 47 hospitals. Both guides and literature discussions show that the planning stage is crucial in VOC measurements. When the measurement results made in 26 different hospitals in this study are evaluated, it is seen that there is no standard regarding the parameters measured. It is not understood for what purpose, in which units, and which parameters are measured in hospitals. It is noteworthy that the risk of VOCs has not been measured in 4 of the 26 hospitals where other occupational risks have been measured. This finding brings to mind the

Table 1. Characteristics of hospitals where occupational hygiene measurement was performed and parameters measured

Hospital	The number of employees	Total OHS parameters measured	The number of VOCs	Measurement locations	The number of VOC measurements exceeding the permitted limit value	Participation of OHS specialists in measurements
H1	235	1	1	Dental technician lab.	0	Yes
H2	300	3	3	Pathology lab	0	No
H3	798	138	6	ICU/operating room	0	Yes
H4	870	36	7	General	0	No
H5	Data not available	19	8	General	0	No
H6	847	496	28	General	0	No
H7	300	108	7	General	0	No
H8	Data not available	143	8	Central lab/operating room	0	No
H9	3150	357	56	General	10	No
H10	200	111	7	General	0	No
H11	Data not available	28	2	Pathology lab	0	No
H12	1322	235	65	General	4	Yes
H13	1650	90	6	General	3	Yes
H14	Data not available	97	74	General	0	Yes
H15	194	26	7	Operating room/ sterilization unit	0	No
H16	430	44	7	Data not available	0	Yes
H17	1650	100	22	General	2	Yes
H18	2	2	1	Pathology lab	0	Yes
H19	Data not available	11	11	General	0	Yes
H20	4500	36	1	Dental technician lab.	0	Yes
H21	4500	14	0	General	0	Yes
H22	300	46	1	General	0	Yes
H23	490	28	13	General	0	Yes
H24	700	16	0	General	0	Yes
H25	25	143	0	General	0	No
H26	250	14	0	General	0	No

"Total OHS Parameters Measured" refers to the total number of occupational hygiene parameters measured, ICU: Intensive care unit, OHS: Occupational health and safety, VOCs: Volatile organic compounds

Table 2. Regulations in national legislation related to chemical risks in hospitals

Regulation name	A year of acceptance	Section/s related to chemical risks
Law no. 6331 on occupational health and safety	2012	Concepts of hazard and risk, employer duties and responsibilities in risk identification and control activities
Regulation on duties, authorities and responsibilities of workplace physicians	2013	Activities to guide the employer in health surveillance of employes and surveillance of the working environment within the scope of OHS services
Regulation on duties, authorities and responsibilities of occupational safety experts	2012	Guidance to the employer in risk assessment, risk control activities, planning occupational hygiene measurements, and controlling applications
Occupational health and safety services regulation	2012	In the activity areas of the OHSBs, provided that they obtain approval from the general directorate, OHSBs can keep the necessary equipment for all kinds of measurements and analyzes related to occupational health and safety at the address where the OHSB operates, limited to the employes and the workplace where they provide service, and can employ the relevant personnel
Regulation on occupational health and safety services to be conducted by the employer or employer representative at workplaces	2015	Measurements to be made in the workplace according to the provisions in the law and sub-regulations are carried out by laboratories authorized by the ministry
Regulation on health and safety measures in work with chemical substances	2013	The employer is obliged to determine whether there is a dangerous chemical substance in the workplace and to make a risk assessment to determine the adverse effects on the health and safety of the workers in case of a dangerous chemical substance. The employer ensures that measurements and analyzes of chemical substances that may pose a risk to employeshealth are made regularly. These measurements are repeated when there is any change in conditions that could affect employesexposure to chemical substances. Measurement results are evaluated considering the occupational exposure limit values specified in the annexes of this regulation
Regulation on the procedures and principles of occupational health and safety training for employees	2013	Chemical risks and health effects in training subjects
Regulation on occupational health and safety risk assessment	2012	Multiple articles - it is recommended to read in detail
Dental prosthetics laboratories regulation	2005	Laboratory types and mandatory tools and equipment Vacuum dust collector workbench, mask, and obligation to provide occupational safety gloves that can prevent chemical exposure
Regulation on improving and evaluating quality in health 2023 quality evaluations in health standards (general hospital) Measurements of formalin and xylene in pathology units and comparison with the permitted limit value in ministry of health circular	2015	Employee safety score and management of chemical, biological, radiological, and nuclear (CBRN) hazards measurement of formalin and xylene in pathology units and comparison with the permissible limit value Ventilation should be available in pathology units for volatile chemicals
regulation on health and safety measures in work with carcinogenic or mutagenic substances	2013	Risk assessment, measurement of chemicals and risk control studies, occupational exposure limit values in Annex-2 of the regulation
Regulation on occupational hygiene measurement, test and analyses	2023	Multiple articles - it is recommended to read in detail
Medical waste control regulation	2017	Pathological waste treated with any chemical, volatile and semi-volatile organic substances, mainly chemical substances, genotoxic/cytotoxic agents, radiological waste and pressurized containers cannot be found among the waste to be sterilized
Regulation on private health institutions providing oral and dental health services	2022	The measures specified in the relevant legislation are taken for the provision and protection of patient and employe safety in health institutions

Repealed regulations are excluded. OHS: Occupational health and safety

question of whether it was thought that there was no VOC risk in that hospital when planning. It was observed that the number of parameters measured in hospitals measuring VOCs is very variable. In the hospital that made the least measurements, only one (excluding the number of hospitals not making any measurements) in the hospital that made the most measurements, 74 VOC measurements were made. Accordingly, there are differences in VOC measurement planning in certain units common in hospitals -central laboratory, operating room, pathology- units. In the study by Ndlele and Naidoo[16] on cleaning workers in hospitals, it has been defined that there are many chemical risks for cleaning jobs only. In this study, it was seen that no special evaluation was made for cleaning workers in the measurements made in hospitals[16]. Considering that the number of measurements exceeding the permissible limit value is 19 (5.8%) and 10 of the 19 measurements were measured in the pathology laboratory of the same hospital, it is striking that only 10 measurement results are high. If it is assumed that this could be due to the lack of sufficient regulations regarding the planning and execution of measurements, possible errors related to measurement and analysis, it is thought that national legal regulations and inspections on the subject are insufficient. However, studies with larger data are needed.

In Table 2, it is seen that the regulations collected in two separate headings are general OSH regulations and regulations related to quality in health in the compilation made specifically for chemical risks in hospitals. It is seen that the legislation talks about the subject with general definitions of its activities in the field of OSH. It is striking that the regulations related to quality in health define the parameters to be measured for pathology laboratories in detail along with measurement periods. This explains the result that the unit with the most measurements in the results of the study was the pathology laboratory. However, in Turkey, the delay in the implementation of law no. 6331 on OHS, which is the main regulation regarding OSH, for hospitals is at the forefront of the problems in the implementation of the legislation in the field. According to the Business Inspection Board activity report, a total of 8.592 inspections consisting of 148 scheduled and 8.444 unscheduled inspections from the perspective of the conduct of work in 2022 and a total of 17,842 inspections consisting of 15,761 scheduled and 2.081 unscheduled inspections in terms of OSH in 2022 have been conducted. No inspection activity in hospitals was encountered in the details of the report. A similar result was reached in the reports of the previous year[17]. The positive results of regulations such as the applications of health quality systems, guidance, application, and inspection activities are obvious. Although the awareness about OSH and health issues of healthcare workers has increased with Coronavirus, it is thought that the lack of sufficient activity in the inspection leg, postponement of regulations, etc. hinder the development of occupational hygiene activities in hospitals[18-20].

Study Limitations

In this study study's reliance on evaluations based on a single data set constitutes a significant limitation. However, it should not be forgotten that voluntary assessments are inevitable due to the lack of the publication of measurement data on the subject by a national authority.

Conclusion

In conclusion, hospitals are distinctive workplaces in terms of the chemical risks they harbor. However, there is a need first to ensure the implementation of existing legal regulations on the subject and then to provide guidance to the field with new regulations. The preparation of guideline documents and the conduct of constructive inspections are important for the standardization of occupational hygiene activities. Regulations related to quality in healthcare, which are effectively implemented and audited in the field and which guide the field, are considered to be good examples of practice.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Ethics Committee of Dokuz Eylül University, İzmir (decision no: 45269, date: 04.09.2021).

Informed Consent: Not applicable.

Footnotes

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Authorship Contributions

Concept: A.C.B., B.M., E.B., Design: A.C.B., Data Collection or Processing: A.C.B., B.M., E.B., Analysis or Interpretation: A.C.B., B.M., E.B., Literature Search: A.C.B., B.M., E.B., Writing: A.C.B., B.M., E.B.

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A New Approach to Acute Pulmonary Embolism: Coronary Sinus Diameter to Inferior Vena Cava Diameter Ratio

Akut Pulmoner Embolide Yeni Bir Yaklaşım: Koroner Sinüs Çapı - İnferior Vena Kava Çapı Oranı

Uğur Küçük[1], Ercan Akşit[1], Ali Kılınç[2]

[1]Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Cardiology, Çanakkale, Turkey
[2]Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Radiology, Çanakkale, Turkey

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Abstract

Objective: This study aimed to explore whether the coronary sinus (CS) diameter to the inferior vena cava (IVC) diameter (CS/IVC) ratio measured by computed tomography pulmonary angiography (CTPA) can be used to predict pulmonary embolism (PE) and its relationship with worse clinical outcomes.

Methods: Our study included 198 patients. Study patients were divided into groups according to the presence of PE. CS and IVC diameters were measured using CTPA. While PE was not detected in 132 patients, it was detected in 66 patients.

Results: The CS/IVC ratio (78.3±18.8% and 49.3±17.2%, p<0.001) was higher in the PE group. The CS/IVC ratio was established as a predictor of PE (odds ratio: 4.189, 95% confidence interval: 1.990-8.819, p<0.001). The cut-off value for the CS/IVC ratio value was ≥60.8 (sensitivity: 86.4%, specificity: 77.3%, positive predictive value: 66.67%, and negative predictive value: 94.44%) in PE. It was observed that clinical outcomes were higher in patients with CS/IVC ratio ≥60.8%.

Conclusion: The CS/IVC ratio was predictive of PE in patients diagnosed with acute PE. The CS/IVC ratio may be useful in estimating patients hospitalized for PE who require close monitoring.

Keywords: Pulmonary embolism, coronary sinus, computerized tomographic, diameter

Öz

Amaç: Bu çalışmada bilgisayarlı tomografi pulmoner anjiyografide (BTPA) ölçülen koroner sinüs (KS) çapının inferior vena kava (İVK) çapına (KS/İVK) oranının pulmoner emboliyi (PE) öngörmede kullanılıp kullanılamayacağı ve bunun daha kötü klinik sonuçlarla ilişkisi araştırılmıştır.

Yöntem: Çalışmamıza 198 hasta dahil edildi. Çalışma hastaları PE varlığına göre gruplara ayrıldı. KS ve İVK çapları BTPA kullanılarak ölçüldü. PE 132 hastada saptanmazken, 66 hastada saptandı.

Bulgular: KS/İVK oranı (%78,3±18,8 ve %49,3±17,2, p<0,001) PE grubunda daha yüksekti. KS/İVK oranı PE'nin öngörücüsü olarak belirlenmiştir (olasılık oranı: 4,189, %95 güven aralığı: 1,990-8,819, p<0,001). PE'de KS/İVK oranı değeri için kesme değeri ≥60,8 (duyarlılık: %86,4, özgüllük: %77,3, pozitif prediktif değer: %66,67 ve negatif prediktif değer: %94,44) idi. KS/İVK oranı ≥%60,8 olan olgularda klinik sonuçların daha yüksek olduğu gözlenmiştir.

Sonuç: KS/İVK oranı akut PE tanısı konan hastalarda PE için öngörücüdür. KS/İVK oranı, PE nedeniyle hastaneye yatırılan ve yakın izlem gerektiren hastaların tahmin edilmesinde yararlı olabilir.

Anahtar Kelimeler: Pulmoner emboli, koroner sinüs, bilgisayarlı tomografi, çap

Address for Correspondence/Yazışma Adresi: Assoc. Prof. Uğur Küçük, Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Cardiology, Çanakkale, Turkey
E-mail: drugurkucuk@hotmail.com
ORCID ID: orcid.org/0000-0003-4669-7387

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Introduction

Pulmonary embolism (PE) is a common cardiovascular emergency[1]. The following heart attack and stroke, PE is the third major cardiovascular cause of death[2]. PE can have various clinical manifestations in patients, ranging from asymptomatic cases to cases presenting with right ventricular dysfunction and life-threatening clinical outcomes, depending on the severity of the obstruction in the pulmonary artery (PA). D-dimer, transthoracic echocardiography (TTE), and computed tomography pulmonary angiography (CTPA) are some tests used to diagnose PE[3,4]. CTPA is the diagnostic imaging technique that is generally used worldwide for the diagnosis of PE because of its high accuracy rate, as well as its easily accessible and non-invasive nature. Moreover, CTPA provides vital prognostic information; hence, it remains useful for the physicians[5].

The coronary sinus (CS) is an intrapericardial vein that drains into the right atrium (RA). It has a tubular structure and is located in the atrioventricular groove in the posterior part of the heart[6]. Extracardial veins, which are involved in the body's essential venous circulation, drain into the RA along with the intrapericardial veins[7]. Because the RA receives a large portion of the venous circulation in a normally functioning heart, clinical conditions involving primary or secondary cardiac involvement, such as right heart failure and pulmonary hypertension, which can cause increased pressure in the RA, will result in impaired venous drainage and a change in CS and inferior vena cava (IVC) diameter[8,9]. In cases of PE, where the PA bed is fully or partially blocked, increased pulmonary artery pressure (PAP) and pressure in the right ventricle (RV) afterload develops[10]. Invasively measured systolic PA and RA pressures were shown to be correlated with CS and IVC diameters in studies[11,12].

Based on this information, we believe that full or partial obstruction of the PA bed causes secondary changes in the right cardiac cavities and associated anatomical structures in patients with PE and that these changes can help detect the PE. Therefore, the current study investigates the CS/IVC ratio, which compares the CS diameter to the IVC diameter measured in CTPA, to determine whether this ratio can be used to predict PE and its relationship with worse clinical outcomes (in-hospital mortality and hospital stay duration).

Materials and Methods

Patients and the Study Design

Our study encompassed patients eligible for inclusion who underwent contrast-enhanced thoracic computed tomography (CT) and received a preliminary diagnosis of PE at a tertiary health center between January 1, 2015, and July 1, 2021. A total of 3,310 patients who were prediagnose with PE upon admission to our hospital were retrospectively reviewed. A total of 198 patients were included in our study, comprising 66 patients who had recently been diagnosed with PE and 132 patients who met the age- and gender-related inclusion criteria but were not diagnosed with PE. CTPA was performed on the patients when they were admitted to the emergency department. The PE diagnoses and types were determined using current guidelines[13]. Obstruction of the PA branch and blockage of blood flow to the distal pulmonary section were defined as PE.

The exclusion criteria were as follows: Chronic kidney disease (epidermal growth factor receptor <30 mL/min/1.73 m^2), stroke, active infection, diagnosed malignancy, history of PE or pulmonary hypertension, history or previous treatment for congenital valvular heart disease, diagnosed chronic obstructive pulmonary disease, cardiac tamponade, permanent pacemaker, moderate to severe valvular disease, severe pulmonary disease, intubation, anomalies (such as duplication and persistent left superior vena cava), documented left ventricular systolic dysfunction (left ventricular ejection fraction <50%), and diastolic dysfunction, along with a history of right ventricular dysfunction and age 18 years.

The hospital's electronic medical records were used to obtain data on patients' information and laboratory values.

This study received Çanakkale Onsekiz Mart University's Ethical Committee approval (decision no: 2011-KAEK-27/2021-2100135640) and was conducted in accordance with the Declaration of Helsinki.

Image Data

Thoracic vascular examinations were performed by the same radiologist. The images, which were taken with 320-slice MSCT (Aquilion One Vision Edition, Toshiba Medical Systems, Nasu, Japan), were analyzed. The CT scan was 5-mm slice thick and featured 1.5 steps. Contrast agent was used for thoracic images during the full inspiratory phase of the CT scan (an injection rate: 2 to 2.5 mL/s). CS diameter was calculated from a distance of 1 cm from the CS ostium[14]. While measuring the diameter of the IVC, the short axis of the vein is evaluated. The IVC diameter was measured between the right atrial orifice and hepatic vein. A sample image showing the CS and IVC measurements is presented in Figure 1.

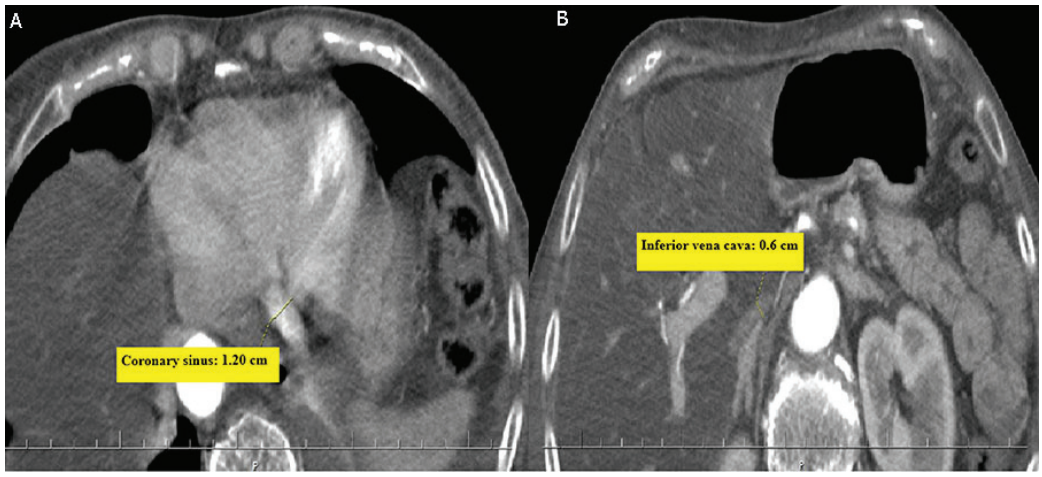

Figure 1. Measurement of the coronary sinus and inferior vena cava diameters

Statistical Analysis

SPSS 19.0 (SPSS Inc, Chicago, IL, USA) software was used for statistical analysis. Continuous variables were analyzed using the Kolmogorov-Smirnov test. The data were presented as mean ± standard deviation or median (interquartile range). Numbers and percentages are used to express categorical variables. The t-test and Mann-Whitney U test were used to compare normally and non-normally distributed parameters. Chi-square tests were used to compare the odd ratios of categorical variables. Pearson's test was used for correlation analysis. Receiver operating characteristic (ROC) curves were created for the CS/IVC ratio, and their cut-off values were determined. PE predictors were analyzed using multivariate logistic regression. P-values of <0.05 were considered statistically significant.

Using G*Power (effect size: 0.50, alpha error: 0.05, and power 95%), the sample size for our study was calculated to be 66 patients in group 1 and 132 patients in group 2.

Results

The study included 198 patients, with 66 patients diagnosed with acute PE (29 males, 37 females) and 132 patients in the control group (60 males, 72 females). The D-dimer and cardiac troponin (Tn) values were statistically and numerically higher in the PE group. CS diameter (12.70±3.40 mm and 8.87±2.60 mm, p<0.001), IVC diameter (18.57±4.47 mm and 17.01±4.52 mm, p=0.023), CS/IVC ratio (78.3±18.8% and 49.3±17.2%, p<0.001), and CS/IVC/body surface areas (BSA) (41.4±9.9% and 25.9±9.9%, p<0.001) were higher in the PE group (Table 1).

CS diameter was positively correlated with D-dimer, sPAP, and cardiac Tn. IVC diameter was correlated with sPAP. CS/IVC ratio was positively correlated with D-dimer, sPAP, and cardiac Tn (Table 2). The correlation analysis between the CS/IVC ratio and sPAP was performed using Pearson's test and presented using Scatter dot analysis (Figure 2).

According to the analysis performed on the variables to determine their predictive value for PE, the model had a coefficient value of 93.3%. The CS/IVC ratio was established as the predictor of PE [odds ratio (OR): 4.189, 95% confidence interval (CI): 1990-8.819, p<0.001] (Table 3).

According to the analysis performed on the CS/IVC ratio to determine its predictive value in PE, the cut-off value was ≥60.8. According to the analysis performed on the CS/IVC/BSA ratio to establish its predictive value in PE, the cut-off value was ≥30.3 (Table 4). Receiver operating characteristic (ROC) curve analysis was performed to assess CS [area under the curve (AUC): 0.813, 95% CI: 0.751-0.876, p<0.001], CS/IVC ratio (AUC: 0.865, 95% CI: 0.815-0.916, p<0.001) and CS/IVC/BSA (AUC: 0.869, 95% CI: 0.818-0.919, p<0.001) for their predictive value in PE (Figure 3).

When patients with PE were analyzed as two groups according to CS/IVC ratio (%) ≥60.8 and CS/IVC ratio (%) <60.8%, differences were observed between the groups in terms of hospital stay and mortality [7.24±2.32 and 5.84±1.49 days, respectively, p<0.001; hospital stay duration] and [5 (5.6) and 0 (0) n (%), respectively, p=0.017; in-hospital mortality] (Table 5).

Table 1. Demographic, echocardiographic, and laboratory findings of patients with pulmonary embolism and the control group

	Pulmonary embolism group (n=66)	Control group (n=132)	p-value
Age (years)	67.2±15.9	69.8±13.6	0.231
Gender (n)			0.840
Male	29	60	
Female	37	72	
Smoking (n)	14	23	0.519
Hypertension (n)	6	22	0.149
Diabetes mellitus (n)	11	24	0.792
Body mass index, (kg/m^2)	24.75±1.45	24.76±1.44	0.972
Heart rate (beats/min)	84.48±12.16	81.91±13.24	0.188
SBP (mmHg)	117.69±5.89	119.64±7.78	0.075
DBP (mmHg)	81.03±7.03	83.18±7.14	0.160
Glucose (mg/dL)	118.92±40.75	118.23±48.78	0.921
Creatinine (mg/dL)	0.93±0.16	0.96±0.14	0.235
Hemoglobin (g/dL)	13.16±2.27	13.16±2.30	0.990
D-dimer, ng/mL	77 (55-88)	3 (2-4)	<0.001
Cardiac Tn, ng/L	9.5 (2.5-36)	6 (2-7)	0.003
LVEF (%)	57.96±3.68	58.77±3.48	0.144
LA diameter (mm)	31.45±5.22	30.25±5.24	0.131
RA diameter (mm)	29.45±4.62	25.37±5.03	<0.001
sPAP (mmHg)	35 (25-50)	21 (20-25)	<0.001
CS (mm)	12.70±3.40	8.87±2.60	<0.001
IVC (mm)	18.57±4.47	17.01±4.52	0.023
CS/IVC ratio (%)	78.3±18.8	49.3±17.2	<0.001
CS/IVC/BSA (mm/m^2) (%)	41.4±9.9	25.9±9.0	<0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Tn: Troponin, LVEF: Left ventricular ejection fraction, LA: Left atrium, RA: Right atrium, sPAP: Systolic pulmonary artery pressure, CS: Coronary sinus, IVC: Inferior vena cava, BSA: Body surface areas

Table 2. Correlation of variables with computed tomography-derived measurements in patients with pulmonary embolism

	CS		IVC		CS/IVC ratio	
	r value	p-value	r value	p-value	r value	p-value
BMI	0.040	0.576	0.039	0.585	0.131	0.066
SBP	0.008	0.916	0.026	0.711	0.004	0.959
DBP	0.025	0.725	0.081	0.256	0.059	0.407
sPAP	0.507	<0.001	0.159	0.025	0.605	<0.001
Cardiac Tn	0.153	0.031	0.036	0.611	0.223	0.002
D-dimer	0.421	<0.001	0.139	0.050	0.339	<0.001

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, sPAP: Systolic pulmonary artery pressure, Tn: Troponin, CS: Coronary sinus, IVC: Inferior vena cava

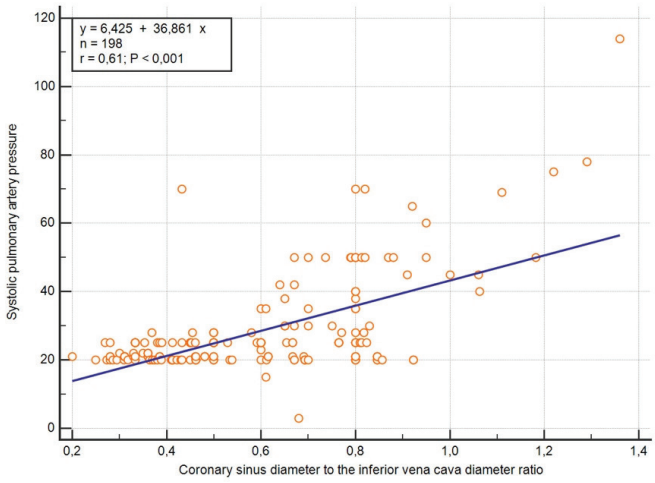

Figure 2. Correlation analysis of CS/IVC ratio and sPAP

CS: Coronary sinus, IVC: Inferior vena cava, sPAP: Systolic pulmonary artery pressure

Discussion

We demonstrated that the CS/IVC ratio was predictive of PE on CTPA imaging in patients who were diagnosed with acute PE for the first time compared with healthy individuals. Second, in cases of PE, the increased CS/IVC ratio may lengthen the duration of hospitalization and increase in-hospital mortality.

Table 3. Predictors of pulmonary embolism

	p	OR	(95% CI)
D-dimer	<0.001	2.814	(0.956-1.021)
CS/IVC ratio	<0.001	4.189	(1.990-8.819)
sPAP	0.003	1.141	(1.044-1.246)
Cardiac Tn	0.458	0.988	(0.956-1.021)

CS: Coronary sinus, IVC: Inferior vena cava, sPAP: Systolic pulmonary artery pressure, Tn: Troponin, OR: Odds ratio, CI: Confidence interval

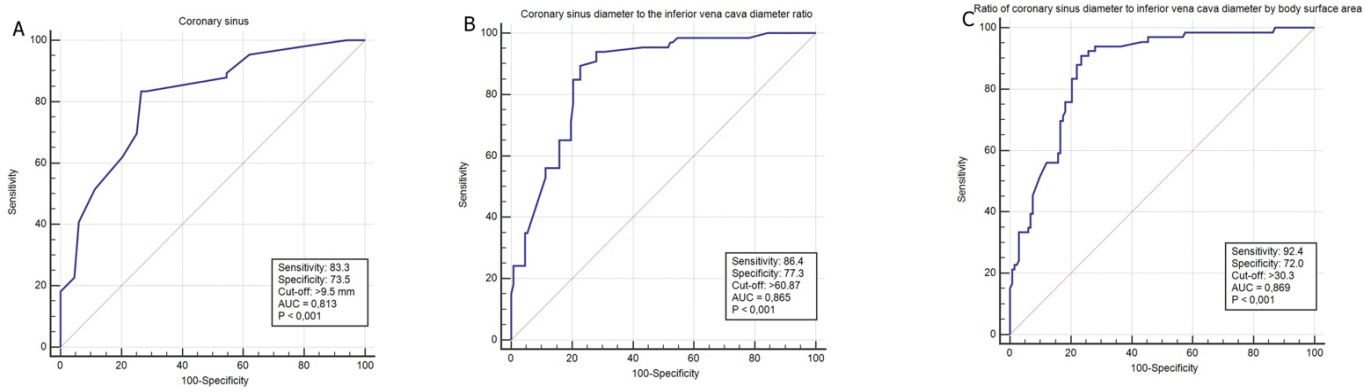

Figure 3. Receiver operator characteristic (ROC) curve analysis of CS, CS/IVC ratio, and CS/IVC/BSA to predict pulmonary embolism

AUC: Area under the curve, CS: Coronary sinus, IVC: Inferior vena cava, BSA: Body surface areas

Table 4. Diagnostic performance results of the CS/IVC ratio in pulmonary embolism

	Cut-off value	Sensitivity	Specificity	PPV	NPV
CS (mm)	≥9.5	83.3	73.5	59.34	88.79
CS/IVC ratio (%)	≥60.8	86.4	77.3	66.67	94.44
CS/IVC/BSA (mm/m^2) (%)	≥30.3	92.4	72.0	65.56	93.52

CS: Coronary sinus, IVC: Inferior vena cava, BSA: Body surface areas, PPV: Positive predictive value, NPV: Negative predictive value

Table 5. Clinical outcomes of patients

	All (n=66)	CS/IVC ratio (%) ≥60.8	CS/IVC ratio (%) <60.8	p
In-hospital mortality, n (%)	5 (7.6)	5 (5.6)	0 (0)	0.017
Hospital stay duration (days)	6.47±2.03	7.24±2.32	5.84±1.49	<0.001

CS: Coronary sinus, IVC: Inferior vena cava

Acute PE is an important cardiovascular disease with a mortality rate ranging from 15% to 20%. The severity of RV dysfunction that develops because of PA obstruction has an adverse effect on survival[15]. Vasoconstriction caused by mechanical obstruction in the pulmonary bed results in increased right ventricular afterload[16]. An acute increase in right ventricular afterload can lead to various clinical symptoms, such as dilatation in the tricuspid annulus, elevated RA pressure, increase in right ventricular end-diastolic volume, impairment of left ventricular functions, and hemodynamic instability[17]. Specific treatments, such as early reperfusion therapy, are required for survival in patients with PE, particularly in the presence of hemodynamic instability[18]. Therefore, early detection and treatment of PE will be highly beneficial in avoiding poor clinical outcomes.

CTPA, in addition to being the gold technique for the diagnosis of PE, has the benefit of allowing intrapericardial and extrapericardial structures, such as the CS and IVC, to be easily detected[19]. Imaging of the coronary venous system is overshadowed by that of the coronary artery. Along with their widespread use in the current clinical world, such as stem cell therapy, left ventricular pacemakers have been implanted in an increasing number of cases and studied in an increasing number of electrophysiological studies, emphasizing their connection to clinical diseases[20,21]. Because CS has a thin wall structure, it is easily dilated in clinical diseases, including right heart failure and pulmonary hypertension, which can result in increased pressure in the RA and ventricles[22]. Previous studies have shown that CS dilatation can be used to predict the severity of heart failure and poor functional capacity; another study has shown that CS diameter correlates with RA size and pressure of the RA[23,24]. In a study investigating the prognostic value of CTPA parameters in acute PE, it was observed that a dilated CS (>9 mm) carries an additional prognostic value when associated with echocardiographic signs of right heart dysfunction and elevated Tn-I levels[25]. These findings may hold clinical significance in assessing the severity of PE and aiding in the risk stratification and management of patients in emergency departments and intensive care units. CS diameters in patients with PE were found to be significantly higher both numerically and statistically than those in healthy individuals in our study. In our study, CS diameter exceeding 9.5 mm demonstrated reasonable diagnostic performance for PE. In addition, D-dimer, sPAP, and cardiac Tn were substantially correlated with CS diameter. Because CS reflux and increased coronary venous pressure have previously been associated with coronary slow flow, it is possible that this explains why cardiac Tn levels rise in some patients without the right ventricular pressure or volume load[25].

Moreover, IVC (unlike CS) is the main channel that provides venous rotation to the RA from the lower extremities and internal abdominal organs[27]. In the non-contrast post-mortem CT study in PE, it was stated that increased IVC may suggest PE. However, the study emphasizes that IVC distension may be a finding that may suggest PE rather than being used as a radiological finding alone[28]. Considering our study and literature findings, we believe that hemodynamic results, especially in the right heart, may be related to IVC dilatation. Our study concluded that sPAP and IVC diameter were significantly correlated. The increases in both CS and IVC diameters, as seen in the study data, indicate the impact of right ventricular volume elevations on indirect venous structures. When considering the literature reviews and our study results together, the potentially more significant contribution of CS dilation compared with IVC dilation to the increase in the CS/IVC ratio may be attributed to various underlying factors.

RV differs from the left ventricle in several ways. Pulmonary circulation pressures are much lower than systemic circulatory pressures in patients without pulmonary vascular disease. Because RV is formed of a thin layer of myofibrils extending parallel to the long axis of the heart, it will be severely affected by sudden changes in PAP[29]. In patients with PE, a reduction in RV reserve is likely to affect filling pressures, resulting in a high pressure in the right cardiac cavities and a change in the anatomical structures around them. Our hypothesis is supported by a previous study that used invasive methods to show that higher pressure in the RA was related to CS and IVC diameters[30].

In addition to CTPA, the use of bedside transthoracic echocardiography (TTE) (presence of right ventricular strain findings, such as D-sign and McConnell's sign) may help in diagnosis[31]. Although TTE may seem more advantageous than CTPA because it does not contain radiation, alternative findings are needed because the parameters have low sensitivity for PE[32]. According to studies in the literature, CTPA has become more often used in cases with suspected PE, whereas diagnostic efficiency has decreased[33,34]. However, the proficiency level of clinicians who choose CTPA is also important for the diagnostic efficiency of CTPA. In addition, according to recent studies, CTPA is used for screening purposes rather than for diagnostic

testing[35,36]. This statement is also supported at the low PE detection rate (range: 6-25%) of CTPAs reported in the literature[37,38]. To make the diagnosis, auxiliary examinations should be considered before opting for advanced imaging examinations, risk of developing cancer due to radiation, and risk of nephropathy in CTPA[39,40]. The CS/IVC ratio had acceptable sensitivity, specificity, and normalized pulse volume values for the diagnosis of PE, according to the data obtained in our study.

In this study, we evaluated the effectiveness of a new algorithm for PE diagnosis using CTPA imaging. Despite the availability of advanced diagnostic and treatment methods, PE remains an important health issue. Death often occurs during the period following the diagnosis. The current guidelines contain no information about the utility of the CS/IVC ratio in patients newly diagnosed with PE, although, as shown in our study, this ratio may be a useful parameter for early diagnosis in acute patients with PE. According to our study results, the CS/IVC ratio may be a useful clinical algorithm for predicting PE patients requiring close follow-up.

Study Limitations

The diameters of the CS and IVC can be easily determined using contrast CT imaging. Patients with poor image quality were eliminated from the study, and measurements were taken with patients during the inspiration phase. The respiratory phase may affect the diameters of the CS and IVC. Although it is anticipated that the use of electrocardiography may help obtain optimal diameter measurements, the current guidelines exclude any information about the use of electrocardiogram (ECG) in CTPA in patients with PE. The use of ECG-assisted procedures in cases such as PE, which require emergency diagnosis and treatment, remains controversial due to the risk of patients being exposed to more radiation. Although our aim is to evaluate these patients using a routine practical approach, new prospective studies are needed to address these shortcomings.

Conclusion

We demonstrated that the CS/IVC ratio on CTPA imaging was predictive of PE in patients diagnosed with acute PE for the first time. Although CTPA is commonly used in many patients who have been prediagnose with PE, PE is only diagnosed in some cases. According to the results of our study, the CS/IVC ratio is understood to be a strong predictor of worse clinical outcomes in PE. Our novel findings may provide physicians with useful information on worse clinical outcomes in the diagnosis of PE, and they may also serve as a guide for future studies, including CS/IVC measures using various diagnostic tools.

Ethics

Ethics Committee Approval: This study received Çanakkale Onsekiz Mart University's Ethical Committee approval (decision no: 2011-KAEK-27/2021-2100135640) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Evaluation of the Appropriateness of Fresh Frozen Plasma Indications and Cost Analysis: A Comprehensive Study

Taze Dondurulmuş Plazma Endikasyonlarının Uygunluğunun Değerlendirilmesi ve Maliyet Analizi: Kapsamlı Bir Çalışma

Yiğithan Güzin[1], Yeşim Oymak[2], Canan Vergin[2]

[1]University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Pediatric Neurology, İzmir, Turkey
[2]University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Clinic of Pediatric Hematology, İzmir, Turkey

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Abstract

Objective: Fresh frozen plasma (FFP) has limited indications despite its frequent use. This study aimed to investigate the clinical and laboratory findings of patients who received FFP transfusion. The suitability and effectiveness of transfusion were also examined.

Methods: We retrospectively reviewed the files of patients who underwent FFP transfusion for any reason below the age of 18 years. Transfusion suitability was determined based on the transfusion guidelines.

Results: Two hundred eight FFP transfusions to 134 patients were included in the study. In total, 429 units of FFP were transfused. Of the 208 transfusions, 156 (75%) were appropriate based on indication and 52 (25%) were considered inappropriate. In total, 87 out of the 429 units of the product (20.2%) were transfused inappropriately. None of the patients who received inappropriate transfusions exhibited signs of bleeding. Significant improvements in prothrombin time and activated partial thromboplastin time were observed in patients who received transfusions with appropriate indications.

Conclusion: In this study, the incidence of inappropriate FFP transfusion was lower compared to other centers. However, 3 out of 4 patients received prophylactic FFP for bleeding prevention. The cost of inappropriate transfusions in this study was estimated at $1640 annually. Since transfusion practices are mostly based on adult studies, our study will increase awareness regarding transfusion practices among children. Consequently, there is a need for educational programs that can reduce the rate of FFP transfusions.

Keywords: Fresh frozen plasma, transfusion, suitability, effectiveness, children

Öz

Amaç: Taze donmuş plazma (TDP) sık kullanılmasına rağmen sınırlı endikasyona sahiptir. Bu çalışmanın amacı TDP transfüzyonu yapılan hastaların klinik ve laboratuvar bulgularını araştırmaktır. Ayrıca transfüzyonun uygunluğu ve etkinliği de incelenmiştir.

Yöntem: Herhangi bir nedenle TDP transfüzyonu yapılan 18 yaş altı hastaların dosyaları retrospektif olarak incelendi. Transfüzyon uygunluğu transfüzyon kılavuzuna göre belirlendi.

Bulgular: Çalışmaya 134 hastaya yapılan iki yüz sekiz TDP transfüzyonu dahil edildi. Toplam 429 ünite TDP transfüzyonu yapıldı. Yapılan 208 transfüzyonun 156'sı (%75) endikasyonlara göre uygunken, 52'si (%25) uygunsuz olarak değerlendirildi. Toplam 429 ünite ürünün 87'si (%20,2) uygunsuz olarak transfüze

Address for Correspondence/Yazışma Adresi: Yiğithan Güzin MD, University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Pediatric Neurology, İzmir, Turkey
E-mail: yguzin@hotmail.com
ORCID ID: orcid.org/0000-0002-8748-5586

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Öz

edilmiştir. Uygunsuz transfüzyon yapılan hastaların hiçbirinde kanama belirtisi görülmemiştir. Uygun endikasyonlarla transfüzyon yapılan hastaların protrombin zamanı ve aktive parsiyel tromboplastin zamanı değerlerinde anlamlı iyileşmeler gözlendi.

Sonuç: Bu çalışmada, diğer merkezlere kıyasla uygunsuz TDP transfüzyonu insidansı daha düşüktü. Bununla birlikte, her dört hastadan üçü kanamayı önlemek için profilaktik TFP almıştır. Bu çalışmada uygunsuz transfüzyonların maliyeti yıllık 1640$ olarak hesaplanmıştır. Transfüzyon uygulamaları çoğunlukla yetişkin çalışmalarına dayandığından, çalışmamız farkındalığı artıracaktır.

Anahtar Kelimeler: Taze donmuş plazma, transfüzyon, uygunluk, etkinlik, çocuklar

Introduction

Fresh frozen plasma (FFP) is a component of blood that contains coagulation factors, antibodies, electrolytes, and plasma proteins. FFP transfusion is commonly used for the treatment of bleeding disorders or hemostasis in patients at high bleeding risk. It is important to note that FFP transfusion should be performed based on careful consideration of each patient's clinical condition, laboratory values, and specific needs. The decision to administer FFP should be made by healthcare professionals following appropriate guidelines and protocols[1,2]. The number of regular, voluntary blood donors in our country is below the national level. Therefore, the acquisition of blood products is difficult and costly. The unnecessary use of blood products not only poses risks of side effects but also contributes to the early depletion of high-cost products that are difficult to obtain. The indications for FFP transfusion are notably limited. Similar to other blood components, FFP has the potential for transfusion reactions and infection risks.

Materials and Methods

The medical records of patients aged 18 years and younger who received TFP transfusion at the University of Health Sciences Turkey, Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital were retrospectively evaluated. The suitability of transfusion indications was determined according to the transfusion guidelines[3,4]. The FFP dose was adjusted according to the patient's weight[1,3].

Clinical and demographic characteristics of the patient (gender, age, blood type, diagnosis), clinical department where the patient was hospitalized, indication for hospitalization, and coagulation parameters were recorded.

The indication for FFP administration, acute reactions, and post-transfusion laboratory values specific to the patient were documented. According to the Turkish Healthcare Practice Directive, the total cost of FFP transfusions performed with inappropriate indications was calculated, with each unit of FFP priced at 18.85 USD.

This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital. Ethics committee approval number and date: 2017/08-05, 08/06/2017. Informed consent was not obtained as this was a retrospective study.

Statistical Analysis

Data were analyzed using SPSS software. Normality was checked via the Shapiro-Wilk test. For normally distributed data, mean ± standard deviation was presented; for non-normal data, median (IQR) was used. Categorical variables were compared with the chi-square or Fisher's exact test, while continuous variables were analyzed using independent t-tests or Mann-Whitney U tests. ANOVA or Kruskal-Wallis tests were used for comparisons across multiple groups, with post-hoc tests as needed. Statistical significance was set at $p<0.05$.

Results

A total of 208 FFP transfusions were included in our study, including 134 patients. Among the 134 patients, 55 (41%) were female, and 79 (59%) were male, with a median age of 1 years (minimum: 1 month-maximum: 18 years). Of the patients, 52 (38.8%) were from surgical departments (30 from cardiovascular surgery and 22 from pediatric surgery), whereas 82 (61.2%) were from pediatric services (neonatal intensive care 31). In total, 429 units of FFP were administered, with 165 units (38.5%) administered in surgical clinics and 264 units (61.5%) administered in pediatric clinics.

Of the 208 transfusions administered, 156 (75%) were classified as appropriate based on the defined criteria, whereas 52 (25%) were categorized as inappropriate (Table 1). Regarding the total product units, 20.2% (87/429 units)

was transfused inappropriately (Table 2). It was observed that there was a significantly higher rate of inappropriate transfusions in surgical departments compared with internal medicine clinics (p=0.001).

Among the eight inappropriate transfusions in internal medicine clinics, four showed disseminated intravascular coagulation without bleeding, and two exhibited prolonged coagulation parameters. None of the patients who received inappropriately transfused FFP at internal medicine clinics presented with bleeding symptoms. In surgical departments, out of the 44 inappropriate transfusions, 34 (77.2%) were performed during surgeries, nine (20.5%) were due to coagulation disorders, and one (2.7%) was classified as "other". None of the patients who received inappropriate transfusions at the surgical branches showed signs of bleeding.

In terms of appropriate transfusions, pre- and post-transfusion values of prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer were evaluated, revealing no significant differences in D-dimer and fibrinogen, whereas pre-transfusion PT and aPTT values were found to be longer. No significant differences were found in all evaluated coagulation parameters before and after inappropriate transfusions (Table 3, 4).

Patients who received the highest number of FFP transfusions were those diagnosed with sepsis and those undergoing preoperative preparation. When examining the coagulation parameters of patients with sepsis, a significant decrease in the pre-transfusion PT median value from 18.0 to 15.9 s was observed after transfusion (p=0.001). Likewise, pre-transfusion aPTT decreased from 36.1 to 34.3 after transfusion (p=0.001). No complications related to transfusion were

Table 1. The number of appropriate transfusions and the amount of product used

	Number of transfusions	Amount of product used (units)
Preoperative preparation	37 (23.9%)	98 (28.9%)
Coagulation disorder + bleeding	14 (9.0%)	33 (9.8%)
DIC + bleeding	94 (59.9%)	197 (57.9%)
Massive transfusion and blood exchange	9 (5.8%)	9 (2.8%)
Liver failure	1 (0.7%)	1 (0.3%)
TTP	1 (0.7%)	1 (0.3%)
Total	156 (100%)	342 (100%)

DIC: Disseminated intravascular coagulation, TTP: Thrombotic thrombocytopenic purpura

Table 2. Inappropriate fresh frozen plasma transfusions and the amount of product used

	Number of transfusions	Amount of product used (units)
Preoperative preparation	34 (65.4%)	48 (55.1%)
Burn diagnosis	11 (21.2%)	25 (28.8%)
Sepsis	7 (13.4%)	14 (13.1%)
Total	52 (100%)	87 (100%)

Table 3. Pre and post-transfusion coagulation parameters in transfusions with appropriate transfusion indications

	BT	AT	p
PT Median (min-max)	19.0 (11.2-60)	16.6 (8-54.6)	**0.001**
aPTT Median (min-max)	39.5 (20.3-109.8)	34.3 (20.6-80)	**0.001**
D-dimer Median (min-max)	1784 (72-43433)	1752 (72-42213)	0.860
Fibrinogen Median (min-max)	188 (42-751)	185 (36-835)	0.362

BT: Before transfusion, AT: After transfusion, PT: Prothrombin time, aPTT: Activated prothrombin time

Table 4. Pre and post-transfusion coagulation parameters in transfusions with inappropriate transfusion indications

	BT	AT	p
PT Median (min-max)	12.7 (10.5-20.4)	13.8 (10.7-17.9)	0.777
aPTT Median (min-max)	32.5 (24-41.4)	32.0 (26.9-41)	0.469
D-dimer median (min-max)	931 (122-6787)	762.5 (303-4915)	0.674
Fibrinogen Median (min-max)	210 (98-523)	261 (132-336)	0.735

BT: Before transfusion, AT: After transfusion, PT: Prothrombin time, aPTT: Activated prothrombin time

observed. A significant decrease in PT and aPTT values was detected in the majority of patients who received FFP transfusion with appropriate indications compared with pre-transfusion values, indicating effective improvement of laboratory findings with appropriate FFP transfusion.

Discussion

FFP is used for both prophylactic (prevention of bleeding) and therapeutic (stopping bleeding) purposes. Despite the specified indications for FFP in national guidelines, clinical practice can vary significantly[5]. Inappropriate usage rates can reach 50%[6]. Non-evidence-based uses were reported approximately 30 years ago[7-9]. In this study, we evaluated the rates and distributions of transfusions performed outside the indications of FFP transfusion according to the national transfusion guidelines at our center.

FFP transfusion is most commonly used in surgical, intensive care, and hematology services[10]. In our study, transfusions were predominantly performed in pediatric and neonatal intensive care units (n=89), surgical services (n=44), and hematology services (n=27).

In this study, the rate of inappropriate FFP transfusion was 25%. This rate was found to be similar to our study (21%) in the study conducted by Moiz et al.[11], whereas Kakkar et al.[12] reported a rate of 60.3%.

In certain centers, a significant variation in this rate is observed, encompassing a wide range from 37% to 73%. [13,14]. In a study conducted by Camkurt et al.[15]. In our country in 2011, the rate was found to be 67% among 204 patients. Another study emphasized that this rate could be reduced through educational programs[16]. Kakkar et al.[12] demonstrated that this rate decreased to 26.6% with educational campaigns targeting clinicians.

In our center, inappropriate FFP transfusions were most commonly observed in the following order: Preoperative preparation (n=34), burn cases (n=11), and sepsis cases (n=7). A study conducted by Camkurt et al.[15] reported that the most frequent indication for FFP transfusion was correction of elevated ınternational normalized ratio (INR).

In our study, however, none of the patients received FFP transfusion specifically to correct INR prolongation.

This finding is believed to be associated with a lower rate of warfarin use among pediatric patients.

In a study by Moiz et al.[11], the most common inappropriate transfusions occurred in patients undergoing bypass surgery without bleeding, liver disease, or coagulation disorders.

Furthermore, their study identified cases in which FFP transfusion was administered without clear indications[11].

In our study, only one patient with liver failure received an inappropriate transfusion: FFP was administered prophylactically prior to an invasive procedure. It is recommended to consider FFP transfusion in cases of liver failure with bleeding and abnormal coagulation parameters before invasive procedures[17].

To prevent unnecessary transfusions, thromboelastography is recommended. However, our retrospective study did not include thromboelastography data.

Preoperative preparation accounted for the majority of inappropriate FFP transfusions at our center. However, it has been shown that even in high-risk surgeries involving significant bleeding, such as cardiac bypass procedures, FFP transfusion does not contribute to a difference in the amount of blood lost during or after the surgery[18].

Burns were ranked second as a frequent cause of inappropriate transfusions. Transfusions were inappropriate for all 11 burn patients. Although a study conducted in the UK in 2007 suggested that toxic shock syndrome-related mortality could occur in pediatric patients even in minor burns, and FFP could be administered to support passive immunization[19], such indications are not present in the national blood transfusion guidelines[20]. Furthermore, it is emphasized that FFP should not be used as a substitute for immunoglobulin, as stated in 1992[21].

In this study, preoperative FFP administered with appropriate indications accounted for 28.7% (98/342) of the total number of FFP units. On the other hand, in a study by Moiz et al.[11], the utilization rate of FFP with appropriate indications preoperatively was 13.2%. However, the rate of invasive procedures increased to 35.6%. In our center, the rate of inappropriate FFP use preoperatively accounted for 14% of the total FFP units. Comparatively, in the study by Moiz et al.[11] even though the study focused solely on cardiac bypass surgeries, the rate of inappropriate FFP use was significantly lower compared with our center (4.6%).

In our center, the rate of inappropriate FFP use was found to be significantly low (2/55) in the pediatric intensive care unit, where the highest number of FFP transfusions was administered. Reiter et al.[22], in a study focusing solely on intensive care units published in 2013, reported that one-third of transfused FFP units were administered without appropriate indications, indicating a high rate of inappropriate use. In that study, the use of FFP was considered inappropriate unless there were abnormal coagulation parameters accompanied by bleeding or prophylactic use prior to procedures[22]. It is recommended to avoid transfusion for mild coagulation abnormalities during minimally bleeding invasive procedures in intensive care units to reduce the number of FFP transfusions[23]. Some studies have shown an association between FFP transfusion volume, mortality scoring systems, and length of stay in intensive care units. Therefore, evaluating FFP utilization in conjunction with mortality scoring systems may enhance the effectiveness of FFP use from a clinical perspective[20]. Additionally, it is known that 25% of coagulation abnormalities in intensive care units are due to vitamin K deficiency[24]. Pybus et al.[25] suggested that regular use of vitamin K in intensive care units can reduce the need for FFP transfusions. However, we did not evaluate the extent of improvement with vitamin K supplementation in patients with coagulation abnormalities or those in whom FFP transfusion was not performed in our intensive care unit.

In our study, 28% of the FFP transfusions were performed in the neonatal intensive care unit. Similarly, in a study conducted by Puetz et al.[23], neonatal patients accounted for 29% of the pediatric group. In the same study, prophylactic FFP was administered to 63% of neonatal patients without bleeding. In our study, this percentage was slightly higher at 75%. Factors such as the association between FFP transfusion and a lower incidence of retinopathy of prematurity[26] may influence the decision for higher transfusion rates. However, further studies are needed to explore this association.

Massive transfusion in children is defined as the transfusion of blood components equal to one or more blood volumes within a 24-hour period or half of the blood volume within 12 hours[27]. Neff et al.[28] defined massive blood transfusion as a situation in which all blood products given at any time during the first 24 hours exceeded the threshold of 40 mL/kg. Exchange transfusion in neonates is one of the situations in which massive blood transfusion is seen.

In our study, nine massive transfusions were performed in the neonatal intensive care unit as exchange transfusions. The approximate ratio of FFP to red blood cell suspension used in each exchange transfusion was approximately 1:2, which is consistent with the recommended ratio for massive transfusions. Studies have not demonstrated the superiority of a 1:1 ratio of FFP to red blood cell suspension over a 1:2 ratio in massive transfusions[29].

In our center, coagulation parameters were evaluated in nearly all patients following FFP transfusion. In a study conducted by Pybus et al.[25], the evaluation of coagulation parameters after transfusion was performed in only 34.5% of cases.

Improvements in aPTT and PT were observed in patients who received FFP transfusion with appropriate indications, whereas no significant differences were found in fibrinogen and D-dimer levels pre- and post-transfusion. In patients who received FFP transfusion with inappropriate indications, no significant differences in any of the coagulation parameters were observed between pre- and post-transfusion values. In a study by Motta et al.[30] that focused on the neonatal age group, significant shortening of PT and aPTT values was interpreted as an effective dose being administered based on pre-transfusion values. In our study, significant shortening of aPTT and PT values, especially in patients diagnosed with

sepsis and those who received transfusion with appropriate indications, suggests that an adequate amount of FFP was transfused.

No transfusion reactions were observed during FFP transfusions in our study. In line with our findings, Camkurt et al.[15] also reported the absence of transfusion reactions during FFP transfusions in their study. However, enhancing awareness and reducing the rate of inappropriate transfusions. In addition to transfusion reactions, FFP transfusion has been shown to increase the systemic inflammatory response in relation to the volume of the transfused product[31] and does not correct for coagulation abnormalities in critically ill patients. Furthermore, higher FFP transfusion rates were associated with increased mortality. Despite the knowledge that FFP transfusion is not effective and not recommended in many clinical scenarios, inappropriate usage continues to persist, as highlighted in several studies[23]. Moreover, it has been suggested in multiple studies that FFP transfusion should not be performed for mild prolongation of coagulation parameters[32-34]. Specifically, when the INR value is below 1.7, FFP administration has been shown to have no laboratory correction effect[35].

Moreover, considering that 20.2% of the product volume was transfused inappropriately, the cost of inappropriate FFP transfusions was calculated to be $1640 within 1 year. Each inappropriate transfusion not only carries the risks associated with transfusion but also results in a significant loss of labor and material resources during product procurement. Therefore, it is evident that improvement efforts would also provide financial benefits.

The lack of calculation of the administered FFP dose was a limiting factor in evaluating the effectiveness of transfusion in terms of dose in our study. Additionally, not considering the prematurity status and the number of days of life in the evaluation of patients transfused in the neonatal intensive care unit suggested the need for a separate study specifically focusing on this age group.

Conclusion

Considering that existing knowledge regarding transfusion practice is mostly based on studies conducted in adults, we believe that this study, which focused on the pediatric age group, will contribute to raising awareness regarding TDP transfusion practice. This, in turn, can facilitate the implementation of targeted educational programs designed to achieve defined transfusion goals.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital. Ethics committee approval number and date: 2017/08-05, 08/06/2017.

Informed Consent: Informed consent was not obtained as this was a retrospective study

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.G., Y.O., Concept: Y.G., Y.O., Design: Y.G., Y.O., C.V., Data Collection or Processing: Y.G., Analysis or Interpretation: Y.G., Y.O., Literature Search: Y.G., Y.O., Writing: Y.G., Y.O., C.V.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Assessing the Efficacy of A Scoring System in Surgical NEC Diagnosis

Cerrahi NEK Tanısında Bir Skorlama Sisteminin Etkinliğinin Değerlendirilmesi

Bade Toker Kurtmen, Fatma Merve Üstün

University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Department of Pediatric Surgery, İzmir, Turkey

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Abstract

Objective: To evaluate the efficacy of the necrotizing enterocolitis-treatment-aid (NEC-T-Aid) tool for diagnosing perforated NEC in preterm infants, particularly in cases in which pneumoperitoneum is absent.

Methods: This retrospective study included patients with surgically confirmed perforated NEC at a single-center from 2012 to 2022. Patients were assessed using the NEC-T-Aid assessment tool, which includes the clinical, abdominal signs, serological markers, and X-ray findings. Patients without pneumoperitoneum were specifically analyzed to determine the tool's diagnostic accuracy.

Results: Among the 39 patients included in the study, 25% of those with perforated NEC without pneumoperitoneum could not be definitively diagnosed using the NEC-T-Aid tool. Patients in the pneumoperitoneum group also experienced longer delays from initial evaluation to surgery, more extensive bowel resections, and a higher incidence of pediatric intestinal failure compared with patients in the pneumoperitoneum group.

Conclusion: The NEC-T-Aid tool has limitations in diagnosing perforated NEC in patients lacking pneumoperitoneum, highlighting the need for enhanced diagnostic methods. Improving early detection and intervention strategies are crucial for better managing NEC and reducing complications, such as extensive bowel resection and pediatric intestinal failure.

Keywords: Necrotizing enterocolitis, NEC-T-Aid tool, pneumoperitoneum, pediatric intestinal failure, diagnostic accuracy

Öz

Amaç: Nekrotizan enterokolit-tedavi-yardım (NEC-T-Aid) aracının preterm bebeklerde, özellikle pnömoperitoneumun olmadığı durumlarda, perfore NEC tanısı koymadaki etkinliğini değerlendirmektir.

Yöntem: 2012'den 2022'ye kadar tek bir merkezde cerrahi olarak doğrulanmış perfore NEC'li hastalar üzerinde retrospektif bir analiz yapılmıştır. Hastalar klinik bulgular, abdominal bulgular, serolojik belirteçler ve röntgen bulgularını içeren NEC-T-Aid değerlendirme aracı kullanılarak değerlendirilmiştir. Pnömoperitoneumu olmayan olgular, aracın tanısal doğruluğunu belirlemek için özel olarak analiz edilmiştir.

Bulgular: Çalışmaya dahil edilen 39 hasta arasında, pnömoperitoneumu olmayan perfore NEC'li hastaların %25'ine NEC-T-Aid aracı kullanılarak kesin tanı konulamamıştır. Bu grupta ayrıca ilk değerlendirmeden ameliyata kadar daha uzun gecikmeler, daha kapsamlı bağırsak rezeksiyonları ve pnömoperitoneumlu hastalara kıyasla daha yüksek pediyatrik bağırsak yetmezliği insidansı görüldü.

Sonuç: NEC-T-Aid aracı, pnömoperitonyumu olmayan olgularda perfore NEC tanısı koymada sınırlamalara sahiptir ve gelişmiş tanı yöntemlerine olan ihtiyacı vurgulamaktadır. Erken teşhis ve müdahale stratejilerinin iyileştirilmesi, NEC'nin daha iyi yönetilmesi ve geniş bağırsak rezeksiyonu ve pediyatrik bağırsak yetmezliği gibi komplikasyonların azaltılması için çok önemlidir.

Anahtar Kelimeler: Nekrotizan enterokolit, NEC-T-Aid aracı, pnömoperitoneum, pediyatrik intestinal yetmezlik, tanı doğruluğu

Address for Correspondence/Yazışma Adresi: Bade Toker Kurtmen MD, University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Department of Pediatric Surgery, İzmir, Turkey
E-mail: badetoker@gmail.com
ORCID ID: orcid.org/0000-0001-8963-5755

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Introduction

Necrotizing enterocolitis (NEC) is an inflammatory disease of the bowel and is the leading cause of death due to gastrointestinal disease in preterm neonates. The symptoms of NEC can be slow and mild at the beginning of the disease, progress rapidly, and have devastating consequences. NEC is one of the most frequently encountered surgical emergencies in neonates, with operative intervention being necessary for 25-50% of diagnosed patients[1,2]. The mortality rate of NEC ranges between 20% and 30%, with the highest rate among NECs requiring surgery[3].

Managing NEC in premature infants poses a challenge, particularly in determining the appropriate surgical timing. Although radiological findings like pneumatosis and portal venous gas, confirm the diagnosis of NEC, reliance solely on these findings is not sufficient to suggest surgery, as some cases resolve medically. The only definitive indication for surgical intervention in NEC patients continues to be the presence of intestinal perforation[4-7]. NEC can lead to short-bowel syndrome, particularly when diagnosed late and involving multiple segments of the intestine[8]. In our study conducted in 2022, we focused on perforated NEC cases without pneumoperitoneum on abdominal X-ray and observed that diagnosis is often delayed in such patients, who typically present with multi-segmental involvement necessitating more extensive bowel resection procedures[9].

In 2022, Coles et al.[6] introduced a scoring system for accurate diagnosis and appropriate management. The objective of this study was to assess the effectiveness of this scoring system in the surgical diagnosis of NEC in patients who did not exhibit pneumoperitoneum on abdominal X-rays.

Materials and Methods

Data Collection and Study Group

The study was approved by the institutional review board (2023/07-19), retrospective data review analysis of patients who underwent surgery for NEC at a single-center from 2012 to 2022 was performed. Local ethics committee approval was obtained from the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethical Committee in compliance with the Declaration of Helsinki ethical standards for this retrospective single-center study (approval no: 2023 7-13, date: 02.08.2023). The study included neonates with surgically confirmed perforated NEC, whereas patients with incomplete medical records, those who received percutaneous drain placement during the initial operation, and surgically and histopathologically confirmed non-perforated NEC were excluded from the study.

A total of 39 patients were included in the study, and all private health information was collected in adherence to strict privacy protocols. Informed consent was obtained from all parents of the enrolled patients. Examination and imaging findings of the patients were compared with the operative findings. All patients were evaluated using the NEC-treatment-aid (NEC-T-Aid) assessment tool.

NEC-T-Aid Assessment Tool

The NEC-T-Aid assessment tool[6] has four sections; clinical signs, abdominal signs, serological markers and X-ray findings. Patients were evaluated using NEC-T-Aid parameters. These parameters were;

- General signs; increased frequency of desaturation/bradycardia, tachycardia, apnea, temperature instability, and sudden increase in ventilation setting
- Abdominal signs; worsening abdominal distension/discoloration, abdominal tenderness, increased number of aspirates, vomiting, visible blood in the stool, and bilious aspirates
- Investigations; new/worsening metabolic acidosis, new/worsening metabolic changes, white cell count suggestive of sepsis, high/worsening C-reactive protein, low/falling platelets
- Abdominal X-ray; evidence of perforation, pneumatosis, peritoneal fluid, bowel dilatation, normal X-ray

In our previous study, the NEC-T-Aid score was categorized as follows:

- 0-3: Normal/dysmotility,
- 4-7: Sepsis,
- 8-10: Suspected NEC,
- >10: Confirmed NEC.

Statistical Analysis

For discrete and continuous variables, descriptive statistics (mean, standard error, median, and quartiles value) were calculated. In addition, the homogeneity of variances, which is a prerequisite for parametric tests, was checked using Levene's test. The assumption of normality

was tested using the Shapiro-Wilk test. To compare the differences between the two groups, an independent sample t-test was used when the parametric test prerequisites were fulfilled, and the Mann-Whitney U test was used when such prerequisites were not fulfilled. The chi-square test was used to determine the relationships between the two discrete variables. When the expected sources were less than 20%, the values were determined using the Monte Carlo simulation method to include them in the analysis. Data were evaluated using SPPS version 25 (IBM Statistics, New York, USA). Statistical significance was set at $p<0.05$.

Results

A total of 72 patients were diagnosed with NEC during the study period, and 39 patients (19 girls and 20 boys) were included in the study. The mean maternal age was 27 years, gestational age was 31 weeks, and birth weight was 1877 g. The most common hospitalization diagnosis was respiratory distress syndrome (61.5%). The most common examination findings were abdominal distention (97.4%) and abdominal color discoloration (64.1%). A palpable mass was detected in 23.1% of patients. Gas deposition (82%) was the most common finding on direct standing abdominal X-ray, while pneumoperitoneum was observed in 49% of the patients. The median time from the initial evaluation of the cases by the surgical team to surgery was 24 hours (1-144). This time was found to be statistically higher in patients with perforated NEC without pneumoperitoneum (30-hours) than in patients with pneumoperitoneum (6-hours) ($p<0.001$; Mann-Whitney U test). In addition, in these cases, NEC involvement was more frequently multi-segmental ($p=0.048$; Fisher's Exact test) and the resected bowel length was longer ($p=0.003$; Mann-Whitney U test). However, no significant difference was found in mortality between groups ($p=0.695$; Fisher's Exact test). A comparative analysis of demographic characteristics and prognosis between groups is shown in Table 1.

The evaluation of all patients was conducted using the NEC-T-Aid. A comparison was performed between patients with NEC and those without pneumoperitoneum across 20 parameters. With the exception of one parameter (bowel dilatation on X-ray, $p=0.003$; Fisher's Exact test), no significant differences were observed between the two groups. Notably, the total NEC-T-Aid score exhibited a noteworthy increase in the group of patients with pneumoperitoneum ($p<0.001$; Independent Samples t-test). It is important to note that even though all patients in our study had perforated NEC, the NEC-Aid assessment tool failed to definitively diagnose NEC in 25% of cases in which pneumoperitoneum was absent. A comparison of NEC-T-Aid parameters and the overall scores between the two groups is provided in Table 1. Although all of our patients had perforated NEC, the NEC-Aid assessment tool could not diagnose 25% of patients did not have pneumoperitoneum as confirmed NEC. The comparison of NEC-T-Aid parameters and total scores between the groups is shown in Table 2.

Discussion

NEC stands as a prominent contributor to morbidity and mortality among newborns, with the highest risk observed in premature and very low birth weight infants, those weighing less than 1500 g. The mortality rate of patients with this condition varies from 15% to 30%[10,11]. Conventionally, the

Table 1. Comparative analysis of demographic characteristics and prognosis between groups

	Patients with pneumoperitoneum (n=19)	Patients without Pneumoperitoneum (n=20)	p
Mean maternal age: year ± SE	28±1	27±1	0.529[a]
Mean gestational age: month ± SE	31±1	33±1	0.164[a]
Mean birth weight: gram ± SE	1662±171	2081±164	0.087[a]
Median time from the initial evaluation to the operation: hours (Q1-Q3)	6 (4.5-24)	30 (24-36)	**0.001[b]**
Resected bowel length: cm (Q1-Q3)	5 (2-9)	11 (7.5-30)	**0.003[b]**
Multi-segmental: percentage	21%	55%	**0.048[c]**
Mortality: percentage	16%	25%	0.695[c]
Short bowel syndrome: percentage	0	20%	0.101[c]

Bold values indicate significant p-values ($p<0.05$), [a]: Independent Samples t-test, [b]: Mann-Whitney U test, [c]: Fisher's Exact test, SE: Standard errors, Q1-Q3: Quartiles

Table 2. Comparison of NEC-T-Aid parameters and total score between groups

	Patients with pneumoperitoneum (n=19)	Patients without pneumoperitoneum (n=20)	p
Increased frequency of desats/bradys	57.9%	80.0%	0.251[a]
Tachycardia	15.8%	15.0%	1.000[b]
Apnea	0	0	
Temperature instability	0	0	
Sudden increase in ventilation settings	78.9%	80.0%	1.000[b]
Worsening abdominal distention/discoloration	100%	94.7%	0.487[b]
Abdominal tenderness	100%	95.0%	1.000[b]
Increased aspirates	63.2%	85.0%	0.155[b]
Vomiting	26.3%	45.0%	0.378[a]
Visible blood in stool	31.6%	55.0%	0.250[a]
Bilious aspirates	78.9%	65.0%	0.541[a]
New/worsening metabolic acidosis	78.9%	85.0%	0.695[b]
New/worsening metabolic changes	26.3%	25.0%	1.000[b]
WCC suggestive of sepsis	73.7%	90.0%	0.235[b]
High/worsening CRP	84.2%	90.0%	0.661[b]
Low/falling platelets	57.9%	65.0%	0.266[a]
Evidence of perforation on X-ray	100%	0	<0.001[b]
Evidence of pneumatosis on X-ray	21.1%	20.0%	1.000[a]
Evidence of peritoneal fluid on X-ray	15.8%	10.0%	0.661[b]
Bowel dilatation on X-ray	63.2%	100%	**0.003[b]**
Total score: mean ± SE	23.0±1.2	15.1±1.0	**<0.001[c]**
NEC-T-Aid category			
-Normal/dysmotility	0	0	
-Sepsis	0	0	**0.047[b]**
-Suspected NEC	0	25%	
-Confirmed NEC	100%	75%	

Bold values indicate significant p-values (p<0.05), [a]: Yates Continuity Correction test, [b]: Fisher's Exact test, [c]: Independent Samples t-test, desats/bradys: Desaturations/bradycardias, SE: Standard errors, NEC: Necrotizing enterocolitis, NEC-T-Aid: Necrotizing enterocolitis-treatment-aid, CRP: C-reactive protein, WCC: White cell count

diagnosis of NEC relies on Bell's Modified Staging Criteria, which classifies NEC into three distinct stages: Mild (referred to as Bell's Stage I), moderate (Bell's Stage II), and severe (Bell's Stage III). Advanced NEC, denoted as Bell's Stage III, requires surgical intervention and is characterized by bowel perforation resulting in pneumoperitoneum, hypotension, signs indicative of peritonitis, and severe metabolic acidosis[4,12]. It is estimated that approximately 20-40% of infants afflicted with NEC will require surgical management, and the mortality rate among these infants can soar as high as 50%[7].

The principal objectives of surgical intervention in NEC include the containment of enteric spillage and removal of necrotic intestinal segments while preserving the maximum length of viable intestine[13]. Evidence of pneumoperitoneum on plain radiography is the only absolute indication for operation[7,14,15]. However, it is worth highlighting that pneumoperitoneum is detected in less than half of all infants with intestinal perforation or necrosis during surgery, highlighting its limited sensitivity as a marker for identifying infants requiring surgical intervention for NEC[16]. In our study, similar to findings in the existing literature, it was observed that more than half of the patients with

perforated NEC did not present with radiographic evidence of pneumoperitoneum.

Although Bell's criteria hold historical significance, their clinical utility has diminished over time. Consequently, numerous diagnostic scoring systems have been developed to enhance the identification and management of NEC[17-19]. In our study, when evaluating patients using the NEC-T-Aid parameters, we found that 25% of patients in the perforated NEC group without pneumoperitoneum could not be definitively diagnosed.

Pediatric intestinal failure is a complex and potentially life-threading condition that can result from various underlying causes; including congenital anomalies, surgical complications, and acquired diseases. NEC is the leading cause of pediatric intestinal failure[2]. In our series, the median time from the initial evaluation to surgery and resected bowel length were significantly longer in the NEC group without pneumoperitoneum. Pediatric intestinal failure developed in 10.3% of patients, all of whom were also in the NEC group without pneumoperitoneum.

Study Limitations

Our study had several limitations. It was retrospective in design, conducted at a single center, and involved a relatively small sample size, limiting the generalizability of its findings.

Conclusion

NEC continues to be a major cause of morbidity and mortality in preterm infants, and diagnostic challenges are particularly evident in cases without pneumoperitoneum. These cases often result in more extensive bowel resections and a higher risk of pediatric intestinal failure. Our retrospective evaluation using the NEC-T-Aid tool revealed that 25% of perforated NEC cases without pneumoperitoneum could not be definitively diagnosed. This study underscores the limitations of current diagnostic tools and emphasizes the need for improved methods to enhance early diagnosis and intervention in NEC.

Ethics

Ethics Committee Approval: Local ethics committee approval was obtained from the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethical Committee in compliance with the Declaration of Helsinki ethical standards for this retrospective single-center study (approval no: 2023 7-13, date: 02.08.2023).

Informed Consent: Informed consent was obtained from all parents of the enrolled patients.

Footnotes

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Knowledge and Approaches to Family Medicine Assistants' Artificial Intelligence

Aile Hekimliği Asistanlarının Yapay Zekaya İlişkin Bilgi ve Yaklaşımları

İsmail Çifçi[1], Esra Meltem Koç[2]

[1]Turkish Ministry of Health, Karabağlar 27th Family Medicine Centre, İzmir, Turkey
[2]İzmir Katip Çelebi University Faculty of Medicine, Department of Family Medicine, İzmir, Turkey

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Abstract

Objective: The aim of this study was to determine the areas of use of artificial intelligence (AI) by family medicine assistants and to evaluate their knowledge and approaches to the use of AI in the field of health.

Methods: This study was designed as a descriptive research. The participants were family medicine residents in 4 university hospitals in İzmir province. Data were collected using an online questionnaire prepared by the researchers. The questionnaire included preliminary information about the participants' use of AI as well as various sections aiming to evaluate their approaches towards AI in the field of health.

Results: A total of 204 participants, 108 (52.9%) female and 96 (47.1%) male, were included in the study. While 64.7% (n=132) of the participants defined themselves as having basic knowledge about AI, 69.1% (n=141) had knowledge about the use of AI in the field of medical imaging. While 85.3% (n=174) of the participants wanted to have AI applications courses in specialty education, only 35.3% (n=72) found AI reliable. 98.5% (n=201) of the participants thought that AI could keep records like a physician, 75% (n=153) thought that it could analyze disease prognosis, 97.1% (n=198) thought that the time taken for diagnosis would be shortened with the use of AI, and 80.9% (n=165) thought that treatment costs would be reduced.

Conclusion: AI is a development that will play a more active role in healthcare, especially in primary care, in the future. Many participants believed AI could perform certain health services like a physician, would have positive effects in various areas, and wanted AI included in health courses in specialty education. Therefore, increasing the knowledge level of family medicine assistants through AI training will contribute to the delivery of health services.

Keywords: Artificial intelligence, family medicine, education, telemedicine, digital health

Öz

Amaç: Bu çalışmanın amacı, aile hekimliği asistanlarının yapay zeka kullanım alanlarını tespit etmek ve yapay zekanın sağlık alanında kullanımı ile bilgi ve yaklaşımlarını değerlendirmektir.

Yöntem: Bu çalışma tanımlayıcı tipte araştırma olarak tasarlandı. Katılımcıları İzmir ilindeki 4 üniversite hastanesinde aile hekimliği eğitimi alan asistanlar oluşturdu. Veriler online yöntemle araştırmacılar tarafından hazırlanmış anket kullanılarak toplanmıştır. Anket katılımcıların yapay zeka kullanımları ile ilgili ön bilgilerin yanı sıra sağlık alanında yapay zekaya yönelik yaklaşımlarını değerlendirmeyi amaçlayan çeşitli bölümleri içeriyordu.

Bulgular: Araştırmaya 108'i (%52,9) kadın, 96'sı (%47,1) erkek olmak üzere toplam 204 katılımcı dahil edildi. Katılımcıların %64,7'si (n=132) yapay zeka özelinde kendini temel düzeyde bilgi sahibi olarak tanımlarken, %69,1'i (n=141) tıbbi görüntüleme alanında yapay zeka kullanımı ile ilgili bilgiye sahipti. Katılımcıların %85,3'ü (n=174) uzmanlık eğitiminde yapay zeka uygulamaları dersleri olmasını isterken sadece %35,3'ü (n=72) yapay zekayı güvenilir buluyordu. Katılımcıların

Address for Correspondence/Yazışma Adresi: İsmail Çifçi, Turkish Ministry of Health, Karabağlar 27th Family Medicine Centre, İzmir, Turkey
E-mail: dr.ismailcifci@gmail.com
ORCID ID: orcid.org/0000-0003-0693-8190

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Öz

%98,5'i (n=201) yapay zekanın bir hekim gibi kayıt tutabileceğini, %75'i (n=153) hastalık prognozu analiz edebileceğini düşünüyor, %97,1'i (n=198) yapay zeka kullanımı ile teşhis için geçen sürede kısalma olacağını, %80,9'u (n=165) tedavi maliyetlerinde azalma olacağını düşünüyordu.

Sonuç: Yapay zeka gelecekte sağlık alanında ve özellikle birinci basamakta daha aktif yer bulacak gelişmelerden biridir. Katılımcıların önemli bir kısmı yapay zekanın bazı sağlık hizmetlerini bir hekim gibi gerçekleştirebileceğini, birçok alanda olumlu etkiler yapacağını ve uzmanlık eğitiminde sağlıkta yapay zeka dersleri olmasını istiyordu. Bu sebeple aile hekimliği asistanlarının yapay zeka alanında eğitim alarak bilgi düzeylerinin artırılması verilen sağlık hizmeti sunumuna katkı sunacaktır.

Anahtar Kelimeler: Yapay zeka, aile hekimliği, eğitim, teletıp, dijital sağlık

Introduction

Artificial intelligence (AI), which is used to describe a wide range of fields, refers to systems that exhibit intelligent behavior such as learning, visual perception, speech recognition, algorithm and statistical model development, categorization, prediction, decision-making, benchmarking, and creativity, by analyzing data to achieve a certain goal. AI reduces the differences between computer systems and humans' daily activities[1-4].

The foundations of AI can be traced to Alan Turing, the founder of modern computers. In 1950, Turing proposed the idea of using computers to simulate intelligent behavior and critical thinking and proposed the Turing test to evaluate this. John McCarthy planned a conference to develop his ideas in this field and called this field "Artificial Intelligence". In 1956, a conference on thinking machines that can imitate human intelligence and behavior was held at Dartmouth College, New Hampshire, USA, and this was considered the official beginning of research on AI. These studies have continued to accelerate in recent years[4].

AI applications are now integrated into daily life with many advantages and industry support. AI facilitates decision-making processes by analyzing large amounts of data at a speed and with a low error rate it provides in repetitive tasks, personalized recommendations it provides with the data it obtains, security it provides against cyberattacks and other fraud attempts, and mobility it provides to disabled individuals. These opportunities may also cause job anxiety in those who undertake these jobs. In the industry, AI is widely used for voice assistants, e-commerce applications, online TV platforms, cybersecurity, social networks, banking transactions, academic research, etc. In the field of health, applications developed with AI are used in processes such as keeping health records, radiological and pathological diagnosis processes, prognosis determination, treatment protocols, medical imaging, symptom tracking, personalized medicine, and drug and vaccine development, with increasing data density. AI applications are compared with doctors in many areas, such as pathological examinations of cancer and metastases, dermatological diagnosis processes, eye diseases, such as diabetic retinopathy, congenital cataracts, macular degeneration, polyps detected in colonoscopy, and echocardiography findings, especially radiological imaging. Computer applications developed with AI intelligence support the provision of personalized healthcare services to patients in primary care, which is the most common application area for these patients. Physicians can use AI to record patient history and physical examination findings. Thus, they save the time they can spare for their patients. It is obvious that AI will be used in medical applications in the future. For this reason, the opinions and knowledge levels of family medicine assistants who will work in primary care regarding AI are important[5-10].

The importance of the use of AI in primary healthcare is increasing daily. Long-term care and coordination services provided to certain populations enable the use of AI in this field. For this reason, primary care physicians must adapt to working with AI. The prejudiced approach of physicians toward the use of AI and their lack of sufficient knowledge are among the obstacles to working together. Providing physicians adequate training on AI and enabling them to practice can eliminate these obstacles. It is noteworthy that two-thirds of medical faculty students do not have knowledge about AI[11].

Medical education should include competencies in the use of modern technology and simulations, data collection, analysis skills, and utilization through AI applications. Physicians should therefore have sufficient knowledge of the diagnostic, therapeutic, and rehabilitation services offered to patients using AI and be able to resolve any concerns, confusion, or questions about the process. Physicians are also responsible for making AI a useful technology for patient care[12].

Health systems are currently faced with increasing chronic and multimorbidity, and the clinical and economic burden of this situation poses a major challenge for optimal healthcare delivery. Health systems must adapt to new challenges to meet growing healthcare needs. Innovations in digital health around the world have been taking place in primary care for some time, but the extent of its use still varies widely both within and between countries. Digital health in family medicine has great potential for chronic disease monitoring and patient management, disease prevention, and reduced healthcare costs. It is also very useful to use technology to provide individualized health care.

In this study, we aimed to determine the areas of AI use and evaluate the use of AI in the field of health and the knowledge and approaches of family medicine residents.

Materials and Methods

The study population consisted of 430 resident physicians who received specialty training in family medicine at university hospitals in İzmir. The sample size was calculated using Open Epi as at least 204 people with a 95% confidence interval of 5% margin of error when 50% was taken as the unknown frequency. Before starting the study, ethics committee approval was obtained from İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (decision no: 0458, date: 26.10.2023). In our study, a data questionnaire prepared by the researchers by making use of the literature was used to collect data. The questionnaire was completed online via Google forms. In the first part of the questionnaire form, the participants' internet usage habits and their use of AI applications in daily life were questioned (7 questions), and in the second part, their opinions on the use of AI in the field of health were questioned (12 questions). The questionnaire was kept open for about 2 months until the quorum was reached.

Statistical Analysis

The data were analyzed using the SPSS 24.0 statistical package and evaluated using descriptive statistics. The conformity of variables to normal distribution was analyzed by visual (histogram) and analytical methods (Kolmogorov-Smirnov tests). Numerical data collected in the study were expressed as mean, median, standard deviation, or range of values; categorical data were expressed using descriptive methods, such as ratios and percentages[13-15].

Results

A total of 204 participants were included in our study, 108 (52.9%) of whom were female, 96 (47.1%) were male, and the mean age was 28.88 (min: 25, max: 45). The distribution was as follows: 33.8% from Dokuz Eylül University, 29.4% from İzmir Katip Çelebi University, 20.6% from Bozyaka Training and Research Hospital, and 16.2% from University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital. Moreover, 82.4% of the participants spent more than 3 hours a day on the internet. All participants had a mobile phone, while 82.4% had a laptop computer.

When the purposes of using the internet were evaluated, it was determined that the most common reasons for using the internet were social media (88.2%), education/research 72.1% and shopping 69.1% (Table 1).

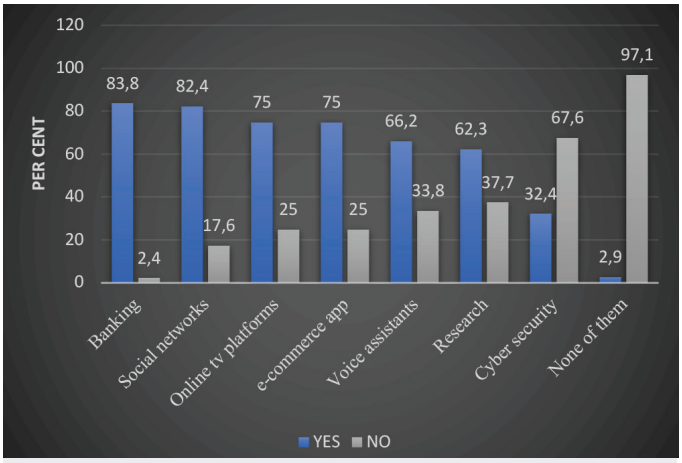
When the knowledge of the participants in terms of examples of AI used in daily life was questioned, it was observed that they were most frequently informed about banking (83.8%), social networks (82.4%), online TV platforms (75%) and e-commerce applications (75%) (Graphic 1).

When asked to evaluate their level of knowledge about the use of AI in the field of health, 64.7% of the participants stated that they had basic knowledge. The percentage of those without knowledge in this field was 17.6% (Graphic 2).

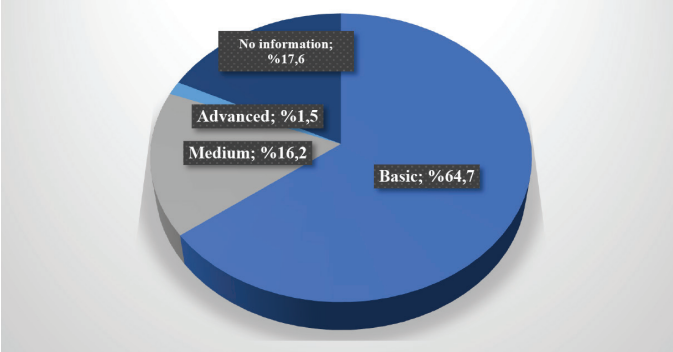
Table 1. Areas of use of the ınternet by the participants

	Yes (percentage)	n	No (percentage)	n
Social media	88.2%	180	11.8%	24
Education	72.1%	147	27.9%	57
Shopping	69.1%	141	30.9%	63
Spending time	67.6%	138	32.4%	66
Communication	63.2%	129	36.8%	75
Entertainment/games	57.4%	117	42.6%	87

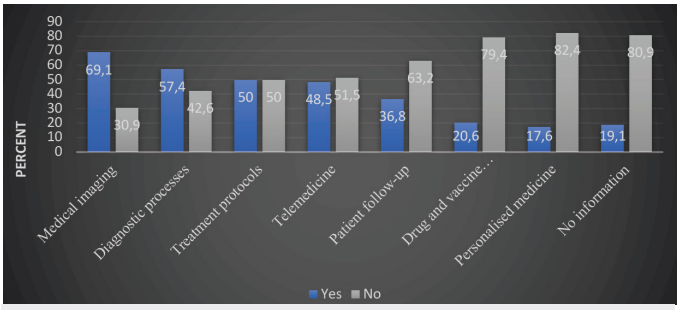
When the level of knowledge of the participants regarding AI topics used in the field of health was evaluated, medical imaging ranked first with 69.1%, followed by diagnostic processes with 57.4%, and treatment protocols with 50% (Graphic 3).



Graphic 1. Participants' knowledge on artificial intelligence areas used in daily life



Graphic 2. Distribution of participants' level of knowledge on artificial intelligence



Graphic 3. Participants' level of knowledge on health and AI topics

AI: Artificial intelligence

Considering the increasing inclusion of AI in our lives; 82.4% of the participants expressed curiosity, 61.8% excitement, and 39.7% anxiety. When asked about the effect of AI on medical diagnosis and treatment processes, 57.4% of the participants stated that it had a positive effect, whereas 26.5% stated that they had no opinion on the effect. When asked about their opinions on which areas of medicine AI will be used in the coming years, 89.7% of the participants answered in internal medical sciences, 83.8% in basic medical sciences, and 63.2% in surgical medical sciences. Moreover, 83.8% of the participants had not attended any training, congress, conference, or symposium on AI to date, and 85.3% wanted to have AI in health courses in specialty education.

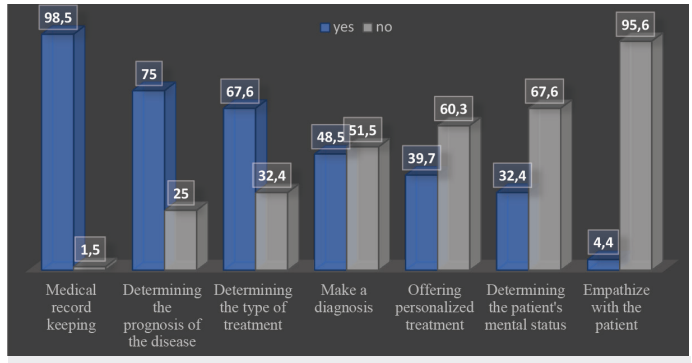
One of the questions asked the participants was to evaluate whether AI could perform some tasks similar to a physician. The highest response rate was obtained from medical records 98.5%. The lowest empathizing rate was 4.4% (Graphic 4).

When the effect of AI on examination processes was evaluated, it was thought that AI would contribute 97.1% to the time taken for diagnosis and 80.9% to the decrease in treatment costs (Graphic 5).

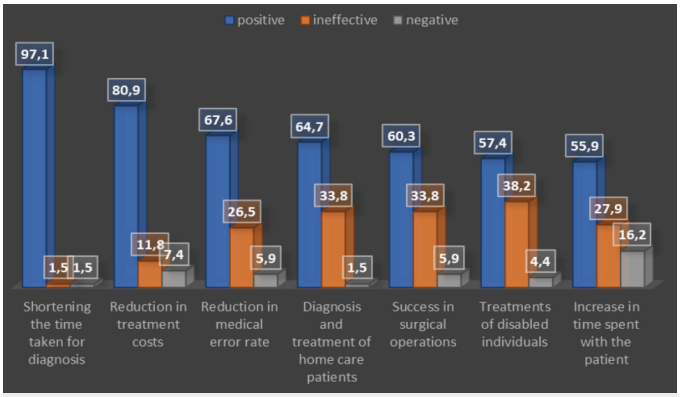
66.2% of the participants did not think that AI would take over their jobs in the future. In addition, 20.6% were undecided and 13.2% thought that AI could take over their jobs. In terms of determining whether AI was reliable, 60.3% of the participants were undecided, 35.3% found it reliable, and 4.4% did not find it reliable.

Discussion

In this study, we aimed to evaluate the knowledge and approaches of family medicine assistants regarding the use of AI in healthcare. AI technologies are now used in various fields, such as disease diagnosis, treatment planning,



Graphic 4. Which tasks can artificial intelligence perform like a physician



Graphic 5. Impact of artificial intelligence on examination processes

prognosis determination, and patient follow-up, in family medicine practice. The applications support physicians in areas like early diagnosis of chronic diseases, radiological image analysis, drug interactions, contraindications, rational drug use, reminders for missed vaccinations, risk score calculation, and monitoring of target values. Most family medicine assistants in our study were knowledgeable about AI applications in medical imaging, diagnostic processes, and treatment protocol determination. However, less than half were aware of AI applications in areas like telemedicine, patient follow-up, drug and vaccine development, and personalized medicine. This could be attributed to the fact that many family medicine assistants primarily focus on clinical practice, where telemedicine or drug development may not be frequently encountered, leading to less exposure to such AI applications. Approximately 20% of the participants were unaware of AI applications in healthcare, likely due to the lack of outpatient clinic experience among family medicine assistants. This suggests that exposure to real-world AI applications in clinical settings may significantly enhance patient awareness and understanding, highlighting the importance of hands-on experience in AI training programs.

When asked to evaluate their knowledge level regarding AI usage in healthcare, 64.7% of participants stated that they had basic knowledge, while 17.6% claimed to have no knowledge at all. This percentage is similar to the 78.4% reported in Waheed and Liu's[16] study on AI application in primary healthcare in Qatar. The similarities between the family medicine systems of Qatar and Turkey may explain this resemblance. Both countries' healthcare systems share common characteristics in their approach to family medicine, particularly in managing chronic diseases and providing continuous care. Therefore, it is likely that similar levels of AI knowledge are rooted in these shared systemic structures. In a study by Antes et al.[17] in the U.S., younger individuals were found to be more open to AI usage, a trend reflected in our study, as participants were predominantly younger, internet-savvy individuals. other studies in Turkey have also emphasized the need for training to increase the knowledge and awareness of healthcare professionals regarding the effective use of AI systems[18-21]. The young demographic in our study could also explain the higher levels of optimism and willingness to engage with AI technology, as younger professionals tend to be more adaptable and tech-savvy. The awareness level could be further increased through symposiums, conferences, and conferences, as well as training in this field.

Among the physicians in our study cohort, 83.8% had not attended any training, congress, conference, or symposium on AI, and 85.3% expressed a desire for AI courses in their specialties. In Ganapathi's study exploring the experiences and views of doctors working with AI in English healthcare, participants similarly reported a need for education and mentorship in this area. Baser et al.[18] study in Turkey also showed that 95% of family physicians had not received any AI training[21]. These results highlight the significant gap in AI education. This gap could stem from the relatively recent integration of AI technologies into healthcare and the lack of updated curricula in medical schools, particularly in family medicine programs. Addressing this gap requires not only introducing AI topics but also offering practical workshops where physicians can interact with AI systems. The World Medical Association advocates for adjustments in medical training curricula to help physicians better understand AI. Numerous studies have also suggested that current medical education is insufficient in terms of AI knowledge and call for reform. Incorporating AI-related knowledge and skill-building activities during residency can facilitate physicians' adaptation to future AI applications[11,22-26].

When asked about the impact of AI on medical diagnosis and treatment, more than half of the respondents were optimistic. Almost all participants believed that AI would shorten diagnosis times. Furthermore, the participants expressed positive views regarding various parameters, including reducing treatment costs, decreasing medical error rates, contributing to home care diagnosis and treatment, improving surgical outcomes, and increasing the time allocated to patients. These findings mirror global trends in healthcare, where AI is increasingly recognized for

its ability to optimize time management, cost efficiency, and accuracy in medical procedures. In Turkey, where healthcare resources are limited, AI could play a crucial role by enhancing workflow and reducing the burden on physicians. These findings suggest that family medicine assistants have a positive outlook on AI use. Similar studies have reported favorable attitudes toward the use of AI in clinical settings[27-30]. Consistent results across different physician groups indicate that physicians are generally willing to incorporate AI-supported applications into their decision-making processes for diagnosis and treatment.

The majority of participants believed that AI could maintain medical records, determine disease prognosis, and select treatment types that are similar to those of a physician. However, nearly all of the participants believed that AI lacked the empathy skills of a physician, and two-thirds believed that AI could not replace physicians. This observation is important because it reinforces the notion that AI, while powerful, lacks the human touch required in patient care. Physicians' ability to communicate, show compassion, and understand patients' emotional and cultural contexts is something AI currently cannot replicate. These findings align with those of other studies in the literature[16-18,21,22,27,30-34]. The increasing use of computer systems for medical record, diagnosis, and prognosis determination may have contributed to the belief that AI can perform certain tasks like a physician. However, participants likely recognized that empathy involves more than basic skills because it requires understanding the cultural background and patient knowledge levels. Family physicians often build long-term relationships with patients, making them more likely to value the personal aspects of care, which AI has yet to achieve. Given that empathy is a fundamental component of patient-physician communication, participants may have concluded that AI cannot fully replace human doctors.

Study Limitations

Our study was applied to family medicine residents who were receiving specialty training in İzmir province using the online survey method. The limitations of our study are that the questionnaire may have been completed only by residents who are interested in the subject because it was administered by an online survey method and that it may not be sufficient to reflect the country in general because it was conducted in a single province.

Conclusion

Our study on AI knowledge levels of family medicine residents emphasizes the importance of education and awareness in this field. Our research results revealed that most participants had a basic knowledge of AI, but a deeper understanding and training of the medical applications of this technology are required. In particular, family medicine residents require more comprehensive training programs to fully understand the potential of AI in areas such as diagnosis, treatment planning, and patient management, and to use this technology effectively.

These findings demonstrate the importance of integrating AI into medical education. We suggest that educational institutions should offer specialized courses and workshops on topics such as AI applications, ethical considerations, and patient data protection for family medicine residents. In addition, innovation and developments in this field should be encouraged through continuing professional development programs.

In conclusion, increasing the level of AI knowledge among family medicine residents is critical for both increasing the quality of patient care and improving the efficiency of healthcare services. In this regard, updating training programs and supporting continuous professional development will facilitate the integration of progress in this field into health services and ensure effective use of AI in family medicine practice.

Ethics

Ethics Committee Approval: The study was approved by İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (decision no: 0458, date: 26.10.2023).

Informed Consent: Our study was conducted using a survey method with physicians, and information was provided before the survey and their approval was obtained. Physicians who agreed to participate completed the survey.

Footnotes

Authorship Contributions

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

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Pregnancy, Infection, and Refugee Health: A Study on Seroprevalence of Key Pathogens in Turkey's Refugee Population

Gebelik, Enfeksiyon ve Sığınmacı Sağlığı: Türkiye'deki Sığınmacılarda Önemli Patojenlerin Seroprevalansı Üzerine Bir Çalışma

İlkay Akbulut[1], Zeynep Sedef Varol[2]

[1]University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic o of Infectious Diseases and Clinical Microbiology, İzmir, Turkey
[2]İzmir Health Directorate, Department of Public Health, İzmir, Turkey

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Abstract

Objective: Pregnant refugees in Turkey are at high risk for infectious diseases due to limited access to healthcare services and suboptimal hygiene conditions. This study aims to assess the risks posed by infections, particularly toxoplasmosis, Rubella, hepatitis, human immunodeficiency virus (HIV), and cytomegalovirus (CMV), during pregnancy. These pathogens have adverse effects on maternal and fetal health during gestation, and early diagnosis and management are crucial.

Methods: This retrospective study analyzes serological test results from pregnant refugees who presented at University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital between March 1, 2018, and March 1, 2020. Tests evaluated included anti-Toxoplasma immunoglobulin (Ig)M, anti-Toxoplasma IgG, anti-hepatitis C virus (HCV), hepatitis B surface antigen (HBsAg), anti-HIV, anti-HBs, anti-Rubella IgM, anti-Rubella IgG, anti-CMV IgM, and anti-CMV IgG. Seroprevalence rates were analyzed annually.

Results: Of the pregnant participants, 94.7% were Syrian, and 5.3% were Afghan. Seroprevalence rates for Toxoplasma IgG, Rubella IgG, and CMV IgG were found to be 51.3%, 85.3%, and 57.6%, respectively. No significant variation in test results was observed over the years. The positive rates for anti-HCV, HBsAg, and anti-Rubella IgM were low; chi-square analysis was limited by low cell frequencies, affecting statistical power.

Conclusion: This study reveals a high prevalence of infections such as toxoplasmosis, Rubella, hepatitis B, and CMV among pregnant refugees in Turkey. Expanding screening and vaccination programs for refugee women is recommended to mitigate infection risks. Improving access to healthcare services and regular screenings is crucial to curbing the spread of these infections.

Keywords: Pregnancy, refugees, seroprevalence

Address for Correspondence/Yazışma Adresi: İlkay Akbulut, University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic o of Infectious Diseases and Clinical Microbiology, İzmir, Turkey
E-mail: ilkayakbulutdr@gmail.com
ORCID ID: orcid.org/0000-0002-4840-6865

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Öz

Amaç: Türkiye'deki sığınmacı gebeler, sağlık hizmetlerine erişim ve hijyen koşullarındaki kısıtlılıklar nedeniyle enfeksiyon hastalıkları açısından yüksek risk altındadır. Bu çalışma, özellikle toksoplazma, Rubella, hepatit, insan immün yetmezlik virüsü (HIV) ve sitomegalovirüs (CMV) enfeksiyonlarının gebelik sürecinde oluşturduğu riskleri değerlendirmeyi amaçlamaktadır. Bu patojenler, gebelik döneminde anne ve fetüs sağlığı üzerinde olumsuz etkiler yaratabilir ve erken tanı ile yönetilmesi önem taşır.

Yöntem: Bu retrospektif çalışma, 1 Mart 2018-1 Mart 2020 tarihleri arasında Sağlık Bilimleri Üniversitesi, İzmir Tepecik Eğitim ve Araştırma Hastanesi'ne başvuran sığınmacı gebelerin serolojik test sonuçlarını analiz etmektedir. Anti-Toksoplazma immünoglobulin (Ig)M, anti-Toksoplazma IgG, anti-HCV, hepatit B yüzey antijeni (HBsAg), anti-HIV, anti-HBs, anti-Rubella IgM, anti-Rubella IgG, anti-CMV IgM ve anti-CMV IgG testleri değerlendirilmiştir. Yıllara göre seroprevalans oranları analiz edilmiştir.

Bulgular: Çalışmaya katılan gebelerin %94,7'si Suriye, %5,3'ü ise Afganistan uyrukludur. Toksoplazma IgG seroprevalansı %51,3, Rubella IgG %85,3 ve CMV IgG %57,6 olarak bulunmuştur. Test sonuçlarında yıllara göre anlamlı bir değişiklik saptanmamıştır. Anti HCV, HBsAg ve anti Rubella IgM testlerinde pozitiflik oranları düşük kalmıştır, ki-kare analizinde bazı hücre frekanslarının düşük olması nedeniyle istatistiksel güç sınırlanmıştır.

Sonuç: Bu çalışma, Türkiye'deki sığınmacı gebeler arasında toksoplazma, Rubella, hepatit B ve CMV gibi enfeksiyonların yüksek prevalansını göstermektedir. Sığınmacı kadınların enfeksiyon hastalıkları açısından korunması için tarama ve aşı programlarının genişletilmesi önerilmektedir. Sağlık hizmetlerine erişim koşullarının iyileştirilmesi ve düzenli taramalar, bu enfeksiyonların yayılımını azaltmak için kritik öneme sahiptir.

Anahtar Kelimeler: Gebelik, sığınmacılar, seroprevalans

Introduction

Globally, migrant and refugee populations are at high risk for infectious diseases due to restricted access to healthcare and suboptimal hygiene conditions[1]. Infections such as toxoplasmosis, Rubella, hepatitis, human immunodeficiency virus (HIV), and cytomegalovirus (CMV) pose significant health concerns, particularly among pregnant women[2]. The World Health Organization estimates that around 1.5 million people globally are infected with the hepatitis B virus each year, with migrant populations showing higher prevalence rates[3]. HIV infection rates are also elevated among migrant populations, especially among individuals from low- and middle-income countries[4,5]. Migrants from conflict zones such as Syria and Afghanistan face increased risks for infectious diseases due to poor living conditions, lack of hygiene, and limited access to healthcare services[6]. Infections such as toxoplasmosis, CMV, and Rubella are particularly concerning in these communities. Studies have indicated that toxoplasmosis seroprevalence ranges from 30% to 60%, whereas Rubella seroprevalence remains high among unvaccinated individuals[7-9]. CMV infection is also prevalent among migrant populations, with transmission risks heightened in environments with inadequate hygiene. Early diagnosis and treatment of these infections are crucial because they can lead to severe complications during pregnancy.

In Turkey, similar patterns are observed among migrant communities. Turkey hosts a large refugee population, particularly from Syria, and the prevalence of infectious diseases within these communities is notably high. Studies among refugee women in Turkey reported hepatitis B carriage rates of approximately 4-7%[10]. Although HIV infection is relatively rare among the migrant population in Turkey, it remains a concern in high-risk groups. Infections such as Rubella and CMV can lead to severe complications during pregnancy, affecting both the mother and the fetus. Challenges in accessing healthcare further exacerbate the spread of these infections among refugee populations in Turkey.

Refugee women face economic and social hardships that hinder access to healthcare, increasing the risk of developing infectious diseases. Exposure to infections during pregnancy can result in significant adverse outcomes for both maternal and fetal health[11]. Screening for infections during pregnancy is crucial to safeguard maternal health and ensure the birth of a healthy child. Specifically, infections such as toxoplasmosis, hepatitis, Rubella, HIV, and CMV can lead to complications during pregnancy and pose risks to the infant's health postpartum[12]. Preventive measures against these infections are essential to minimize potential health risks[13].

Regular serological testing of pregnant women presenting to University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital is crucial for assessing the prevalence of infection in this group. This study aimed to analyze the annual distribution of serological test results for specific infectious agents among pregnant refugee women admitted to University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital between March 2018 and

March 2020. The study examined anti-Toxoplasma IgM, anti-Toxoplasma IgG, anti-HCV, HBsAg, anti-HIV, anti-HBs, anti-Rubella IgM, anti-Rubella IgG, anti-CMV IgM, and anti-CMV IgG tests.

Materials and Methods

This study evaluated the annual distribution of serological test results among pregnant women who presented to University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital between March 1, 2018 and March 1, 2020. The study aims to determine immunity or infection status against certain infectious agents in pregnant women, including anti-Toxoplasma IgM, anti-Toxoplasma IgG, anti-HCV, HBsAg, anti-HIV, anti-HBs, anti-Rubella IgM, anti-Rubella IgG, anti-CMV IgM, and anti-CMV IgG serological tests. Annual positivity, negativity, and untested (not examined) rates for each serological test were analyzed.

Statistical Analysis

In data analysis, the distribution percentages of positive, negative, and untested results for each serological test were calculated by years. The positivity, negativity, and untested rates for each serological test were compared, and the chi-square test was applied to detect differences between years when the validity conditions were met. For test groups with cell frequencies below 5, only percentage summaries were provided because of the invalidation of the test under these conditions. The percentage distribution of positivity and negativity rates in the serological tests was presented using descriptive statistics, and seroprevalence was calculated.

The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee on March 06, 2024, with approval number 2024/02-07.

Results

The mean age of the study population was 25.6±3.9 years (range: 18-39). Of the pregnant women, 94.7% (n=1,042) were of Syrian nationality, while the remaining 5.3% (n=58) were of Afghan nationality. Serological testing was conducted for 552 women (50.2%) in 2018, 225 women (20.5%) in 2019, and 323 women (29.4%) up to March 1, 2020.

The seroprevalence of anti-Toxoplasma IgM and anti-Toxoplasma IgG was 2.81% and 51.28% (Table 1). For anti-HCV, the seroprevalence was 0.37%; for HBsAg, 1.85%; and for anti-HBs, 22.29% (Table 2). Anti-Rubella IgM and anti-Rubella IgG seroprevalence was 0.64% and 85.30% (Table 3). The seroprevalence of anti-CMV IgM was 3.49%, and for anti-CMV IgG was 3.49% and 57.55% (Table 4).

No significant changes were observed in the distribution of serological test results across years within the study group. Although anti-Toxoplasma IgM and IgG positivity rates were higher in 2018, they remained stable in 2019 and 2020 ($p>0.05$). Due to the low positivity in anti-HCV, HBsAg, and anti-Rubella IgM tests, chi-square analysis was limited by the expected cell counts below 5 for certain categories. Additionally, no significant changes were found across years in anti-HIV, anti-HB, and anti-Rubella IgG levels, with p-values exceeding 0.05. The positivity rates for anti-

Table 1. Distribution of toxoplasma serology results of the study group

Anti Toxoplasma IgM	
Positive (%)	22 (2%)
Negative (%)	761 (69.2%)
Not tested (%)	317 (28.8%)
Anti Toxoplazma IgG	
Positive (%)	402 (36.6%)
Negative (%)	380 (34.5%)
Not tested (%)	318 (28.9%)
Ig: Immunoglobulin	

Table 2. Distribution of hepatitis and HIV serology results of the study group

Anti HCV	
Positive (%)	4 (0.4%)
Negative (%)	1081 (98.3%)
Not tested (%)	15 (1.3%)
HBsAg	
Positive (%)	20 (1.8%)
Negative (%)	1063 (96.6%)
Not tested (%)	17 (1.6%)
Anti HBs	
Positive (%)	173 (15.7%)
Negative (%)	603 (54.8%)
Not tested (%)	324 (29.5%)
Anti HIV	
Positive (%)	0 (0.0%)
Negative (%)	1065 (96.8%)
Not tested (%)	35 (3.2%)
HIV: Human immunodeficiency virus, HCV: Hepatitis C virus, HBsAg: Hepatitis B surface antigen	

CMV IgM and IgG were similarly distributed across years, with annual differences not reaching statistical significance (p>0.05). Overall, no notable annual increase or decrease was observed in serological test results; statistical analyses were limited to certain tests due to low cell counts. These findings indicated no significant year-over-year changes in the serological test results of the study group (Table 5).

Discussion

This study revealed the seroprevalence of various infectious agents among pregnant refugee women in Turkey, highlighting infectious disease risks as a significant public health concern in migrant populations. The high prevalence of infections, including toxoplasmosis, Rubella, hepatitis B, HCV, and CMV, in this group is associated with challenges in accessing healthcare and insufficient hygiene conditions. A global review by Saseetharran et al.[14] noted that viral hepatitis infections such as hepatitis B and C are widespread among migrant populations, and barriers to accessing healthcare complicate the treatment and monitoring of these diseases. This finding aligns with our study results, underscoring the importance of expanding viral hepatitis screening among pregnant refugee women[14].

Table 3. Distribution of Rubella serology results of the study group

Anti Rubella IgM	
Positive (%)	5 (0.5%)
Negative (%)	779 (70.8%)
Not tested (%)	316 (28.7%)
Anti Rubella IgG	
Positive (%)	570 (36.7%)
Negative (%)	118 (10.7%)
Not tested (%)	315 (28.6%)

Ig: Immunoglobulin

Table 4. Distribution of cytomegalovirus serology results of the study group

Anti CMV IgM	
Positive (%)	22 (2%)
Negative (%)	610 (55.5%)
Not tested (%)	468 (42.5%)
Anti CMV IgG	
Positive (%)	633 (57.6%)
Negative (%)	0 (0%)
Not tested (%)	467 (42.4%)

Ig: Immunoglobulin, CMV: Cytomegalovirus

In our study, the Rubella IgG seropositivity was 85.3%. Similarly, a study by Gürses et al.[15] on Syrian refugees in Şanlıurfa found a high Rubella seropositivity rate (99.5%). This high seropositivity may be attributed to widespread Rubella vaccination or natural immunity among refugees. However, a study by Fahme et al.[16] on sexually transmitted infections in pregnant Syrian refugees in Lebanon indicated that this population does not receive adequate screening services during the antenatal period. This finding highlights the need to expand screening programs for detecting infections during pregnancy.

The prevalence of hepatitis B and C infections among refugee women is also noteworthy. In a study by Hansu and Cikim[17], anti-HCV positivity was found to be higher in Syrian migrant pregnant women in Turkey compared to Turkish pregnant women, which may be linked to poor hygiene and inadequate healthcare services. In our study, anti-HCV seroprevalence was found to be 0.37%, which is lower than in other studies; however, expanding health screenings among refugee populations remains essential to reduce potential transmission risks.

CMV infection can cause serious complications during pregnancy and is more common in communities with poor hygiene. A study by Köse et al.[18] on Syrian refugee children in İzmir reported high CMV seroprevalence, which was linked to the hygiene conditions among refugees. Similarly, our study found a CMV IgG positivity rate of 57.6%, which is consistent with other findings in the literature. CMV screening during pregnancy is critical to reduce the risk of prenatal infection.

Toxoplasma infection is more prevalent in developing countries and poses serious risks to fetal health during the prenatal period. A study conducted in Kahramanmaraş found high toxoplasma seropositivity among Syrian refugee women[19]. Similar findings were observed in a study by Hansu et al.[20], which reported high toxoplasma seroprevalence among refugee women, associating it with increased hygiene issues due to displacement. Consistent with these studies, our study found a toxoplasma IgG positivity rate of 51.3%, indicating the impact of poor hygiene conditions and limited access to healthy nutrition.

Study Limitations

This study has several limitations. First, it employed a retrospective design and included only pregnant refugee women presenting to University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital. Therefore, the findings cannot be generalized to the entire refugee population

Table 5. Evaluation of the distribution of serologic test results of the study group according to years				
Serological test	**Year of serological testing**			**Chi-square test statistic**
	2018 n (%)	**2019 n (%)**	**2020 n (%)**	**p-value**
Anti-Toxoplazma IgM				
Positive	7 (31.8%)	9 (40.9%)	6 (27.3%)	0.091
Negative	377 (49.5%)	151 (19.8%)	233 (30.6%)	
Not tested	168 (53%)	65 (20.5%)	84 (26.5%)	
Anti-Toxoplasma IgG				
Positive	191 (47.5%)	78 (19.4%)	133 (33.1%)	0.339
Negative	193 (50.8%)	81 (21.3%)	106 (27.9%)	
Not tested	168 (52.8%)	66 (20.8%)	84 (26.4%)	
Anti-HCV				
Positive	2 (50.0%)	0 (0.0%)	2 (50.0%)	***
Negative	539 (49.9%)	224 (20.7%)	318 (29.4%)	
Not tested	11 (73.3%)	1 (6.7%)	3 (20.0%)	
HBsAg				
Positive	10 (50.0%)	4 (20.0%)	6 (30.0%)	***
Negative	531 (50.0%)	218 (20.5%)	314 (29.5%)	
Not tested	11 (64.7%)	3 (17.6%)	3 (17.6%)	
Anti-HIV				
Negative	529 (49.7%)	220 (20.7%)	316 (29.7%)	0.175
Not tested	23 (65.7%)	5 (14.3%)	7 (20.0%)	
Anti-HBs				
Positive	83 (48.0%)	31 (17.9%)	59 (34.1%)	0.491
Negative	298 (49.4%)	128 (21.2%)	177 (29.4%)	
Not tested	171 (52.8%)	66 (20.4%)	87 (26.9%)	
Anti-Rubella IgM				
Positive	2 (40.0%)	1 (20.0%)	2 (40.0%)	***
Negative	382 (49.0%)	160 (20.5%)	237 (30.4%)	
Not tested	168 (53.2%)	64 (20.3%)	84 (26.6%)	
Anti-Rubella IgG				
Positive	59 (50.0%)	20 (16.9%)	39 (33.1%)	0.556
Negative	326 (48.9%)	141 (21.1%)	200 (30.0%)	
Not tested	167 (53.0%)	64 (20.3%)	84 (26.7%)	
Anti-CMV IgM				
Positive	10 (45.5%)	4 (18.2%)	8 (36.4%)	0.604
Negative	304 (49.8%)	118 (19.3%)	188 (30.8%)	
Not tested	238 (50.9%)	103 (22.0%)	127 (27.1%)	
Anti-CMV IgG				
Positive	315 (49.8%)	122 (19.3%)	196 (31.0%)	0.306
Not tested	237 (50.7%)	103 (22.1%)	127 (27.2%)	
Total	552 (50.2%)	225 (20.5%)	323 (29.4%)	

***The validity conditions for the chi-square test were not met; in some cells the expected value is less than 5, Ig: Immunoglobulin, HCV: Hepatitis C virus, HBsAg: Hepatitis B surface antigen, CMV: Cytomegalovirus

in Turkey. Additionally, the seroprevalence data cover only a limited time period (2018-2020), which limits the ability to assess long-term trends. Second, the low positivity rates of some serological tests reduced the statistical power of chi-square analysis because of low cell frequencies. This limitation especially affected the analysis of rare infections (e.g., anti-HCV positivity), making it challenging to derive statistically significant results. Furthermore, due to limited access to healthcare services among the refugee population, some individuals may not have been able to receive regular healthcare, limiting the representativeness of serological test results. Future studies should consider the effects of these variables on infection prevalence by incorporating them into the analysis.

Conclusion

Infectious diseases are prevalent among pregnant women in Turkey. This situation is associated with challenges to healthcare access and inadequate hygiene conditions in the migrant population. Expanding screening and vaccination programs is essential to reduce the spread of these infections and to protect the health of refugee women. In addition, improving living conditions and ensuring regular health screenings for refugees play critical roles in preventing infectious diseases.

Ethics

Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee on March 06, 2024, with approval number 2024/02-07.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Bibliometric Analysis of Emergency Medicine in Disasters: 2004-2023

Afetlerde Acil Tıbbın Bibliyometrik Analizi: 2004-2023

Gülbin Aydoğdu Umaç[1], Sarper Yılmaz[2]

[1]İzmir City Hospital, Clinic of Emergency Medicine, İzmir, Turkey
[2]University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Department of Emergency Medicine, İstanbul, Turkey

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Abstract

Objective: This study aims to conduct a bibliometric analysis of research on "emergency medicine in disasters" published between 2004 and 2023, highlighting the scientific developments, key themes, and research gaps in this growing field. With the increasing frequency of disasters due to factors like climate change, urbanization, and population growth, the importance of disaster emergency medicine has become more critical. While technological advancements have improved emergency medical responses, research shows that further development is needed. This analysis seeks to evaluate global trends and collaborations in disaster medicine research to provide a strategic roadmap for future studies and enhance the preparedness and effectiveness of health systems in responding to disasters.

Methods: A bibliometric review of 1,532 articles published between January 1, 2004 and December 31, 2023, was conducted using the Web of Science Core Collection database. The analysis focused on articles published in peer-reviewed journals, limited to the "emergency medicine" field, written in English, and meeting the defined timeframe. The selected articles were examined based on publication trends, citation counts, journal distribution, most-cited authors, and collaborative networks between institutions and countries. Tools such as keyword networks, bibliographic coupling, co-authorship analysis, and citation mapping were used to visualize research collaborations and thematic focus areas. VOSviewer software was employed to map research collaborations and identify the most influential studies in disaster medicine.

Results: The study's findings reveal a significant increase in research output, particularly following global crises such as coronavirus disease-2019 (COVID-19). Countries like the United States of America (USA), Canada, the United Kingdom, and China lead in both publications and international collaborations, demonstrating strong partnerships in disaster medicine research. Institutions such as Harvard University and Johns Hopkins University stand out for their high productivity and impact, with highly cited articles focusing on disaster-related health impacts, triage, and the mental health of responders. Key research themes include disaster preparedness, emergency medical services, and global health crises, underscoring the growing importance of international collaboration in advancing disaster medicine.

Conclusion: The bibliometric analysis of research on "emergency medicine in disasters" from 2004 to 2023 demonstrates a substantial increase in scientific output, especially following the COVID-19 pandemic. Key findings highlight the central role of journals like Prehospital and Disaster Medicine and the influential contributions of institutions such as Harvard University and Johns Hopkins University. Frequently cited articles focus on disaster health impacts, triage, and mental health support for healthcare workers, reflecting the critical importance of preparedness and response strategies. International collaborations, particularly among countries like the USA, Sweden, Iran, and Turkey, have expanded, underlining the growing global significance of disaster medicine. These results underscore the vital role that disaster emergency medicine plays in strengthening global health systems and the increasing academic focus on this field.

Keywords: Emergency medicine, disaster, response, emergencies, mass casualty

Address for Correspondence/Yazışma Adresi: Gülbin Aydoğdu Umaç MD, İzmir City Hospital, Clinic of Emergency Medicine, İzmir, Turkey
E-mail: dr.gulbinaydogdu@gmail.com
ORCID ID: orcid.org/0000-0002-9874-0343

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Öz

Amaç: Bu çalışma, 2004-2023 yılları arasında yayımlanan "afetlerde acil tıp" konusundaki araştırmaların bibliyometrik analizini yaparak bu hızla büyüyen alandaki bilimsel gelişmeleri, temel temaları ve araştırma boşluklarını vurgulamayı amaçlamaktadır. İklim değişikliği, kentleşme ve nüfus artışı gibi faktörlerle afetlerin sıklığının artması, afetlerde acil tıbbın önemini daha da kritik hale getirmiştir. Teknolojik ilerlemeler acil tıbbi müdahaleleri geliştirmiş olsa da araştırmalar bu alanda daha fazla gelişime ihtiyaç olduğunu göstermektedir. Bu analiz, afet tıbbı araştırmalarındaki küresel eğilimleri ve iş birliklerini değerlendirerek, gelecekteki çalışmalar için stratejik bir yol haritası sunmayı ve sağlık sistemlerinin afetlere karşı hazırlık ve etkinliğini artırmayı hedeflemektedir.

Yöntem: Bu çalışma, 1 Ocak 2004 ile 31 Aralık 2023 tarihleri arasında yayımlanan 1.532 makalenin bibliyometrik bir incelemesini içermektedir. İnceleme, Web of Science Core Collection veri tabanında yapılan tarama ile gerçekleştirilmiştir. Çalışma, yalnızca "acil tıp" alanındaki, İngilizce yazılmış ve hakemli dergilerde yayımlanmış makaleleri kapsamıştır. Seçilen makaleler; yayımlanma eğilimleri, atıf sayıları, dergi dağılımı, en çok atıf alan yazarlar ve kurumlar ile ülkeler arasındaki iş birlikleri açısından incelenmiştir. Araştırma iş birliklerini ve tematik odak alanlarını görselleştirmek için anahtar kelime ağları, bibliyografik eşleştirme, ortak yazarlık analizi ve atıf haritalama gibi araçlar kullanılmıştır. VOSviewer yazılımı, araştırma iş birliklerini haritalamak ve afet tıbbındaki en etkili çalışmaları belirlemek için kullanılmıştır.

Bulgular: Çalışmanın bulguları, özellikle koronavirüs hastalığı-2019 (COVID-19) gibi küresel krizlerin ardından araştırma çıktılarında önemli bir artış olduğunu ortaya koymaktadır. Amerika Birleşik Devletleri (ABD), Kanada, Birleşik Krallık ve Çin, hem yayın sayıları hem de uluslararası iş birlikleri açısından lider konumdadır ve afet tıbbı araştırmalarında güçlü ortaklıklar göstermektedir. Harvard Üniversitesi ve Johns Hopkins Üniversitesi gibi kurumlar, yüksek üretkenlik ve etki açısından öne çıkmaktadır; bu kurumların makaleleri, afet kaynaklı sağlık etkileri, triyaj ve sağlık çalışanlarının ruh sağlığı gibi konulara odaklanmaktadır. Temel araştırma temaları arasında afet hazırlığı, acil sağlık hizmetleri ve küresel sağlık krizleri yer almakta olup, uluslararası iş birliğinin afet tıbbının ilerletilmesindeki önemi giderek artmaktadır.

Sonuç: 2004-2023 yılları arasında "afetlerde acil tıp" üzerine yapılan bibliyometrik analiz, özellikle COVID-19 pandemisinin ardından bilimsel yayınlarda önemli bir artış olduğunu göstermektedir. Temel bulgular, *Prehospital and Disaster Medicine* gibi dergilerin merkezi rolünü ve Harvard Üniversitesi ile Johns Hopkins Üniversitesi gibi kurumların etkili katkılarını vurgulamaktadır. Sıkça atıf alan makaleler, afet kaynaklı sağlık etkileri, triyaj ve sağlık çalışanlarına yönelik ruh sağlığı desteği gibi konulara odaklanmaktadır ve bu durum, hazırlık ve müdahale stratejilerinin kritik önemini yansıtmaktadır. ABD, İsveç, İran ve Türkiye gibi ülkeler arasında uluslararası iş birlikleri genişlemiş olup, afet tıbbının artan küresel önemine işaret etmektedir. Bu sonuçlar, afetlerde acil tıbbın küresel sağlık sistemlerini güçlendirmedeki hayati rolünü ve bu alandaki akademik ilginin artan önemini ortaya koymaktadır.

Anahtar Kelimeler: Acil tıp, afet, müdahale, acil durumlar, kitlesel yaralanmalı olaylar

Introduction

Emergency medicine is a specialized area of healthcare that focuses on providing immediate and critical medical services during large-scale emergencies, such as natural disasters, terrorist attacks, and mass casualty events. The primary goal of emergency medicine in such scenarios is to ensure the survival of the maximum number of individuals by providing timely medical interventions, managing injuries, and preventing further health complications. This requires the coordination of healthcare resources, rapid decision-making, and the use of specialized protocols to address the unique challenges presented by high-pressure, unpredictable environments[1].

The importance of emergency medicine during disasters lies in its ability to mitigate the effects of catastrophic events on human health[2]. During a disaster, local medical infrastructure can be overwhelmed or even destroyed, making efficient medical care essential to prevent further loss of life. Emergency medical systems must respond swiftly to assess the scope of the disaster, triage victims based on the severity of their injuries, and ensure the allocation of limited resources where they are most needed[3]. Effective disaster response can dramatically reduce mortality and morbidity rates, making it a critical component of national and global health security[4].

The study of emergency medicine during disasters began to gain prominence in the latter half of the 20th century, largely as a response to an increasing number of natural and man-made disasters. Early work by researchers such as Quarantelli and Taylor[5] emphasized the need for organized, systematic approaches to emergency medical services in times of crisis. Since then, advances in information technology and healthcare systems have further transformed the field. Chan et al.[6] highlighted the role of emerging technologies in enhancing emergency medical care during disasters, facilitating faster communication, and more efficient use of medical resources. In terms of its place in medicine, emergency disaster medicine plays a vital and expanding role. The field blends principles of emergency care, public health, trauma medicine, and logistics, making

it a multidisciplinary field that not only saves lives in acute situations but also contributes to the overall preparedness and resilience of healthcare systems[7-9]. Research on disaster triage and management, such as the systematic reviews by Bazyar et al.[10], continues to refine best practices, ensuring that emergency medical professionals are equipped with the tools and knowledge to handle diverse disaster scenarios[11].

Its importance has grown with the frequency and scale of global emergencies, and its research and practice play pivotal roles in improving outcomes during crises. As the world continues to face an increasing array of disaster threats, the development of more sophisticated disaster medicine approaches remains crucial.

The purpose of this study was to conduct a bibliometric analysis of research in the field of emergency medicine in disasters over the past 20 years to identify scientific developments, focal points, and research gaps in this area. With the increasing frequency of disasters, driven by factors such as climate change, urbanization, and population growth, the importance of disaster emergency medicine has become increasingly critical. While technological advancements have improved emergency medical interventions, research has revealed that further development of these processes is needed.

This analysis evaluates global trends and collaborations in studies on disaster response in healthcare systems, providing a strategic roadmap for future research to enhance preparedness and effectiveness in medical interventions during disasters.

Materials and Methods

This study conducted a bibliometric analysis of research on "emergency medicine in disasters" published between 2004 and 2023. To ensure systematic and transparent reporting, the methodology was revised following the Preliminary guideline for reporting bibliometric reviews of the biomedical literature guidelines[12]. The analysis focuses on identifying key trends, influential publications, and collaborations in the field.

Eligibility Criteria: The study included articles that met the following criteria:

•**Topic:** Research specifically related to emergency medicine in disasters, covering areas such as disaster response, triage, prehospital care, and mass casualty incidents.

•**Publication Type:** Only peer-reviewed journal articles were included. Other publication types such as books, proceedings, and book chapters were excluded.

•**Language:** Articles had to be published in English.

•**Time frame:** The selected studies were published between January 1, 2004, and December 31, 2023.

•**Database:** Articles had to be indexed in the Web of Science (WoS) Core Collection database.

Articles Information Sources: The data for this bibliometric analysis were extracted from the WoS Core Collection database. The WoS was selected due to its extensive coverage of high-quality, peer-reviewed journals in various disciplines. Data collection was conducted between January 2024 and March 2024. had to be indexed in the WoS Core Collection database.

Search Strategy: A comprehensive search strategy was developed to capture all relevant studies on emergency medicine during disasters. The search terms were expanded based on the reviewer's suggestion, incorporating a wider range of keywords related to disaster medicine. The final search string included the following terms: emergency medicine in disasters, disaster medicine, emergency medical services in disasters, mass casualty incidents, disaster response, triage in disasters, prehospital care in disasters, surge capacity, earthquake, pandemic, hurricane, flood. These terms were used to query the titles, abstracts, and keywords of articles in the WoS database.

Study Selection Process: The initial search yielded 2,145 articles. After removing duplicates, a total of 1,932 articles were screened for relevance based on their titles and abstracts. Two independent reviewers assessed the relevance of each article, ensuring that only studies directly related to emergency medicine during disasters were included. Disagreements were resolved through discussion, and the final sample comprised 1,532 articles.

Data Collection Process: For each article, data on the following variables were extracted: Title, authors, publication year, journal name, impact factor, country of origin, institution, number of citations, WoS subject categories, and keywords. The data extraction was performed by two independent reviewers, and any discrepancies were resolved by consensus.

Data Synthesis and Analysis: The data were analyzed using VOSviewer (Leiden University, Netherlands; version 1.6.11) to visualize research trends and collaboration networks. The analysis focused on the following: Analysis of articles by year, analysis of articles by journal, most cited articles: Authors,

article titles, journals, publication years, and citation counts, keyword analysis, institutions associated with authors, analysis of inter-institutional publications, analysis of author collaboration, and citation distribution by country[13].

Statistical Analysis

The data collected for this bibliometric analysis were systematically analyzed to identify trends and patterns. Descriptive statistics, including frequencies and percentages, were used to summarize the number of publications, citation counts, and the distribution of articles across journals and institutions. Temporal trends in publication output were assessed by examining annual variations in article numbers. To understand the relationships between keywords, co-occurrence network analysis was performed using VOSviewer. This analysis focused on identifying clusters and connections among the 200 most frequently used keywords, providing insights into thematic focuses in the literature. The clustering coefficients and the density of keyword connections were calculated to evaluate the strength of relationships within the dataset.Institutional and country-level collaboration networks were visualized using bibliometric mapping techniques. The intensity and frequency of collaborations were measured by the thickness of the connecting lines, and the clusters revealed shared research focuses among countries and institutions.

Results

1. Analysis of Articles by Year

The number of articles published on the topic of "emergency medicine in disasters" by year, according to WoS data, is presented in Figure 1. Figure 1 shows the annual variation in the number of articles published on "emergency medicine in disasters" (disaster emergency medicine) between 2004 and 2023. This graph illustrates how academic interest in the topic has fluctuated over the years and highlights the overall growth trend. In 2004, only 19 articles were published in this field; however, a significant increase was observed in 2005, with 38 articles published. This increase indicates that "emergency medicine in disasters" began to attract increasing attention within the scientific community. In 2006 and 2007, the number of published articles was 74 and 68, respectively. These years have witnessed a growing research agenda in disaster emergency medicine, with many studies being conducted in this area. The increase in 2006 may be explained by the occurrence of various disasters during this period, thus driving the need for more scientific investigation. Between 2008 and 2010, there was a relative stabilization and slight fluctuations in the number of articles. In 2008, 72 articles were published, but the number decreased to 61 in 2009 and 59 in 2010. This variation suggests that the research field was starting to stabilize, with scientific interest leveling off. From 2011 to 2014, there was another increase in the number of publications. Although 64 articles were published in 2011, the number rose to 84 by 2013. Although a slight decrease to 72 articles was observed in 2014, the general trend during this period indicates a rising scientific interest in the topic. The years 2015-2019 represent a steady period of growth in disaster emergency medicine research. In 2015, 86 articles were published, and by 2019, this number had risen to 89. This consistent growth indicates a growing global interest in this field, with more researchers contributing to this field. The years 2020-2023 saw a sharp increase in the number of articles influenced by global crises such as the COVID-19 pandemic. In 2020, 108 articles were published, followed by 104 in 2021, 114 in 2022, and 101 in 2023. This surge reflects the increased importance of disaster emergency medicine during large-scale health crises like the pandemic.

Overall, the graph demonstrates a significant rise in research on "emergency medicine in disasters" in recent years, with continuous academic interest driving the field forward. The increasing need for emergency medicine during disasters has contributed to the sustained growth of research in this area.

2. Analysis of Journal Articles

The number of articles related to "emergency medicine in disasters" published in various journals according to the WoS is presented in Table 1. Table 1 presents the distribution of articles published in the field of disaster emergency medicine across various journals, along with the number of articles and their percentage of total publications. The table indicates that a substantial portion of disaster emergency medicine literature is concentrated in specific key journals, with Prehospital and Disaster Medicine playing a central role in the field. However, other journals also make significant contributions, ensuring a broad and diverse representation of research in this field.

3. Most Cited Articles: Authors, Article Titles, Journals, Publication Years, and Citation Counts

The citation counts, author information, article titles, journals, and publication years of the most cited articles related to "emergency medicine in disasters" are detailed in Table 2. Table 2 provides a detailed overview of the

most cited articles in the field of "emergency medicine in disasters" and highlights the impact of these studies on the literature. This table identifies the most influential articles within a specific research area, showing the most frequently referenced studies and how they have contributed to scientific knowledge. The high citation counts of these articles demonstrate their impact, not only in theoretical research but also in practical application. Such analyses are crucial for understanding which studies are prioritized in the research community and which topics garner the most attention[14].

Table 1. Distribution of articles published in the field of disaster emergency medicine across various journals, along with the number of articles and their percentage of total publications

Rank	Journal name	Number of articles	%
1	Prehospital and Disaster Medicine	653	42.62
2	Academic Emergency Medicine	63	4.11
3	Annals of Emergency Medicine	55	3.59
4	Prehospital Emergency Care	53	3.46
5	Journal of Emergency Medicine	51	3.32
6	European Journal of Trauma and Emergency Surgery	45	2.93
7	Emergency Medicine Journal	39	2.54
8	American Journal of Emergency Medicine	37	2.41
9	European Journal of Emergency Medicine	37	2.41
10	BMC Emergency Medicine	34	2.21
11	Scandinavian Journal of Trauma Resuscitation Emergency Medicine	34	2.21
12	Emergency Medicine Australasia	33	2.15
13	Pediatric Emergency Care	33	2.15
14	Western Journal of Emergency Medicine	28	1.82
15	International Journal of Emergency Medicine	23	1.50
16	Notfall Rettungsmedizin	21	1.37
17	Injury International Journal of the Care of the Injured	20	1.30
18	Trauma Monthly	20	1.30
19	Hong Kong Journal of Emergency Medicine	18	1.17
20	Eurasian Journal of Emergency Medicine	17	1.11
21	Others	212	14,33

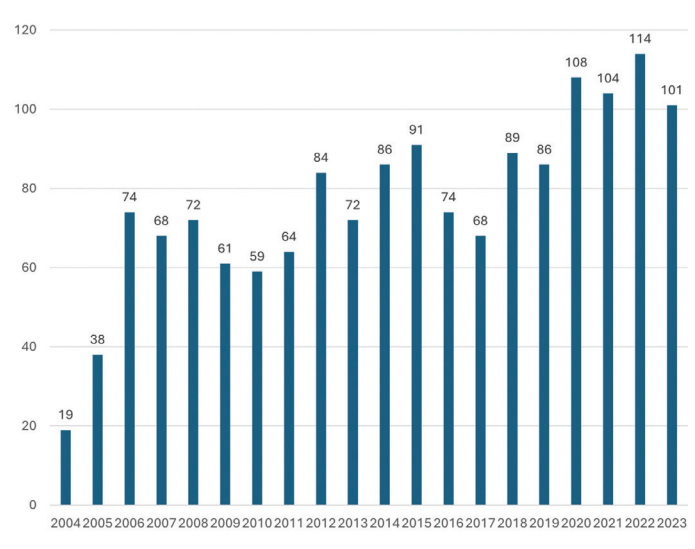

Figure 1. Number of annual articles published on emergency medicine during disasters

4. Keyword Analysis

Researchers carefully select keywords that best represent the core themes and key findings of their work because well-chosen keywords can significantly enhance the visibility and impact of a study[15]. The common keywords and their usage frequencies in studies on "emergency medicine in disasters" from the WoS database are shown in Figure 2. In the analysis, a minimum keyword occurrence of 5 was set, meaning that a keyword must have been used at least 5 times to be included in the analysis. This threshold allows the analysis to focus on frequently used and meaningful terms. In total, 2,918 different keywords were identified; however, only 200 keywords met the criteria of being used at least 5 times. Thus, the analysis examined the relationships among these 200 keywords. This analysis is useful for identifying the most frequently used keywords in a particular research area. Thus, 2,556 connections and 12 distinct clusters were identified among the 200 keywords. Figure 2 provides a detailed overview of the most frequently used keywords in the field of "emergency medicine in disasters" and their frequency of use. This analysis helps us understand which keywords are most prevalent in the literature and how these terms are related to one another. The most frequently used keyword is "disaster" which appears a total of 304 times. This indicates that "disaster" is a central concept in disaster medicine

Table 2. Most cited articles: Authors, article titles, journals, publication years, and citation counts

No	Author(s)	Article title	Journal name	Publication year	Citation count
1	Du WW, FitzGerald GJ, Clark M, Hou XY.	Health impacts of floods	Prehospital and Disaster Medicine	2010	197
2	Hick JL, Hanfling D, Burstein JL, DeAtley C, Barbisch D, Bogdan GM, Cantrill S.	Health care facility and community strategies for patient care surge capacity	Annals of Emergency Medicine	2004	191
3	Naushad VA, Bierens JJLM, Nishan KP, Firjeeth C.P, Mohammad OH, Maliyakkal AM, Hadan SC, Schreiber MD.	A systematic review of the impact of disaster on the mental health of medical responders	Prehospital and Disaster Medicine	2019	184
4	Auf der Heide E.	The importance of evidence-based disaster planning	Annals of Emergency Medicine	2006	182
5	Kahn CA, Schultz CH, Miller KT, Anderson CL.	Does START triage work? an outcomes assessment after a disaster	Annals of Emergency Medicine	2009	137
6	FitzGerald G, Du WW, Jamal A, Clark M, Hou XY.	Flood fatalities in contemporary Australia (1997-2008)	Emergency Medicine Australasia	2010	131
7	Kaji A, Koenig KL, Bey T.	Surge capacity for healthcare systems: A conceptual framework	Academic Emergency Medicine	2006	123
8	Barbisch DF, Koenig KL.	Understanding surge capacity: Essential elements	Academic Emergency Medicine	2006	120
9	Hick JL, O'Laughlin DT.	Concept of operations for triage of mechanical ventilation in an epidemic	Academic Emergency Medicine	2006	118
10	Neyman G, Irvin CB.	A single ventilator for multiple simulated patients to meet disaster surge	Academic Emergency Medicine	2006	117

research, and many studies have focused on this term. The term "disaster medicine" appears 173 times, representing a more specific subfield. This research highlights research focused on the technical aspects of disaster medicine and how health services are organized during disasters. The keyword "disasters" appears 132 times and is closely related to "disasters" showing that the two terms are often used in similar contexts within the literature. "Triage" appears 108 times, reflecting the frequent focus on prioritization and patient sorting processes in disaster research. Studies on how limited resources are allocated during disasters tend to focus on this keyword. "Disaster planning" is used 104 times, indicating that planning and preparation for disasters are common research topics. "Emergency medical services" is another frequently used keyword, with 99 occurrences, highlighting the importance of research on the organization and implementation of healthcare services during disasters. The keyword "earthquake" appears 92 times, underscoring the significant role of earthquakes in disaster medicine research. This reflects the global prevalence of earthquakes and the numerous studies that have focused on how emergency medical services should be organized in response to such events. "Preparedness" and "disaster preparedness" are used 79 and 55 times, respectively, indicating that preparedness plays a crucial role in disaster medicine, with numerous studies dedicated to this subject in the literature. "Emergency medicine" appears 56 times, demonstrating the frequent examination of emergency medical practices in disaster-related research. The term "education" is also used 56 times, highlighting the importance of increasing awareness and

training in disaster medicine in academic literature. "Surge capacity" appearing 49 times, reflects research on increasing healthcare system capacity and strategies for managing sudden patient influxes during disasters. Lastly, "COVID-19" is used 46 times, indicating that the pandemic has become a significant topic of study in disaster medicine. Overall, the keywords in Figure 2 show that the field of disaster emergency medicine covers a broad range of topics, with a strong focus on key concepts such as "disaster" "disaster medicine", "triage" and "preparedness"

5. Institutions Associated with Authors

The institutions to which authors of articles on "emergency medicine in disasters" are affiliated, along with the number of publications and citations, are presented in Table 3. Only institutions with at least 5 publications are included in this analysis. Table 3 provides a detailed overview of the institutions that have published academic articles in the field of "disaster emergency medicine" including the total number of publications and the citation counts of these publications. This table clearly highlights the institutions making significant academic contributions in the field of disaster emergency medicine and the effectiveness of these contributions in the scientific literature. The number of publications and citations provides important insights into the extent to which other researchers embrace and utilize scientific works[16]. Institutions such as Harvard University, the University of California, Irvine, and Johns Hopkins University stand out for their productivity and scientific impact in this field.

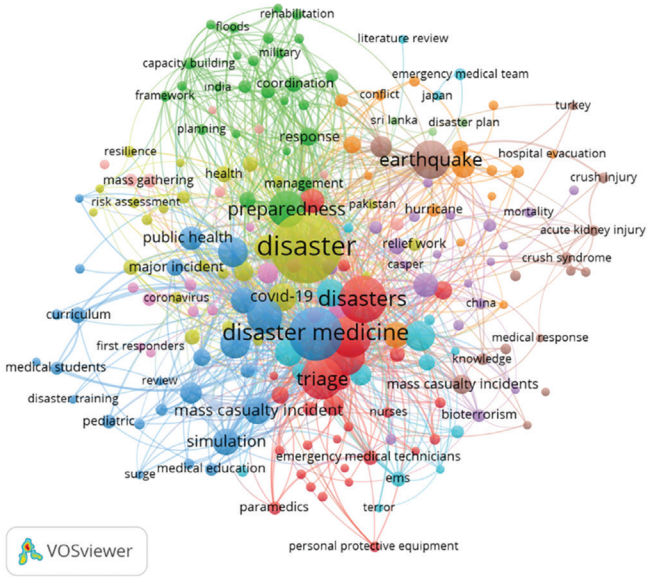

Figure 2. Co-occurrence keywords and their frequency of use

6. Analysis of Inter-Institutional Publications

The results of the analysis of the institutions affiliated with the authors of articles on "emergency medicine in disasters" published in the WoS database, as well as the collaboration relationships between these institutions, are presented in Figure 3 within an academic framework. Figure 3 illustrates the collaboration network between institutions affiliated with the authors of articles published in the WoS on "emergency medicine in disasters". In the analysis, a minimum of 5 documents per institution was set, and 158 out of 2,274 institutions met this criterion. The relationships between these institutions were examined through a bibliometric network analysis, revealing 2,351 connections and 5 clusters. Figure 3 illustrates which institutions are conducting academic studies on "emergency medicine in disasters" and visualizes the collaboration networks between them. This visualization highlights the number of publications by each institution and the intensity of collaboration with other institutions. The circles represent the number of publications from each institution, and the lines between them indicate collaborative relationships. The thickness of the lines reflects the intensity of the collaboration, while colors represent different research groups and clusters. For example, Harvard University has published 54 articles and 153 connections. This demonstrates that Harvard

Table 3. Institutions with the most citations and number of publications in the Web of Science database

No	Institution name	Number of publications	Number of citations
1	Harvard University	54	1049
2	University of California, Irvine	28	1032
3	Johns Hopkins University	39	813
4	Yale University	33	729
5	Karolinska Institutet	38	638
6	University of Michigan	23	586
7	Queensland University of Technology	12	556
8	Brigham and Women's Hospital	33	528
9	Università del Piemonte Orientale	35	525
10	University of Minnesota	6	506

is productive in disaster medicine research and has an extensive network of collaborators. Yale University, with 33 articles and 154 connections, has a broad collaboration network, indicating its active role in this field and its development of international collaborations. Johns Hopkins University, which has 29 articles and 154 connections, also possesses a significant collaboration network. The large number of connections underscores the importance of Johns Hopkins' contributions to disaster medicine through scientific partnerships. Brown University, with 25 articles and 148 connections, also has a wide collaboration network and plays an active role in disaster medicine research. These types of collaboration analyses are crucial for understanding which institutions play a central role in academic research and how they interact with others. Such inter-institutional collaborations play a critical role in accelerating scientific progress and fostering knowledge sharing.

7. Analysis of Author Collaboration

Bibliographic coupling is a method used to examine the relationships between authors in academic works. When two or more authors cite the same sources, a connection between them is assumed[17]. This indicates that the authors are working in similar research areas or are drawing from the same literature. Zhao and Strotmann[18] noted its effectiveness in tracking the dissemination of literature and emphasized the importance of bibliographic coupling as a tool for analyzing scientific literature. The WoS analyzes the collaboration network among authors of articles on "emergency medicine in disasters" has been analyzed in detail. The findings of this analysis are presented in Figure 4. Figure 4 presents the bibliographic relationships between authors who have published at least 5 articles in a specific research field. In this study, a total of 5,958 authors were evaluated, but only 107 met the set criteria. The selection of authors with a minimum of 5 publications ensures that the

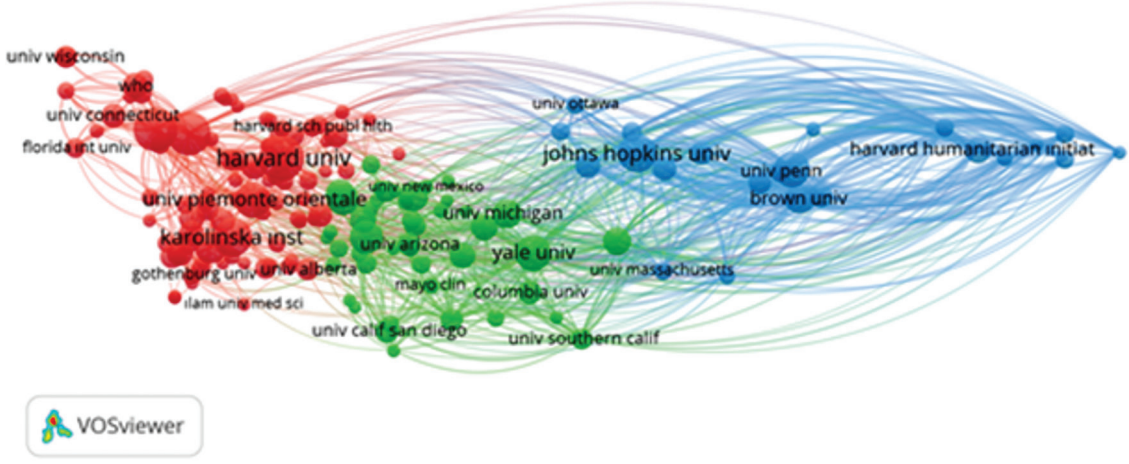

Figure 3. Bibliometric network visualization of inter-institutional collaboration

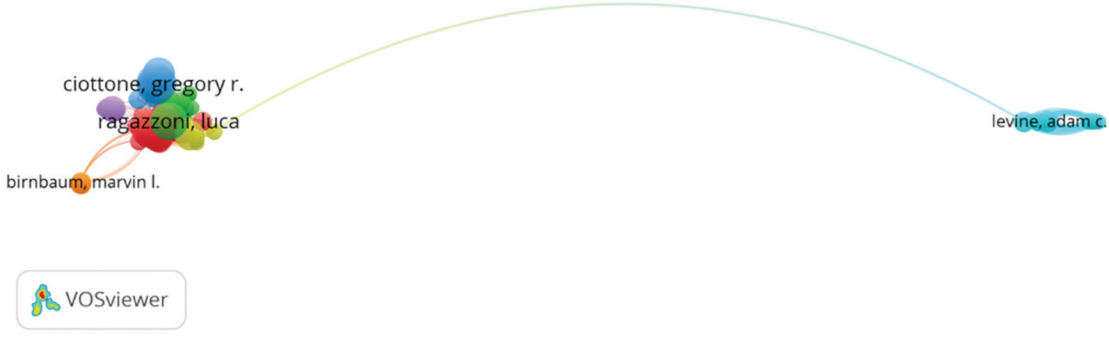

Figure 4. Bibliometric network visualization of author collaboration

analysis focuses on those authors who have made significant contributions to the literature and have enough publications. This threshold allows for a more reliable assessment of authors' productivity and scientific impact. A common method in scientific studies is to set a minimum publication threshold to enhance the accuracy and scope of the analysis. This approach excludes less frequent or isolated studies, allowing for a clearer examination of key contributors in the research area and their relationships[19]. By highlighting researchers who have made a notable impact on the literature and are actively conducting studies, the analysis provides more consistent and meaningful results. The analysis in Figure 4 reveals 7 distinct clusters among the 107 authors. Each cluster represents a group of authors connected through a specific research theme or area. These clusters show how authors are linked through shared references and highlight their focus on specific topics. Such analyses are highly valuable for identifying key figures in a research field and understanding collaborative dynamics in the scientific community[17]. The figure displays bibliographic connections and collaboration networks between authors in the field of "emergency medicine in disasters". Each circle represents an author, and the size of the circle reflects the number of articles the author has published and their scientific contribution. The lines between authors indicate that they have cited the same sources, establishing a bibliographic connection. The thickness of the lines represents the strength of the connection and the frequency with which the two authors reference the same sources. In the cluster on the left, Gregory R. Ciottone and Luca Ragazzoni have been shown to have a strong collaborative relationship. There is a dense bibliographic connection between these two authors. Marvin L. Birnbaum is also a member of this cluster and forms strong connections with other authors. These links demonstrate that these authors are active in similar research areas and frequently associate with one another in scientific literature. These authors focused on a specific theme or topic in disaster medicine and collaborated by citing the same sources. On the right side of the figure is Adam C. Levine appears in a more isolated position.

Levine has fewer bibliographic connections than other authors, which may indicate fewer collaborations or a focus on a different research area. These connections between

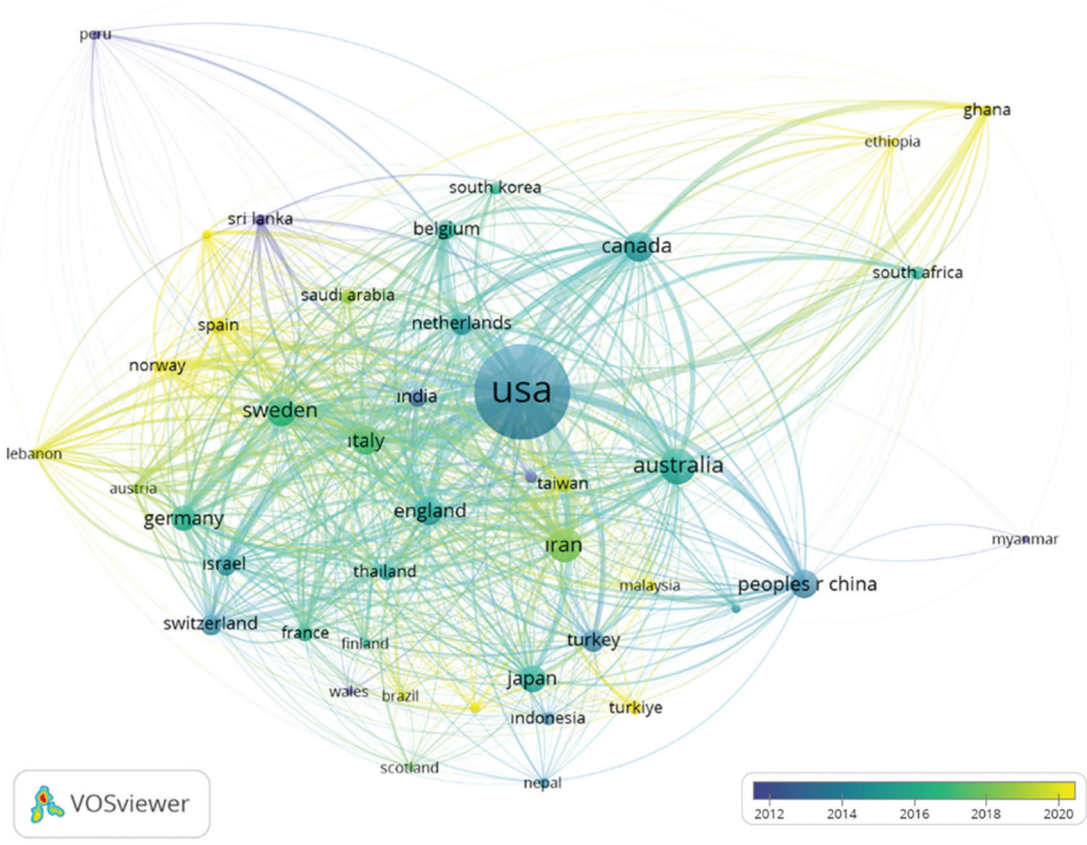

Figure 5. Distribution of citations by country

authors reveal which themes are prominent in the literature and which authors have broader collaboration networks.

8. Citation Distribution by Country

The distribution of citations by country for articles published on the topic of "emergency medicine in disasters" in the WoS database is shown in Figure 4. This analysis shows the extent to which scientists from different countries are active in disaster medicine and how they contribute to the literature. Figure 5 presents a detailed visualization of the distribution of citations across countries for articles published in the WoS database, as well as the academic collaborations between these countries. The analysis considers countries with a minimum of 5 published documents, and 43 countries met this criterion. A total of 8 clusters were identified, with each cluster representing a specific research theme or collaboration network. Figure 5 illustrates the scientific collaboration network between countries in the field of "emergency medicine in disasters" and how these networks have evolved over the years. Each circle represents a country, and the size of the circle indicates the volume of scientific contributions (number of publications and citations) from that country. The lines connecting the circles represent collaborations between countries, whereas the thickness of the lines reflects the intensity of the collaborations. The colors indicate when these collaborations took place, with dark blue representing earlier years (2012) and yellow representing more recent years (2020). The United States (USA) is represented by the largest circle and has 42 connections, indicating that it plays a central role in disaster medicine. The USA is the country with the largest number of global collaborations, with the green-blue tones of the connections indicating that the majority of these collaborations have occurred since 2015. Strong scientific relationships exist between the USA and countries such as Canada, the United Kingdom, Australia, and China. Sweden, with 41 connections, demonstrates a significant increase in its international collaborations in disaster medicine in recent years, as highlighted by the green and yellow tones of its connections. Sweden has established robust partnerships with the USA, Germany, the United Kingdom, and other European countries. Iran, with 40 connections, has recently become more active in international collaborations in disaster medicine. Iran's relationships with the USA, the United Kingdom, China, and Italy stand out. The lighter colors of its connections indicate that most of these collaborations intensified after 2015, indicating Iran's growing contribution to the field in recent years. Turkey, which has 40 connections, has become an important player in disaster medicine research. Turkey has formed strong partnerships with countries like Australia, Japan, and South Korea. The green tones in Turkey's connections indicate that international collaborations have increased in recent years, demonstrating the country's expanding scientific contribution to disaster medicine. China and Japan, as two of Asia's leading countries in this field, have developed strong collaborations with each other and with countries like the USA. China has shown a notable increase in international collaborations in disaster medicine since 2015. Germany and the United Kingdom are among Europe's strongest contributors in this field, with significant collaborations with the United States and Sweden. The United Kingdom's connections reveal extensive relationships with countries across Asia, Europe, and the America. This visualization effectively illustrates the scientific collaborations between countries in disaster medicine and how these collaborations have changed over the years. Countries like the USA, Sweden, Iran, and Turkey have taken on important roles in the field, and their scientific contributions and collaborations have notably increased in recent years.

Discussion

This study presents a bibliometric analysis of research published between 2004 and 2023 on "emergency medicine in disasters", highlighting academic trends, collaboration networks, and key publications in the field. The findings reveal a significant increase in scientific output during the COVID-19 pandemic, demonstrating the growing importance of disaster medicine and its critical role in global health systems. Topics such as disaster planning, triage processes, and the mental health of healthcare workers were among the most studied and cited. These results are consistent with previous studies on the subject[20,21].

Garbern et al.'s[22] bibliometric analysis on global emergency medicine authorship representation emphasized the increasing global participation in emergency medicine literature. Similarly, our study shows that countries like the USA, Sweden, Iran, and Turkey have made significant contributions to disaster medicine literature in recent years. This reflects the expansion of international collaboration networks that have enhanced the dissemination and effectiveness of scientific knowledge in disaster medicine.

The study by Gong et al.[23] on diagnostic imaging in disasters highlighted the growing importance of this area in disaster management and highlighted the increasing volume of related literature. Our findings also revealed that

a substantial portion of the disaster medicine literature (42.62%) was concentrated in the "Prehospital and Disaster Medicine" journal. This journal plays a central role in the dissemination of scientific knowledge, like how diagnostic imaging and triage processes are key focus in disaster management research.

Golfiruzi et al.[24], in their mapping of global research in emergency medicine, emphasized the increasing prominence of disaster medicine as a research area and highlighted the role of international collaborations. Our study similarly identified institutions like Harvard University, Johns Hopkins University, and the University of California, Irvine, as key contributors with extensive collaboration networks. These findings, consistent with those of Golfiruzi et al.[24], underscore the importance of academic productivity and collaboration in advancing disaster medicine literature.

Xu et al.[25] conducted a bibliometric analysis of prehospital emergency care from 2000 to 2020, emphasizing the growing significance of this research area, particularly in triage and disaster planning. Our study also identified "triage" and "disaster planning" as frequently used keywords, reaffirming the long-standing importance of these key areas in disaster medicine literature. These findings indicate that preparation and response strategies continue to be central topics of focus in the field. Bazyar et al.'s[10] systematic review of triage principles highlighted the critical role of effective triage in the success of healthcare services during disasters. In line with this, triage processes were among the most frequently cited topics in disaster medicine literature. This underscores the importance of triage and disaster planning as essential elements in the organization and delivery of healthcare services during emergencies.

Study Limitations

This study acknowledges that the search was limited to the WoS database and articles published in English, which may have resulted in the exclusion of relevant studies published in other databases or languages. Additionally, while efforts were made to expand the search terms, some relevant articles may have been missed because of the specificity of the keywords.

Conclusion

This study shows that disaster medicine research has grown substantially in academic interest and scientific collaboration from 2004 to 2023. Global crises, such as the COVID-19 pandemic, have further amplified the importance of disaster medicine, with a surge in related publications. Institutions such as Harvard University and Johns Hopkins University play a leading role in fostering extensive collaboration networks that contribute to disaster medicine's growing impact on global health systems. Future research in this area will benefit from the expansion of collaborative networks and the promotion of interdisciplinary studies, further enriching the knowledge base in disaster medicine.

Ethics

Ethics Committee Approval: Ethics committee approval is not required.

Informed Consent: Informed consent was not required.

Footnotes

Authorship Contributions

Concept: G.A.U., S.Y., Design: G.A.U., S.Y., Data Collection or Processing: G.A.U., S.Y., Analysis or Interpretation: G.A.U., S.Y., Literature Search: G.A.U., S.Y., Writing: G.A.U., S.Y.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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The Role of Eosinophil Count at Admission in Predicting Cardiac Arrest Prognosis

Kardiyak Arrestte Kabul Anındaki Eozinofil Sayısının Prognozdaki Rolü

Nurullah İshak Işık[1], Melih Çamcı[2]

[1]Ankara Etlik City Hospital, Department of Emergency Medicine, Ankara, Turkey
[2]Ankara Bilkent City Hospital, Department of Emergency Medicine, Ankara, Turkey

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Abstract

Objective: Cardiac arrest, which is characterized by sudden cessation of circulation and cardiac activity, leads to irreversible fatal outcomes without resuscitative interventions. Although various biomarkers have been studied for the prognostic evaluation of cardiac arrest, data on the utility of eosinophil counts remain limited. The current study aimed to investigate the association between eosinophil count and emergency department (ED) mortality among patients experiencing cardiac arrest.

Methods: This retrospective study included patients with cardiac arrest who presented to the ED between 2022 and 2024. In total, 274 patients were analyzed. Data were retrospectively obtained from the hospital information system, including demographic characteristics (age, gender) and biochemical parameters (e.g., white blood cell count, eosinophil count). Outcomes such as ED mortality and hospital admission were also examined.

Results: The study was completed in 274 patients after applying the inclusion and exclusion criteria. The mean age of the patients was 68 years, and 65.3% of them experienced mortality in the ED. Among the blood parameters, eosinophil, lymphocyte, platelet, and albumin levels were significantly higher in patients who survived compared with those who did not ($p<0.001$, $p=0.001$, $p=0.006$, and $p=0.008$, respectively), while no significant differences were observed in other parameters ($p>0.05$). Multivariate logistic regression analysis revealed that a 0.1-unit decrease in eosinophil count increased the mortality rate by 1.482 times ($p=0.006$). The ROC analysis assessing the relationship between eosinophil count and mortality yielded an area under the curve of 0.629, with a cut-off value of 0.055 ($p<0.001$).

Conclusion: Our findings demonstrate that eosinophil levels are a significant biomarker of ED mortality in patients with cardiac arrest. The distinct response of eosinophils to post-cardiac arrest perfusion disturbances suggests their potential role as prognostic indicators in critical illness. Future large-scale, multicenter prospective studies are needed to further clarify the prognostic value of eosinophil levels and their broader clinical applications.

Keywords: Eosinophil, cardiac arrest, eosinopenia, prognosis, emergency department

Öz

Amaç: Kardiyak arrest dolaşımın ani bir şekilde durması ile olan kardiyak aktivitenin sonlandığı, resüsitatif müdahaleler yapılmadan dönüşü olmayan ölümcül durumlardır. Kardiyak arrest durumunda prognoz için çeşitli biyomarkerların kullanımına dair veriler olsa da eozonofil sayısının kullanımıma dair veriler sınırlıdır. Biz de araştırmamızda eozonofil sayısının acil servis (ED) mortalitesi ile olan ilişkisini inceledik.

Address for Correspondence/Yazışma Adresi: Nurullah İshak Işık MD, Ankara Etlik City Hospital, Department of Emergency Medicine, Ankara, Turkey
E-mail: nurullahishak01@gmail.com
ORCID ID: orcid.org/0000-0002-3802-3502

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Öz

Yöntem: Bu retrospektif çalışmada, 2022-2024 yılları arasında ED'ye başvuran kardiyak arrest hastaları incelenmiştir. Toplamda 274 hasta çalışmaya dahil edilmiştir. Veriler, hastane bilgi sistemi üzerinden geriye dönük olarak elde edilmiş ve yaş, cinsiyet, beyaz küre, eozinofil gibi biyokimyasal parametreler ile ED sonlanımları (mortalite, hastane yatışı) analiz edilmiştir.

Bulgular: Çalışmamız dahil edilme ve dışlama kriterleri uygulandıktan sonra 274 hasta ile tamamlandı. Hastaların yaş ortalaması 68 olup, %65,3'ü ED'de mortalite ile sonuçlanmıştır. Hastaların kan parametreleri mortaliteye göre değerlendirildiğinde eozinofil, lenfosit, trombosit ve albümin değerleri mortalite görülmeyenlerde daha yüksek tespit edilirken (sırasıyla p<0,001, p=0,001, p=0,006 ve p=0,008) diğer kan parametrelerinde anlamlı bir fark tespit edilmemiştir (p>0,05). Multivariate lojistik regresyon analizinde eozinofil sayısındaki 0,1 birimlik azalışın mortalite oranını 1,482 kat artırdığı görüldü (p=0,006). Eozinofil sayısı ile mortalite arasındaki ROC analizi ile eğri altında kalan alan değerlendirildi. Buna göre eğri altında kalan 0,629 ve cut-off değeri 0,055 olarak bulundu (p<0,001).

Sonuç: Sonuç olarak, ED'de kardiyak arrest geçiren hastalarda eozinofil düzeylerinin ED mortalitesini öngörmede anlamlı bir biyobelirteç olduğu çalışmamızda ortaya konmuştur. Eozinofillerin kardiyak arrest sonrası perfüzyon bozukluğuna yanıt veren diğer biyobelirteçlerden farklı bir mekanizma ile etkilenmesi, bu hücrelerin kritik hastalıklarda prognozun belirlenmesinde dikkate alınabilecek potansiyel bir gösterge olduğunu düşündürmektedir. Gelecekte yapılacak daha geniş, çok merkezli ve prospektif çalışmalarla eozinofil düzeylerinin prognostik değerinin daha iyi anlaşılacağı ve klinik uygulamalarda daha yaygın kullanılabileceği düşünülmektedir.

Anahtar Kelimeler: Eozonofil, kardiyak arrest, eozonopeni, prognoz, acil servis

Introduction

Cardiac arrest is a fatal condition in which cardiac activity is terminated with a sudden cessation of circulation and no return without resuscitative interventions[1]. Resuscitation for cardiac arrest is performed in the emergency department (ED), except for hospitalized patients admitted to the hospital. Although mortality rates are high as a result of cardiac arrest, ED mortality rates are relatively low[2,3]. Therefore, follow-up of patients who present to the ED with or who have cardiac arrest in the ED is critical.

There are suggestions that various biomarkers (C-reactive protein, procalcitonin, lactate, etc.) can be used as prognostic indicators in intensive care units (ICU)[4]. However, the fact that some of these biomarkers are not available in every center and that the tests take a relatively longer time to complete is a limitation for EDs. Eosinopenia can be used as a prognostic marker in the exacerbation of chronic obstructive pulmonary disease, and eosinopenia can be used as a prognostic marker in areas such as acute infections, myocardial infarction, and sepsis[5-8]. Despite these findings, the pathophysiology related to inhibition of eosinophil release into the intravascular compartment has not been clearly defined. It is hypothesized that glucocorticoid discharge during acute stress blocks eosinophil release through multiple mechanisms, although the exact mechanisms warrant further elucidation[9].

Although some studies in the literature have indicated that eosinopenia can be used in prognosis in critically ill patients, a limited number of studies have indicated that it can be used as a prognostic marker in cardiac arrest[4,10,11]. The fact that some biomarkers used in cardiac arrest are not available in every center and the low specificity of the other markers obtained raises the possibility of using the eosinophil count, which is easily and rapidly obtained, as a biomarker. The present study aimed to investigate the relationship between eosinophil count -a simple and accessible marker that may serve as an indirect indicator of catecholamine discharge- and patient outcomes and prognosis in the context of cardiac arrest.

Materials and Methods

Study Design

This retrospective, observational, and descriptive study was designed. Patients who presented to the ED with cardiac arrest or experienced cardiac arrest within the ED between January 1, 2022, and January 1, 2024, were included in the study. The study complied with the Declaration of Helsinki, and approval was obtained from the Scientific and Ethical Committee for Medical Research at Ankara Bilkent City Hospital before starting the system search (approval number: TABED 2-24-411).

Data Collection

The study was conducted through a retrospective analysis of the data obtained from the hospital information system. Age, gender, white blood cell count, eosinophil count, lymphocyte count, monocyte count, neutrophil count, platelet count, albumin level, lactate dehydrogenase level,

blood pH, bicarbonate, base deficit, lactate, ED waiting time (in days), and ED outcome (hospitalization and mortality) were recorded. All data were collected using a standardized data collection form.

Inclusion Criteria

- Patients aged 18 years or older,

- Patients presenting to the ED due to out-of-hospital cardiac arrest,

- Patients experiencing cardiac arrest in the emergency department.

Exclusion Criteria

- Patients younger than 18 years,

- Cases without complete blood count or blood gas results,

- Patients with traumatic cardiac arrest,

- Patients on beta-blocker therapy,

- Patients administered epinephrine prior to hospital arrival,.

- Patients with a history of steroid use or immunodeficiency.

Statistical Analysis

Descriptive analyses were presented as frequency and percentage (%) for categorical variables and as mean, standard error, median, first quartile, and third quartile for numerical variables (n). The normality of numerical data distributions was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Non-normally distributed numerical data between two independent groups were analyzed using the Mann-Whitney U test. Correlation levels were assessed using Spearman's correlation analysis. A p-value <0.05 was considered statistically significant within a 95% confidence interval for all tests.

Results

The study was completed in 274 patients after applying the inclusion and exclusion criteria. The socio-demographic characteristics of the patients revealed a median age of 68 years [interquartile range (IQR): 52-80], with females comprising 39.4% (n=108) of the cohort. The hospital admission rate was 32.1% (n=88), the median length of hospital stay was 0 days (IQR: 0-1), and the ED mortality rate was 65.3% (n=179) (Table 1).

The blood parameters of the patients are summarized in Table 2. The median eosinophil count was 0.05 (IQR: 0.01-0.14). Additionally, the median pH of the patients was 7.14 (IQR: 6.97-7.34).

When the blood parameters of the patients were evaluated in relation to mortality, eosinophil, lymphocyte, platelet, and albumin levels were found to be significantly higher in patients without mortality (p<0.001, p=0.001, p=0.006, and p=0.008, respectively), while no significant differences were observed in other blood parameters (p>0.05) (Table 3).

Patients were divided into two groups based on a median age of 68 years and a mean length of hospital stay of 2 days to assess eosinophil levels. Eosinophil levels were significantly higher in patients aged ≤68 years, those without comorbidities, those not admitted to the hospital, those hospitalized for ≤2 days, and those who did not experience mortality (p<0.001) (Table 3).

The correlation analysis of patient age and blood parameters is presented in Table 4. A negative correlation was observed between eosinophil count and age, neutrophil count, and pH (p<0.001, p<0.001, and p=0.043, respectively), while a positive correlation was identified between eosinophil count and lymphocyte count, albumin level, and lactate level (p<0.001, p=0.025, and p=0.008, respectively) (Table 5).

In the multivariate logistic regression analysis, a 0.1-unit decrease in eosinophil count was associated with a 1.482-fold increase in mortality risk (p=0.006) (Table 6).

Table 1. Socio-demographic characteristics

	%	n
Age (years) Median (25-75%)	68 (52-80)	
Sex		
Female	39.4	108
Male	60.6	166
Hospitalization		
No	67.9	186
Yes	32.1	88
Length of stay in the emergency department (days) Median (25-75%)	0 (0-1)	
Mortality		
No	34.7	95
Yes	65.3	179
Total	100	274

(%): Frequency, 25-75%: 1st and 3rd quartiles

The relationship between eosinophil count and mortality was further evaluated using receiver operating characteristic curve analysis. The area under the curve (AUC) was determined to be 0.629, with a cut-off value of 0.055 (p<0.001) (Table 7).

Discussion

According to the results of our study, eosinophil counts were significantly lower in the mortality group, whereas no significant differences were observed in other biochemical parameters between patients who survived and those who did not in the ED. Biochemical parameters obtained from blood gas analysis, such as pH, lactate, base deficit, and bicarbonate, are generally associated with the response to perfusion deficiencies. Almost all patients who experience cardiac arrest have perfusion abnormalities. Although the mechanism underlying changes in eosinophil count is not fully explained, our study demonstrated that eosinophil levels were significantly lower in the mortality group among patients with cardiac arrest.

Şener et al.[3] conducted a multicenter study of out-of-hospital cardiac arrests and found that approximately 61% of the patients were male, with a mean age of 67 years. The

Table 2. Patients' blood parameters results

	Mean	Standard deviation	Median	25%	75%
White blood cell count (10^3/µL)	16.6	0.55	14.3	10.58	20.69
Eosinophils (10^3/µL)	0.13	0.02	0.05	0.01	0.14
Lymphocytes (10^3/µL)	3.76	0.37	2.89	1.29	5.14
Monocytes (10^3/µL)	0.95	0.05	0.80	0.51	1.13
Neutrophils (10^3/µL)	12.09	0.53	10.03	5.57	16.17
Platelets (10^3/µL)	215.3	8.56	192.5	116.0	282.0
Albumin (mg/dL)	24.28	1.29	24.4	16.4	32.2
LDH (mg/dL)	613.19	42.39	427	247.0	650.5
pH	7.13	0.02	7.14	6.97	7.34
Bicarbonate (mEq/L)	15.81	0.47	15.7	10.2	20.7
Base excess	-11.69	0.63	-11.3	-19.0	-4.4
Lactate (mmol/L)	12.81	4.28	7.69	3.16	12.74

(%): Frequency, 25-75%: 1st and 3rd quartile 25-75%: 1st and 3rd quartiles, LDH: Lactate dehydrogenase

Table 3. Evaluation of patients' blood parameters based on mortality

	Mortality (+)	Mortality (-)	
	Median (25-75%)	Median (25-75%)	p*
White blood cell count (103/µL)	13.9 (9.9-19.8)	15,6 (11-20.9)	0.181
Eosinophils (10^3/µL)	0.03 (0-0.1)	0,08 (0.01-0.21)	**<0.001**
Lymphocytes (10^3/µL)	2.44 (1.05-4.69)	3,84 (1.59-6.03)	**0.001**
Monocytes (10^3/µL)	0.77 (0.48-1.11)	0,84 (0.53-1.17)	0.278
Neutrophils (10^3/µL)	10.65 (5.55-15.64)	9,72 (6.27-17.84)	0.716
Platelets (10^3/µL)	183 (106-261)	238,5 (147-303)	**0.006**
Albumin (mg/dL)	22.1 (15.9-30.3)	28 (21.4-36.1)	**0.008**
LDH (mg/dL)	408 (275-658)	439 (270-619)	0.758
pH	7.13 (6.96-7.36)	7,15 (7.01-7.32)	0.843
Bicarbonate (mEq/L)	15.12 (9.6-20.6)	15,7 (10.8-20.9)	0.728
Base excess	-11.4 (-20,7- -4.6)	-11,15 (-17.30- -4.30)	0.726
Lactate (mmol/L)	7.62 (2.7-13.6)	7,75 (3.45-12.09)	0.909

(%): Frequency, 25-75%: 1st and 3rd quartiles, LDH: Lactate dehydrogenase 25-75%: 1st and 3rd quartiles

authors reported an ED mortality rate of 72%. In a Swedish cohort study investigating in-hospital cardiac arrests, the mean age was 67 years, approximately 65% of the patients were male, and 56% achieved return of spontaneous circulation (ROSC)[12]. In a study by Widestedt et al.[13] analyzing in-hospital cardiac arrests, 59% of patients were male, with a mean age of 73 years, and 55% achieved ROSC. It is well established that approximately 10% of in-hospital cardiac arrests occur in EDs[14], and outcomes are generally more favorable for witnessed in-hospital arrests. Given that these studies focused on witnessed cardiac arrests in EDs, their relatively lower mortality rates are unsurprising. A meta-analysis of approximately 4.5 million out-of-hospital cardiac arrests reported a ROSC rate of 29.7%, with the highest rate observed in Oceania (38.6%) and the lowest in Asia (22.1%)[15]. Additionally, the literature indicates a predominance of male patients, comprising approximately 60% of cases[2,16]. In another study examining in-hospital cardiac arrests, the mean age was 66 years, with a similar male predominance[17]. Compared with the literature, the age distribution and gender characteristics in our study were consistent. However, the mortality rate of ED was lower in our study than that reported in the literature. We attribute this difference to our study being conducted at one of the largest and most resource-rich centers in the region, which is supported by more experienced and skilled healthcare providers, which likely contributed to better outcomes.

To date, several biomarkers have been used to predict the prognosis of cardiac arrest and critically ill patients. Eosinophils primarily play a role in the pathogenesis of parasitic, allergic, and hematologic diseases. Studies have shown that eosinophil counts decrease during acute

Table 4. Evaluation of Socio-demographic characteristics based on eosinophil counts

	Eosinophil count			
	Median	**25%**	**75%**	**p***
Age				
Under the age of 68 years	0.08	0.02	0.16	**<0.001**
Age >68 years	0.02	0	0.10	
Sex				
Female	0.04	0	0.11	0.061
Male	0.06	0.01	0.16	
Comorbidites				
No	0.06	0.01	0.16	**<0.001**
Yes	0.01	0	0.03	
Number of waiting days				
2 days	0.06	0.01	0.16	**<0.001**
More than 2 days	0.01	0	0.04	
Mortality				
No	0.08	0.01	0.21	**<0.001**
Yes	0.03	0	0.10	

(%): Frequency, 25-75%: 1st and 3rd quartiles, *: Mann-Whitney U test

To date, several biomarkers have been used to predict the prognosis of cardiac arrest and critically ill patients. Eosinophils primarily play a role in the pathogenesis of parasitic, allergic, and hematologic diseases. Studies have shown that eosinophil counts decrease during acute

Table 5. Correlation analysis of age and blood parameters

		Age	Eosinophils	Lymphocytes	Monocytes	Neutrophils	Albumin	pH	Lactate
Age	r	1							
	p	.							
Eosinophils	r	-0.238	1						
	p	**<0.001**	.						
Lymphocytes	r	-0.227	0.608	1					
	p	**<0.001**	**<0.001**	.					
Monocytes	r	0.000	0.112	0.216	1				
	p	0.996	0.064	**<0.001**	.				
Neutrophils	r	0.135	-0.249	-0.287	0.468	1			
	p	**0.026**	**<0.001**	**<0.001**	**<0.001**	.			
Albumin	r	-0.126	0.157	0.173	0.100	-0.101	1		
	p	0.071	0.025	0.014	0.156	0.150	.		
pH	r	0.105	-0.130	-0.377	0.022	0.166	-0.144	1	
	p	0.100	**0.043**	**<0.001**	0.734	**0.009**	0.053	.	
Lactate	r	-0.100	0.168	0.494	0.006	-0.147	0.104	-0.693	1
	p	0.115	**0.008**	**<0.001**	0.931	**0.020**	0.160	**<0.001**	.

P-values were determined using Spearman's correlation analysis

Table 6. Multivariate logistic regression analysis of eosinophil count and mortality

	B	SH	p*	OR (CR)
Mortality (No)				
Yes	-0.730	0.264	**0.006**	1.482 (1.287-1.809)

B: Regression coefficient; SE: Standard error, OR: Odds ratio, CI: Confidence interval, Cox-Snell R square: 0.027; Nagelkerke R square: 0.038. *: Multivariate Logistic Regression Analysis

Table 7. ROC analysis between eosinophil count and mortality and area under the curve

Risk factor	AUC (95%)	Cut-off	p*	Sensitivity	Specifity	PPV (%)	NPV (%)
Eosinophil count	0.629 (0.558-0.699)	0.055	**<0.001**	0.620	0.347	65.3	62.0

AUC: Area under the curve, *: ROC analysis, PPV: Positive predictive value, NPV: Negative predictive value

inflammation and return to normal levels during recovery[7]. Consequently, eosinophil counts have been employed as prognostic markers in various conditions[4-8,10,11]. However, our review of the literature revealed a lack of studies that investigated eosinophil counts as prognostic markers, specifically for ED outcomes in cardiac arrest cases.

Abidi et al.[4] conducted a prospective study in the ICU to evaluate the prognostic value of eosinophil counts for mortality. Their results highlighted that eosinophil levels measured upon admission and during the first 7 days were significant predictors of mortality[4]. Conversely, Escobar-Valdivia et al.[11] reported that eosinophil levels at admission were not significant biomarkers for mortality but noted a marked increase in eosinophil counts among survivors over the first 7 days. Korkmaz et al.[10] identified eosinophil counts at admission as independent predictors of mortality in intensive care patients who achieved ROSC, alongside other parameters, such as platelet count, bicarbonate levels, and pH. The study design differs from that of previous studies by specifically investigating eosinophil counts as prognostic indicators of ED outcomes in cardiac arrest cases. While Korkmaz et al.[10] examined eosinophil counts as post-ROSC prognostic markers, our findings demonstrated a significant association between eosinophil levels and ED outcomes in cardiac arrest patients. In contrast, other commonly used parameters for critically ill patients did not show a significant association with ED outcomes.

The multivariate and receiver operating characteristic analyses in our study further underscore the significance of eosinopenia as a prognostic marker of mortality. Although Korkmaz et al.[10] reported higher AUC and sensitivity values, their study focused on post-cardiac arrest intensive care patients, whereas our study examined all cardiac arrest cases occurring within the ED.

It is well established that cardiac arrest results in tissue perfusion cessation, which is expected to affect all perfusion-related biomarkers. However, eosinophil release into the intravascular compartment occurs through cytokine-mediated mechanisms involving granulocyte-macrophage colony-stimulating factor, interleukin-3, interleukin-5, and complement 5a, among others[18]. This unique regulatory mechanism may explain the relative preservation of eosinophil levels compared with other ischemia-associated biomarkers. Based on our findings, eosinophil levels can be considered a significant biomarker for predicting ED mortality in patients with cardiac arrest.

Study Limitations

The retrospective study design and the limited data available for patients who experienced mortality imposed certain constraints on our findings. Additionally, our inability to assess the impact of other chronic diseases on prognosis limits the generalizability of our results. Nevertheless, our rigorous exclusion criteria and focus on the mechanism of cardiac arrest mitigate potential biases arising from these limitations.

Conclusion

Our study demonstrated that eosinophil levels are significant biomarkers of ED mortality in patients with cardiac arrest. The distinct mechanisms by which eosinophils respond to perfusion abnormalities following cardiac arrest suggest that these cells may serve as potential prognostic indicators in critically ill patients. Larger, multicenter, and prospective studies are needed to further elucidate the prognostic value of eosinophil levels and facilitate their integration into clinical practice.

Ethics

Ethics Committee Approval: The study complied with the Declaration of Helsinki, and approval was obtained from the Scientific and Ethical Committee for Medical Research at Ankara Bilkent City Hospital before starting the system search (approval number: TABED 2-24-411).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: N.İ.I., Design: N.İ.I., M.Ç., Data Collection or Processing: N.İ.I., M.Ç., Analysis or Interpretation: N.İ.I., M.Ç., Literature Search: N.İ.I., M.Ç., Writing: N.İ.I.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Non-invasive TensorTip MTX Hemoglobin Measurement Validation Study

Non-invaziv TensorTip MTX Hemoglobin Ölçümü Validasyon Çalışması

Eren Gökdağ[1], Fatma Sarı Doğan[2], Gülbin Aydoğdu Umaç[3], Özlem Güneysel[4]

[1]İstanbul Health and Technology University Faculty of Medicine, Department of Emergency Medicine, İstanbul, Turkey
[2]University of Health Sciences Turkey, İstanbul Fatih Sultan Mehmet Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[3]İzmir City Hospital, Clinic of Emergency Medicine, İzmir, Turkey
[4]Zincirlikuyu Medicana Hospital, Clinic of Emergency Medicine, İstanbul, Turkey

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Abstract

Objective: Point of care devices are fast and easy to use but their true potential is still waiting to come up. TensorTip MTX is a non-invasive medical device can measure various bioparameters, including hemoglobin. Purpose of this study is to measure the correlation between TensorTip MTX and our routine laboratuvary analysis of hemoglobin and to see that device is useable in emergency department settings for situations like gastroinstestinal bleeding and acute traumatic hemorrhages.

Methods: In the month after the ethical board approval, we conduct our study in 147 patients. Their hemoglobin levels were already measured while their course of emergency department visit. To gather accurate data of hemoglobin measurement of TensorTip MTX, device put on the ring finger of the patients and wait at least 45 seconds for measurement. All measurement documented and recorded by researcher. Measurements from blood samples and TensorTip MTX device are compared with intraclass correlation coefficient (ICC) and Pearson correlation coefficient.

Results: In 147 patients; 61.2% (n=90) were male, 38.8% (n=57) were female and ages are between 18 and 89. Mean age is 55.72±20.30 years; 23.1% (n=34) of them is under 35 years old, 76.9% (n=113) over 35 years. Statistically, the correlation between hemoglobin levels measured by the reference method and TensorTip was found to be 42.4%, which is statistically signficant (p=0.001; p<0.01) [ICC: 0.424; 95% confidence interval (CI): 0.281-0.548]. Correlation between hematocrit level measurements is 46.9% significantly compatible (p=0.001; p<0.01) (ICC: 0.429; 95% CI: 0.333-0.586).

Conclusion: Our study showed that correlation between reference measurement and TensorTip MTX device is fair (ICC: 0.424 for hemoglobin and 0.429 for hematocrit). Further studies needed to determine that this device is suitable or not to identify the need of blood transfusion and management of patients with acute hemorrhages in the emergency settings for now.

Keywords: Non-invasive, hemoglobin, emergency

Öz

Amaç: Hasta başı ölçüm yapabilen cihazların kullanımı kolay ve hızlıdır ancak tam potansiyelleri halen ortaya çıkmamıştır. TensorTip MTX non-invaziv olarak hemoglobin de dahil olmak üzere pek çok vital parametreyi ölçebilen bir cihazdır. Bu çalışmanın amacı TensorTip MTX adlı cihazın ölçtüğü hemoglobin değerlerini rutin laboratuvar analizleri ile karşılaştırarak, bu cihazın acil serviste gastrointestinal kanama ve akut travmatik kanama gibi durumlarda kullanılabilirliğini değerlendirmektir.

Address for Correspondence/Yazışma Adresi: Eren Gökdağ, İstanbul Health and Technology University Faculty of Medicine, Department of Emergency Medicine, İstanbul, Turkey
E-mail: erengokdag@gmail.com
ORCID ID: orcid.org/0000-0002-9653-8491

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Öz

Yöntem: Etik kurul onayı alındıktan sonraki ay içinde çalışmaya dahil edilen 147 hasta üzerinde ölçüm yapılmıştır. Acil servise başvuruları sorasındaki süreçte venöz kandan hemoglobin değerleri ölçülmüştür. TensorTip MTX cihazı ile doğru ölçüm yapabilmek için, 45 saniye boyunca hastaların yüzük parmağından ölçüm yapılmıştır. Toplanan her veri araştırmacı tarafından kaydedilmiştir. Kan örneklerinden ve TensorTip MTX ile ölçülen hemoglobin seviyeleri sınıf içi korelasyon katsayısı (ICC) ve Pearson korelasyon katsayısı ile karşılaştırılmıştır.

Bulgular: Toplamda 147 hastanın %61,2'si (n=90) erkek, %38,8'i (n=57) kadın ve yaş aralığı 18 ile 89 arasındaydı. Ortalama yaş 55,72±20,30; %23,1'i (n=34) 35 yaş altındaydı, %76,9'u (n=113) 35 yaşın üstündeydi. Referans değer ile TensorTip hemoglobin ölçümleri arasındaki %42,4 düzeyinde istatistiksel olarak anlamlı uyum saptandı (p=0,001; p<0,01) [ICC: 0,424; %95 güven aralığı (CI): 0,281-0,548]. Referans ile TensorTip hematokrit ölçümleri arasındaki %46,9 düzeyinde istatistiksel olarak anlamlı uyum gözlendi (p=0,001; p<0,01) (ICC: 0,429; %95 CI: 0,333-0,586).

Sonuç: Çalışmamız gösterdi ki referans ölçümler ile TensorTip MTX cihazı arasındaki korelasyon orta düzeydedir (hemoglobin için ICC: 0,424, hematokrit için ICC: 0,429). Eldeki verilerle şu an için kan transfüzyonu yapılmasına karar vermekte ve akut kanamalı hastaların acil servis yönetiminde bu cihazların kullanımının uygunluğunu değerlendirmek için daha fazla çalışmaya ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Non-invaziv, hemoglobin, acil servis

Introduction

Anemia can present with several symptoms that require emergency care. Anemia caused by trauma, gastrointestinal bleeding, and chronic diseases requires immediate and accurate diagnosis in the emergency department. Prompt treatment is essential. Anemia may not always be detectable by physical examination; therefore, evaluation of hemoglobin and hematocrit values is necessary. It is often impossible to determine these values at the patient's bedside. Delaying the diagnosis of anemia can affect patient outcomes. Devices that can continuously measure at the patient's bedside can assist clinicians in monitoring and guiding treatment for various diseases. Pulse oximeters, which are widely used in clinics today, are pioneering bedside measurement devices.

Devices that enable bedside measurements are easy to use, portable, fast, and inexpensive, making them highly suitable for emergency departments or disaster situations. The rapid results obtained with these devices allow clinicians to use their time more efficiently, thereby accelerating the diagnosis and treatment process.

Although there was initial skepticism when pulse oximeters were first used, years later, Severinghaus noted that there was a 90% decrease in anesthesia-related deaths coinciding with the introduction of pulse oximeters. Rapid and continuous measurement of vital parameters, such as pulse oximeters, is crucial for clinical decision-making[1].

Continuous monitoring of hemoglobin levels in a fast and non-invasive manner in the clinic can provide significant benefits in cases such as trauma and gastrointestinal bleeding. With these devices, excessive transfusions can be avoided in patients with active bleeding or those undergoing surgery.

In this study, we aimed to determine the correlation between the hemoglobin and hematocrit values measured using the TensorTip MTX device (CNoga Medical Ltd., OrAkiva, Israel) and the laboratory values obtained from venous blood to enable faster detection and treatment of anemia in the emergency department.

The history of the oximeter began in 1876 in the city of Tübingen, Germany, where Karl von Vierordt at the university measured the spectral changes in light passing through the tissue when the circulation was cut-off. However, these studies were ignored until Ludwig Nicolai developed a device in 1931 to measure the transmission of red light. In 1939, Karl Matthes introduced an ear oximeter that balances red and infrared light. Squire was the first to notice the change in transmission of red and infrared light in the hand when he cut-off circulation using a pressure cuff in 1940. The pulse oximeter can be considered a continuation of Squire's device and idea[1].

The development of oximeters gained momentum during World War II to protect fighter pilots from dangerous hypoxia. The term "oximeter" was coined in 1942 by Glen Millikan, who developed lightweight, red, and infrared ear oximeters[1].

Earl Wood and his student J. E. in 1949, Geraci combined Millikan's ear device with Squire's pressure cuff in 1949. Wood expanded and mathematically developed Squire's idea by measuring the ratio of red to infrared light intensity under pressure and reperfusion[1]. The pulse oximeter was invented in 1974 by Takuo Aoyagi at Nihon Kohden, but its

clinical use was intially limited due to accuracy concerns regarding oxygen saturation (SpO_2). Initial studies showed differences of >6% during normoxia and 10-20% during hypoxia between arterial blood oxygen saturation (SaO_2) and SpO_2, and familiar signal decreases and errors were observed during movement or low perfusion. Despite these limitations by the late 1980s, pulse oximetry has become a standard in healthcare. In 1989, Tremper and Barker reported that pulse oximetry was one of the most important developments in non-invasive monitoring because it continuously and rapidly evaluates oxygen saturation[1]. Years after these studies, the reliability and benefits of the oximeter have made its routine use essential for patient monitoring in clinics. Devices capable of non-invasive hemoglobin measurement appear to follow a similar path.

Currently, various devices are available for non-invasive hemoglobin measurement, including the NMB200 (OrSense Ltd., NesZiona, Israel), Radical-7, Rad-87, Pronto-7, and Pronto (Masimo Corp., Irvine, CA, USA). However, the practical use and reliability of these devices are limited. In a study conducted by Rice et al.[2] in 2013, it was concluded that the Radical-7 system was insufficient for making transfusion decisions. Similarly, in a study conducted by Lindner and Exadaktylos[3] in 2013, Masimo systems were used for continuous hemoglobin measurement; promising results were obtained when compared with HemoCue capillary measurements and routine laboratory analyses, suggesting that they could help improve patient management. The TensorTip MTX device in our study uses the color distribution of peripheral blood tissue to measure specific vital parameters and biomarkers.

TensorTip MTX Device Structure

a) Hardware: The device consists of a soft gel cover containing the upper part of the finger compartment and a base on which the sensor is protected by a lens located at the bottom. A monitor screen was placed behind the cover. The device contains 4 light emitting diode (LED)s in four different wavelengths, from visible light to infrared (625-950 nm). The image sensor detects light spectra between 350 and 1200 nm. A rechargeable battery can also be used as a power source[4].

b) Software: The device consists of a medical subsystem and microcontroller unit (MCU) containing the color image sensor, LEDs, and digital signal processor (DSP), and a control subsystem containing four buttons, a screen, and additional sensors. The DSP software is responsible for image acquisition, image processing, light control testing, and the collection of clinical parameter values. The MCU software is responsible for user interfaces, process management, data storage, and power management[4].

Indications for Use

The non-invasive TensorTip MTX, produced by Cnoga Medical, is a small, lightweight, portable device developed to measure and display blood pressure (systolic and diastolic), oxygen saturation (SpO_2), peripheral pulse rate, hemoglobin, hematocrit, mean arterial pressure, partial O_2 pressure (PO_2), partial CO_2 pressure (PCO_2), cardiac output, pH, red blood cell count, and some additional parameters. Measurements were performed using capillary finger tissue (excluding the thumb). The ring finger is recommended for this procedure. The device was designed for home use and can be used in blood donor clinics[4].

Materials and Methods

Our study was conducted prospectively in the Emergency Department of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital within one month of obtaining ethical approval on 14.01.2016 (decision number: 2016/514/75/7).

Patients aged >18 years who presented to our emergency department and agreed to participate in the study by signing an informed consent form were included in the study. Patients who did not provide consent, were under 18 years of age, were pregnant, or could not undergo measurements on their fingers due to physical limitations were not included in the study.

Two milliliters of venous blood was taken in an ethylenediaminetetraacetic acid vacutainer (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) from patients participating in the study for their current treatments, or tests were measured in the LH 780 analyzer (Beckman Colter, Inc., Brea, CA, USA) to determine reference values. For LH 780, the accuracy of device measurements with control samples was tested twice a day. The TensorTip MTX device was placed on the patients' ring fingers as specified in the user manual, and hemoglobin and hematocrit values were measured within 45s. The data obtained were recorded by the researcher, and no changes were made to the patients' treatments or interventions.

Statistical Analysis

The NCSS (Number Cruncher Statistical System) 2007 program was used for the statistical analysis. Descriptive

statistical methods (mean, standard deviation, median, frequency, ratio, and minimum and maximum) were used to evaluate the study data.

The Pearson correlation analysis was used to evaluate the relationship between hemoglobin levels and hematocrit measurements. The intraclass correlation coefficient (ICC) was used to evaluate the pairwise agreement between the LH 780 and TensorTip measurements. Statistical significance was evaluated at $p<0.01$ and $p<0.05$.

Results

The study was conducted with a total of 147 cases at the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital between 14.01.2016 and 14.02.2016. The demographic characteristics of the patients are presented in Table 1.

The hemoglobin and hematocrit measurements of the subjects using both the LH 780 and TensorTip MTX devices are shown in Table 2.

The relationship between LH 780 and tensor type hemoglobin/hematocrit is shown in Table 3, and the correlation is shown in Figure 1. A moderate agreement was observed between the LH 780 and TensorTip devices for both hemoglobin (HGB) and hematocrit (HCT) measurements, with ICC values of 0.424 for HGB and 0.469 for HCT, both of which were statistically significant (p=0.001). Gender-based analysis showed stronger agreement in male patients (ICC=0.460 for HGB and 0.484 for HCT, p=0.001) than in females, where agreement was weaker, particularly for HGB (ICC=0.301, p=0.011), although it was still significant for HCT (ICC=0.400, p=0.001). Age-based analysis revealed no significant agreement for HGB in patients under 35 years of age (ICC=0.233, p=0.089), but moderate agreement for HCT (ICC=0.371, p=0.014). For individuals aged 35 years and older, the agreement was stronger, with ICC values of 0.472 and 0.492 for HGB and HCT, respectively (p=0.001).

Table 1. Age and gender distribution

Age (year)	Min-max (Median)	18-89 (59)
	Mean ± standard deviation	55.72±20.30
Age groups; n (%)	<35 age	34 (23.1)
	≥35 age	113 (76.9)
Gender; n (%)	Male	90 (61.2)
	Female	57 (38.8)

Table 2. Distribution of hemoglobin and hematocrit measurements

LH 780 HGB	Min-max (median)	2.8-17.0 (10.1) g/dL
	Mean ± SD	10.44±3.17 g/dL
TensorTip MTX HGB	Min-max (median)	5.4-17.4 (12.2) g/dL
	Mean ± SD	11.84±2.56 g/dL
LH 780 HCT	Min-max (median)	10.5-52.3 (31.1)%
	Mean ± SD	32.16±9.47%
TensorTip MTX HCT	Min-max (median)	17.0-50.0 (34.0)%
	Mean ± SD	34.46±7.25%

HGB: Hemoglobin, HCT: Hematocrit, SD: Standard deviation

Discussion

Devices that can measure hemoglobin at the bedside are suitable for use in emergency rooms or in disaster situations because of their ease of use, portability, speed, and affordability. The rapid results obtained with these devices allow clinicians to use their time more efficiently, which in turn accelerates the diagnosis and treatment process, which is of critical importance.

The emergence of devices capable of non-invasive measurement of hemoglobin levels occurred after 2010. These devices are developed for continuous hemoglobin monitoring and have been used in many different clinical applications. Studies have evaluated various areas, from identifying blood donors to continuously measuring hemoglobin levels in patients during surgery, and different results have been obtained.

All studies were conducted using major devices, but the methods and objectives of the studies varied. In their 2011 study, Miller et al.[5] performed continuous hemoglobin monitoring with Radical-7 in 20 patients undergoing spinal surgery and compared these measurements with measurements taken with arterial blood gas and HemoCue. Their study showed that non-invasive hemoglobin measurement may not be accurate enough in some patients. As expected, more accurate results were obtained as the perfusion increased. They stated that, as technology advances, these devices could be used as standard monitors for patients at risk of bleeding.

In a study conducted in 2012 by Gayat et al.[6], where both the NMB-200 and Pronto-7 devices were used, they compared the measurements of the devices but stated that the clinical benefits of these devices are currently open to debate. In another study conducted in the same year, Kim et al.[7]. The reliability of the NBM-200 device with HemoCue and LH500

Table 3. LH 780 and TensorTip hemoglobin/hematocrit correlation

			LH 780/TensorTİP hemoglobin correlation	LH 780/Tensor Tip hemotocrit correlation
Total (n=147)		**ICC**	0.424	0.469
		p	**0.001****	**0.001****
Gender	**Male (n=90)**	**ICC**	0.460	0.484
		p	**0.001****	**0.001****
	Female (n=57)	**ICC**	0.301	0.400
		P	**0.011***	**0.001****
Age (year)	**<35 age (n=34)**	**ICC**	0.233	0.371
		p	**0.089**	**0.014***
	≥35 age (n=113)	**ICC**	0.472	0.492
		p	**0.001****	**0.001****

ICC: Intraclass correlation coefficient, **: p<0.01, *: p<0.05

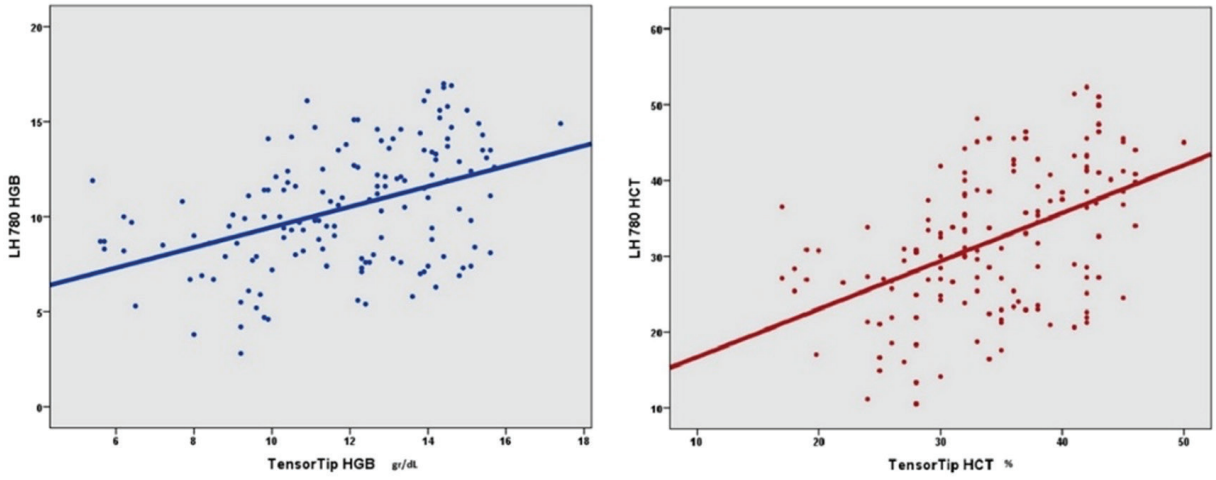

Figure 1. Correlation between LH 780 and TensorTip hemoglobin and hematocrit measurements

HGB: Hemoglobin, HCT: Hematocrit

to determine the suitability of blood donors was compared; however, they mentioned that the non-invasiveness of the device is advantageous for determining the suitability of a patient for blood donation.

Masimo Corp. devices have been used in several studies. In their study of patients in the intensive care unit in 2011, Frasca et al.[8] found that measurements made with Radical-7 were equivalent to the reference measurements. They stated that the use of this device for continuous hemogram monitoring would be beneficial in intensive care units. Rice et al.[2] evaluated the results of many studies using Radical-7 in their review in 2013 and stated that the main purpose of using these devices in operating room conditions is to determine the need for transfusion; however, with the available data, they stated that it does not currently guide clinicians when making transfusion decisions. In a study conducted by DeBarros et al.[9] in 2014 using the Pronto-7 device with the same infrastructure, the device showed a high correlation (r=0.77) with reference values, but in the same study, a weak correlation (r=0.251) was found in patients with anemia.

In an evaluation in which the studies were examined again, Lindner and Exadaktylos[3] concluded that the results of these studies are promising and could be useful in many healthcare settings in the future.

In 2015, Barker et al.[10] three studies that compared devices capable of non-invasive hemoglobin measurement were evaluated. As a result of the evaluation, the authors predicted that one day these devices would reach the accuracy of invasive hemoglobin measurements and could replace them. They also stated that continuous and real-time measurements of these devices could benefit clinicians in monitoring patients, reduce unnecessary transfusions, and save lives by identifying the need for transfusion at the right time, especially in patients with occult bleeding. They mentioned that in the future, these devices will be used as pulse oximeters are currently used[10].

These studies show that although both the NMB-200 and Masimo Corp. devices achieve promising results, they still need further development and time to be used safely in clinical applications. In the coming years, non-invasive hemoglobin monitoring will probably have an indispensable place in clinics for patient monitoring, just like the story of the same pulse oximeter. However, the use of these devices and the related studies are limited. Many clinicians are unaware of these devices or do not have access to them. The widespread use of these devices and the data obtained from these studies will undoubtedly accelerate the development of these devices. With the advancement of technology, we hope that these devices will be used safely for hemoglobin monitoring in the near future.

In 2018, Segman and Sheiman[11] reported that the TensorTip MTX device provided the best solution for the increasing need for rapid, painless monitoring devices in telemedicine, rural areas, community clinics, and homes. However, in 2023, Servaas et al.[12] found that the non-invasive measurements of Hb, Ht, pCO_2, and pO_2 made by the TensoTip MTX device were not as accurate and precise as conventional laboratory measurements, and its use was not recommended in perioperative surgical patients. Nevertheless, the device could still be useful in another setting.

Study Limitations

The many different diagnoses among the selected patients in our study can be considered a limitation in terms of standardization. Additionally, the perfusion index of the patients was not considered before the measurement. It can be anticipated that there may be deviations in the values measured by the TensorTip MTX device in patients with low perfusion index due to the hardware features of the device. In the comparison of hemograms of the sample group, statistically significant differences were not observed in the <35 years age group, which was the smallest group. This result can be attributed to the small sample size.

Conclusion

In our study, a weak correlation was found between the hemogram and hematocrit measurements performed using the reference device and TensorTip MTX (ICC: 0.424 for HGB, ICC: 0.469 for HCT). Further studies are required to evaluate the efficacy and potential benefits of using this device in emergency department settings.

Although many studies have reported the accuracy of these devices, more work and time are needed to fully exploit their potential, as in our study.

In the future, with the development of TensorTip MTX hardware and software, it may be possible to use it in the management of treatment and hemoglobin monitoring in patients with acute bleeding; however, in our study, the use of the TensorTip MTX device in ED conditions was not considered sufficient for clinical decision-making.

Ethics

Ethics Committee Approval: Our study was conducted prospectively in the Emergency Department of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital within one month after receiving the ethics committee approval on 14.01.2016 (decision number: 2016/514/75/7).

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

Footnotes

Authorship Contributions

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

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CASE REPORT / OLGU SUNUMU

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Rare Causes of Chronic Cough: Aberrant Right Subclavian Artery: A Case Report

Kronik Öksürüğün Nadir Nedenleri: Aberran Sağ Subklavian Arter: Olgu Sunumu

Hilal Aksoy, Kübra Karadağ, Emre Sarı, Hale Özer, İzzet Fidancı, Duygu Ayhan Başer

Hacettepe University Faculty of Medicine, Department of Family Medicine, Ankara, Turkey

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Abstract

Aberrant right subclavian artery (ARSA) is a congenital anomaly with a reported frequency of 0.5-1% and generally shows an asymptomatic clinical course. Being rare and usually asymptomatic complicates diagnosis and treatment. Although respiratory symptoms are rare in ARSA, chronic cough may be a symptom for diagnosis. Cases with chronic cough that persists despite treatment should be evaluated using posteroanterior chest X-ray and, if necessary, thorax computed tomography. In our article, we presented a case of a patient who applied to our family medicine outpatient clinic with a complaint of chronic cough and was diagnosed with ARSA.

Keywords: Subclavian artery, congenital abnormalities, cough, primary health care

Öz

Aberran sağ subklavian arter (ASSA), sıklığı %0,5-1 arasında bildirilen ve genellikle asemptomatik klinik seyir gösteren konjenital bir anomalidir. Nadir görülmesi ve genellikle asemptomatik olması tanı ve tedavi sürecini zorlaştırmaktadır. ASSA'da solunum semptomları nadir olmakla birlikte kronik öksürük, hastaların tanı almasını sağlayan semptomlardan biri olabilir. Tedaviye rağmen devam eden kronik öksürüğü olan olgular posteroanterior akciğer grafisi ve gerekiyorsa toraks bilgisayarlı tomografisi ile değerlendirilmelidir. Yazımızda aile hekimliği polikliniğimize kronik öksürük şikayetiyle başvuran ve ASSA tanısı alan bir olguyu sunduk.

Anahtar Kelimeler: Subklavyen arter, konjenital anormallikler, öksürük, birinci basamak sağlık hizmeti

Introduction

A cough that lasts longer than eight weeks in adults is called chronic cough[1]. Chronic cough is a symptom that can be seen in most chronic lung diseases and some non-pulmonary diseases.

While the most common causes include upper airway cough syndrome, asthma, and gastroesophageal reflux, there are many causes of upper respiratory tract origin (such as allergic rhinitis, chronic sinusitis), lower respiratory tract origin [such as asthma, chronic obstructive pulmonary disease (COPD), foreign body], and non-respiratory origin [such as gastroesophageal reflux disease (GERD), drug use, and cardiovascular diseases][2]. Aberrant right subclavian artery (ARSA) is clinically the most common embryological abnormality of the aortic arch. This abnormality was first

Address for Correspondence/Yazışma Adresi: Assoc. Prof. Hilal Aksoy, Hacettepe University Faculty of Medicine, Department of Family Medicine, Ankara, Turkey
E-mail: hilal.aksoy35@gmail.com
ORCID ID: orcid.org/0000-0002-3330-9317

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described by Hunauld in 1735. Bayford described dysphagia lusoria as a clinical entity in a woman with a long history of dysphagia and ARSA at autopsy in 1787. Therefore, it is also known as Bayford-Autenrieth dysphagia[3]. ARSA can cause dysphagia, dyspnea, or chronic cough due to compressive mechanisms with adjacent organs[4].

In our article, we present a case of a patient who presented to our family medicine outpatient clinic and was diagnosed with ARSA.

Case Report

A 59-year-old male patient was admitted to our family medicine outpatient clinic with a cough complaint. The patient said that he works in the food industry. However, he is not working now. The patient had a 60 pack/year smoking history. He had no history of alcohol or substance abuse. The cough has been going on since childhood. The patient's cough was accompanied by colorless sputum. He added that he had shortness of breath on exertion for the past few years. When his additional complaints were questioned, he said that he had a reflux complaint that had been going on since childhood.

The patient had a history of diabetes, hypertension, and chronic obstructive pulmonary disease.

The diagnosis of hypertension was present for approximately 6 years, and the diagnosis of diabetes was present for 10 years.

The diagnosis of COPD was made 3 years ago by the physician to whom he applied due to cough.

The patient had a stent because of myocardial infarction 12 years ago.

Drugs used by the patient: Metformin 2x1000 mg/day, lercanidipine hydrochloride, salbutamol 100 mcg inhaler (if needed), salmeterol fluticasone propionate inhaler, montelukast 1x10 mg/day, and desloratidine 1x5 mg/day.

However, the drugs he used did not improve the patient's cough and shortness of breath complaints. The patient's family history was unremarkable.

The patient had previously applied to the chest diseases outpatient clinic because of cough.

When the patient's past examinations were examined, it was seen that the thorax computed tomography (CT) imaging requested by the chest diseases outpatient clinic on 09.07.2019 was reported as the right subclavian artery with aberrant origin.

However, he stated that he was not told anything about the patient's condition, but only that he had a problem with his lungs. In addition, he did not apply to the cardiovascular surgery outpatient clinic for this reason.

Physical examination: Fever: 36.5 °C, pulse 100/min, blood pressure 114/70 mmHg.

Lung sounds are natural. Both lungs accompany breathing. There were no al rhonchus.

Posteroanterior chest X-ray (Image 1) and laboratory tests [complete blood count, kidney function tests, liver function tests, glycosylated hemoglobin (HbA1c), thyroid stimulating hormone (TSH), vitamin B12, ferritin] were requested from the patient.

Laboratory Findings

Glucose -toughness: 150 mg/dL, creatinine: 0.86 mg/dL, blood urea nitrogen: 9.7 mg/dL, estimated glomerular filtration rate: >60 mL/min/1.73 m^2, alanine aminotransferase: 18 U/L, aspartate aminotransferase: 15 U/L, alkaline phosphatase: 124 U/L, gammaglutamyl transferase: 56 U/L, lactate dehydrogenase: 136 U/L, ferritin: 29.8 µg/L, vitamin B12: 84 ng/L, hemoglobin: 14.8 gr/dL, leukocytes: 9.0x10^3/µL, platelets: 300x10^3/µL, sedimentation: 20 mm/h, TSH: 0.517 uIU/mL, free T4: 11.51 pmol/L, HbA1c: 6.9%, C-reactive protein: 3.67 mg/dL.

An enlargement of the distal esophagus was observed on chest X-ray. Lung fields were normal.

When the current condition of the patient was evaluated, the patient was informed that the cough and reflux complaints that did not go away for a long time were connected to the right subclavian artery with aberrant origin. The patient was referred to the cardiovascular surgery outpatient clinic. Surgery was recommended to the patient by cardiovascular surgery.

However, the patient did not accept the operation because of the high risk of mortality in the operation.

Discussion

Typically, three major arteries arise from the aortic arch: The brachiocephalic trunk (divided into the right common carotid artery and right subclavian artery), the left common carotid artery, and the left subclavian artery (Figure 1). However,

in the abnormality of ARSA, the brachiocephalic trunk is absent and four major arteries arise from the aortic arch; right common carotid artery, left common carotid artery, and left subclavian artery. The last one is the most distal left-sided origin, the right subclavian artery, also called arteria lusoria (Figure 2). This artery goes to the right arm, crosses the midline of the body, and usually runs behind the esophagus[3]. ARSA may follow a retroesophageal course, a course between the trachea and esophagus, or a pretracheal pathway. The atypical vessel may compress the trachea and esophagus while forming an incomplete vascular ring around them[5].

The frequency of ARSA is 0.5-1% and varies all over the world, but in Europe, it occurs in 0.11% (England), 0.16% (Greece), 0.3% (France), or 0.36% (Netherlands) of the population, depending on the country detected[6]. Studies have also been conducted on other continents, with Asia accounting for 0.1-0.2% of cases (China and Japan, respectively); North America, 0.5% of cases (United States); and Australia and Oceania, 0.8% of cases (New Zealand)[7]. In a study, it was determined that women have two times more isolated ARSA than men[5].

Although 60-80% of patients can remain asymptomatic throughout their lives, in a study by Michał et al.,[3] who presented a systematic review of 141 reports, the most frequently reported symptoms due to compression of adjacent structures by the ARSA were dysphagia (71.2%), dyspnea (18.7%), retrosternal pain (17.0%), cough (7.6%), and weight loss[7]. In the patient who applied to our clinic, we observed the complaint of cough that has continued since childhood. In this retrospective study, the mean age of all patients evaluated was 49.9 years; however, statistically significant differences were found between the mean ages of male and female subjects (54.0 years and 44.9 years, respectively), and the patient who applied to our clinic was 59 years old[3]. In a publication on the subject in our country, in which 8 cases with ARSA anomaly are presented, 2 cases applied to our clinic with the complaint of chronic cough that has lasted for several years. Similar to our patient, various tests were performed on both patients, and antacid treatments were started with the diagnosis of GERD. Inhaled corticosteroid and long-acting bronchodilator treatment was administered to one of the two patients diagnosed with asthma. However, two patients did not benefit from these treatments. No pathology was detected in the physical examination and chest X-ray, and thoracic CT was performed to detect the etiology of chronic cough and ARSA was detected[8]. In the patient who visited our clinic, the physical examination was

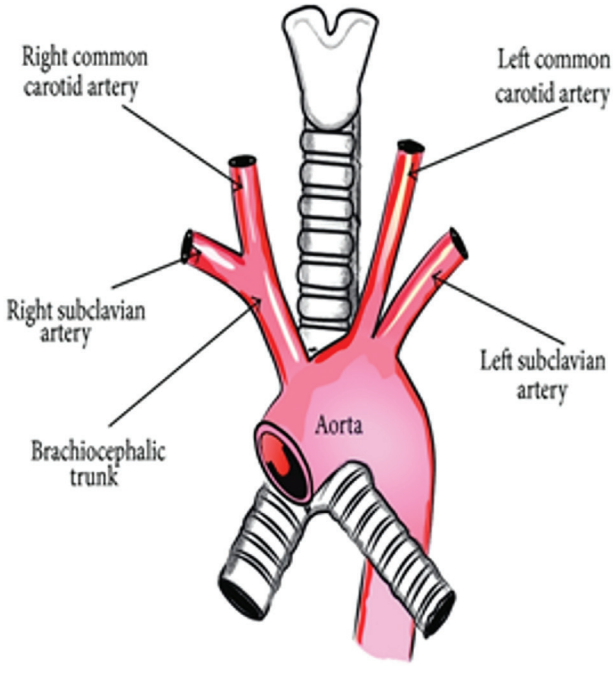

Figure 1. Normal RC

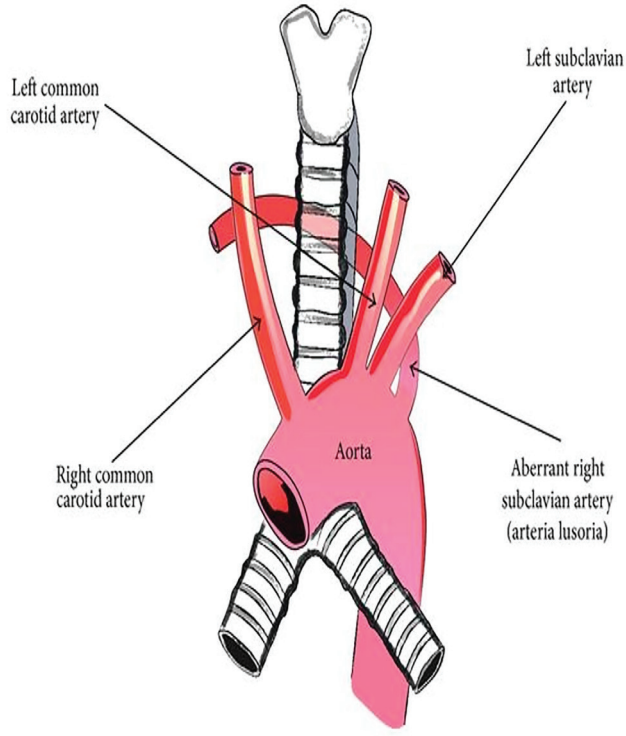

Figure 2. Abnormal RCA

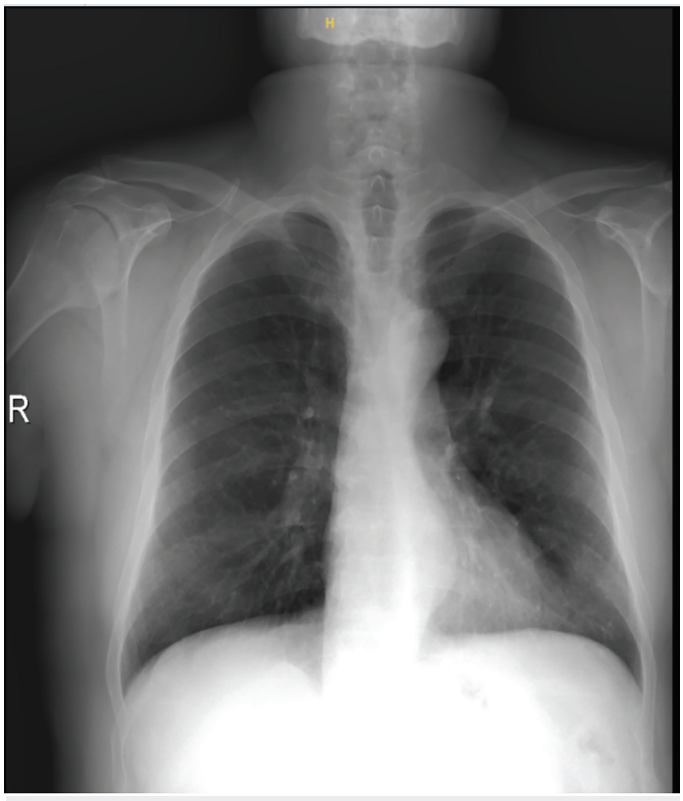

Image 1. PA chest radiograph

normal, and the distal esophagus was enlarged on the chest X-ray.

Chest radiographs should be obtained to rule out most infectious, inflammatory, and malignant thoracic conditions, unless a possible cause is identified[9]. In our patient, we first requested chest radiography to rule out these causes.

Family medicine is a department with six core competencies. One of these core competencies is authentic problem-solving skills. Within the framework of this competence, the family physician can make a unique clinical decision according to the prevalence and incidence of diseases in the society to which he/she is affiliated. It has a unique clinical decision-making feature because serious diseases are encountered less frequently in the primary care setting compared with the hospital environment, and the prevalence and incidence of diseases differ according to the hospital environment. In addition, with a comprehensive approach, which is another core competence, disease management is performed with limited information in the period when the disease is not differentiated yet[10].As in our case, the important thing in the first approach to a patient with ARSA, which is an incompletely differentiated and rarer disease in primary care compared with the hospital, is to examine the patient regardless of the complaint, to evaluate the patient in detail, and to quickly refer the patient to the necessary departments to prevent complications. This situation was probably overlooked in this study because evaluations were made only in their own fields by other clinics in the hospital environment. Thanks to the comprehensive evaluation in the family medicine outpatient clinic, the cause of persistent cough was revealed. Thus, unnecessary hospital admissions and drug use have been eliminated.

Conclusion

Structural anomalies, such as ARSA, should be considered in the differential diagnosis of patients presenting with chronic and persistent cough, and further investigation should be performed.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Concept: H.A., İ.F., Data Collection or Processing: K.K., E.S., H.Ö., Analysis or Interpretation: H.A., İ.F., D.A.B., Literature Search: K.K., E.S., H.Ö., Writing: H.A.

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

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

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ERRATUM

DOI: 10.4274/terh.galenos.2023.01643

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Published in The Anatolian Journal of General Medical Research's volume 33, issue 1 of 2023 "Hasbay E, Sancı M. Incidental Gynecological Findings in Lumbar Spine MRI: The Prevalence of These Findings and Their Importance For Patient Management. J Tepecik Educ Res Hosp 2023;33(1):94-9 doi: 10.4274/terh.galenos.2023.01643" there were inadvertently errors in the figure images. The errors and corrections are as follows:

Published on page 97;

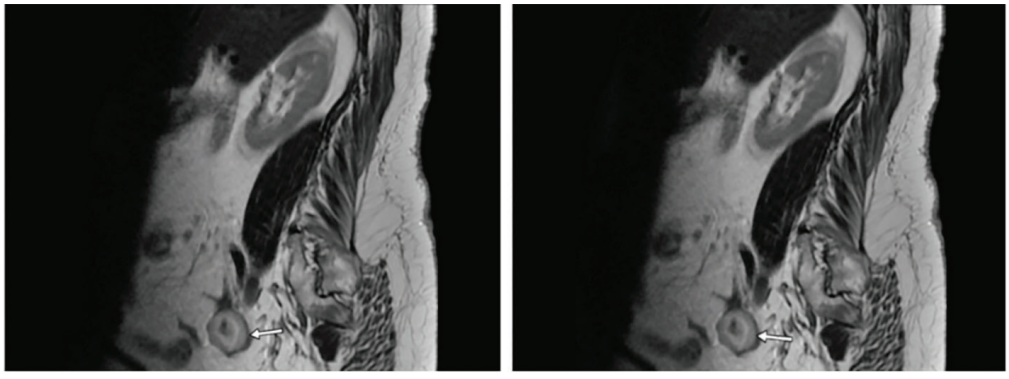

Figure 1.

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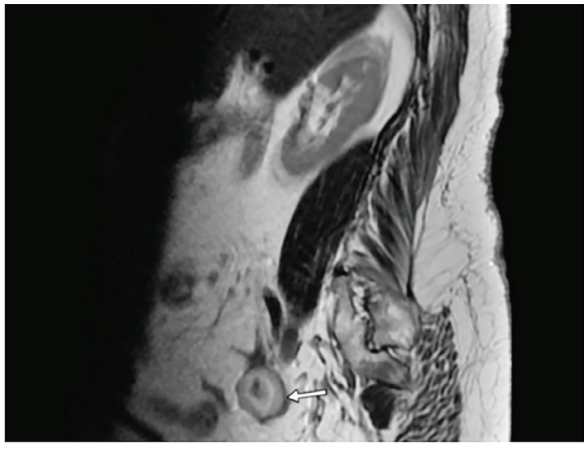

Figure 1.

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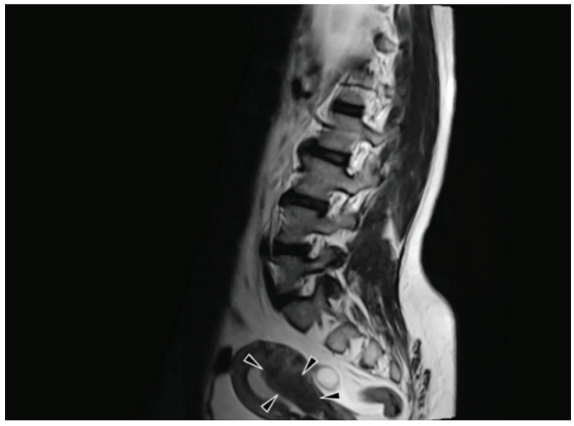

Figure 3.

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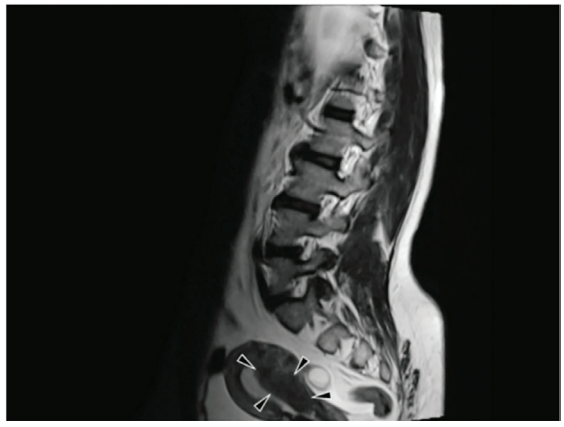

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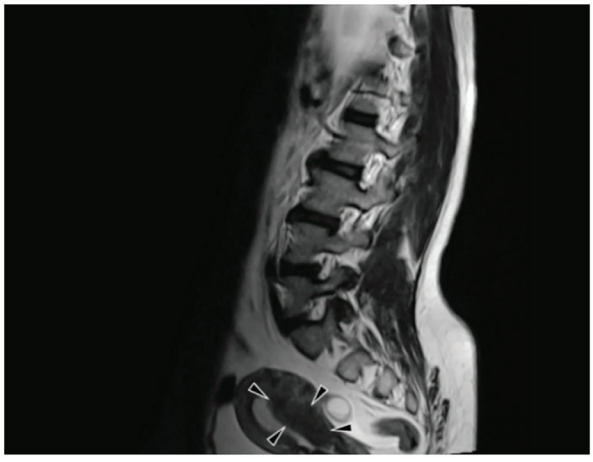

Figure 5.

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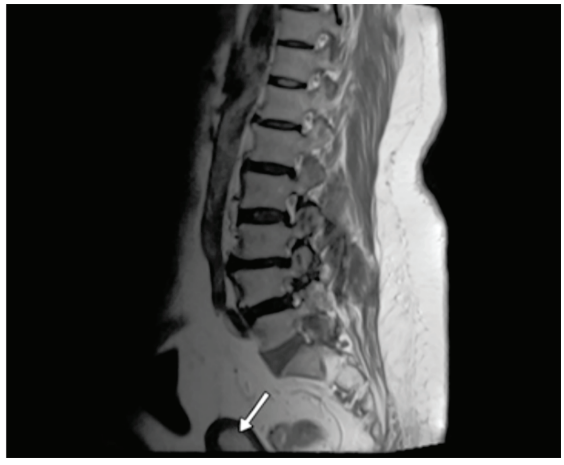

Figure 5.

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Ali Tekin
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Ayşegül Elvan Tüz
Başak Göl Serin
Batuhan Ergani
Bengü Tatar
Berk Göktepe
Burak Bayraktar
Cem Yücel
Cengiz Yılmaz
Deniz İlhan Topçu
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Emel Yıldız
Emre Ayıntap
Ensar Durmuş
Eren Arslan Davulcu
Erhan Ateş
Fatma Ünver
Figen Tokuçoğlu
Füsun Saygılı
Giray Kolcu
Gökhan Akbulut
Gül Caner Mercan
Gülali Aktaş
Gülden Diniz
Gürcan Türkyılmaz
Halil Alışkan
Haluk Mergen
Hasan Çağrı Yıldırım
Hatice Solmaz
Hüseyin Can
Ilgın Yıldırım
İlkay Akbulut
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