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AIMS AND SCOPE

Namık Kemal Medical Journal is the scientific official journal of Namık Kemal University School of Medicine. The journal is electronically publised tri-annualy (April, August, December). Articles accepted until one month before the month of publication are added to the relevant issue. The three issues form a volume.

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Address: Molla Gürani Mah. Kaçamak Sk. No: 21, 34093 Fındıkzade-İstanbul-Turkey

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Title Page: On the title page; The title of the article in Turkish and English, the names and duties (academic titles) of the authors, the institution from which it was sent, if any, the institution supporting the study should be written. If the article has been communicated before in any congress, its place and date should be specified. In addition, the name, surname, addresses, telephone and fax numbers, e-mail address of the author to be corresponded and Ethics Committee Approval must be clearly written on this page.

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Ozkan G, Ulusoy S, Guvercin B, Menteşe A, Karahan SC, Yavuz A. A new player in chronic kidney disease mineral and bone disorder: tenascin-C. Int J Artif Organs. 2015;38:481-7.

For books:

West JB: Respiratory Physiology (2nd ed). Baltimore: Williams and Wilkins, 1974; 72-5.

For chapters taken from the book:

Sagawa K: Analysis of the CNS ischemic feed back regulation of the circulation. In: Reeve EB, Guyton AC (eds), Physical Basis of Circulation Transport. Philadelphia: WB Saunders, 1967; 129-139.

For online articles:

Abood S: Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Webcast]. 2002 Jun [citation 12.08.2002]; 102 (6). Access: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm PMID: 12394070.

For the citations from the thesis:

Kulu A. Evaluation of Quality of Life After Surgical Interventions Applied to Patients with Bladder Tumors, Trakya University, Institute of Health Sciences, Department of Nursing. Master Thesis. 2010; Edirne.

For congress papers:

Felek S, Kılıç SS, Akbulut A, Yıldız M. A case of phylgellosis with visual hallucinations. XXVI. Turkish Microbiology Congress Abstract Book, 22-27 September 2000, Antalya, Mars Printing House, 1994, p.53-6.

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If the reviewers deem necessary, they approve the publication after the changes requested in the article are made by the authors.

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Studies coming to the journal management system pass the pre-evaluation of the editor and the editorial board within 2 weeks at the latest;

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After the study is sent to the reviewer, it states to the editorial board whether it can be evaluated within 2 weeks at the latest. Rewievers who do not specify are removed from the study and a new reviewer assignment is made.

The reviewer opinions for the studies guide the editorial board to make the final decision. The final decision always belongs to the editorial board.

The reviewers can give opinions for the study in 4 ways;

- Publication is acceptable
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A 3rd or 4th reviewer can be appointed to work in line with the reviewer 's opinions, and this process works in the same way as the time specified above.

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Ethic

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CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

Correspondence Address:

Erdoğan Selçuk ŞEBER, MD

Namık Kemal University Faculty of Medicine, Division of Medical Oncology, Tekirdağ, Turkey

Phone: +90 282 250 50 00 E-mail: nkmj@nku.edu.tr

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REVIEW

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Rotator Cuff Syndrome and Current Approaches in Treatment

Rotator Manşet Sendromu ve Tedavide Güncel Yaklaşımlar

Demet TERZİ[1], Ali ZEYBEK[2]

[1]Tekirdağ Namık Kemal University Institute of Health Sciences, Department of Anatomy, Tekirdağ, Turkey
[2]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Anatomy, Tekirdağ, Turkey

ABSTRACT

Rotator cuff syndrome is a common health problem causing serious physical, psychological and material losses. Since the treatment process is long and difficult and the treatment costs are increasing, a lot of research is done especially on risk factors. Both intrinsic and extrinsic factors are among the underlying causes. Although some of these factors could be changed, most of them are unchangeable factors due to anatomical structure and functions. Therefore, it is very important to determine these factors in advance and apply preventive treatments. In this study, it is reviewed to give information about the studies on rotator cuff syndrome risk factors and treatment approaches.

Keywords: Rotator cuff, acromion, subacromial space

ÖZ

Rotator manşet sendromu önemli fiziksel, psikolojik sorunlara ve ekonomik kayıplara sebebiyet veren, sık karşılaşılan bir sağlık problemidir. Tedavi sürecinin uzun ve zorlu olması ve tedavi maliyetlerinin de gittikçe artması nedeniyle özellikle risk faktörleri konusunda oldukça fazla araştırma yapılmaktadır. Altında yatan sebepler içinde hem intrinsik hem ekstrinsik faktörler bulunmaktadır. Bu faktörlerden bir kısmı değiştirilebilir olsa da çoğu anatomik yapı ve fonksiyonlara bağlı değiştirilemeyen faktörlerdir. Bu nedenle bu faktörlerin önceden belirlenmesi ve koruyucu tedavilerin uygulanması oldukça önemlidir. Bu çalışma rotator manşet sendromu risk faktörleri ve tedavi yaklaşımları üzerine yapılan çalışmalar hakkında bilgi vermek amacıyla derlenmiştir.

Anahtar Kelimeler: Rotator manşet, akromion, subakromial boşluk

INTRODUCTION

Rotator cuff syndrome is one of the most common causes of shoulder pain and loss of functionality, which can develop due to many intrinsic or extrinsic reasons and mostly occur due to compression of the musculus (m.) subscapularis, m. supraspinatus, m. infraspinatus and m. teres minor, which are commonly referred as rotator cuff muscles, in the subacromial space or due to their tearing for some reason[1,2].

Patients with rotator cuff tears have a reduction in their quality of life equivalent to those with congestive heart failure, diabetes, myocardial infarction or depression[3]. Therefore, determining potential risk factors for the development of rotator cuff pathologies has been chosen as a subject for more studies in recent years.

In addition to reduced quality of life, treatment costs are increasing rapidly for patients with rotator cuff pathology. Pre-operative and outpatient costs can range from $ 5,500 to 11,000, excluding rotator cuff repair, follow-up, care, and post-operative physical therapy[4]. In addition to affecting health, loss of function and psychological problems, it causes significant economic losses. Therefore, rotator cuff syndrome is a clinically important picture that should be emphasized. In this study, it was aimed to examine rotator cuff syndrome and its treatment approaches.

Rotator Cuff Biomechanics

When the rotator cuff muscles, which are independent from each other, reach the end point, they mix with the fibers of the adjacent tendons and adhere to the humerus. It is very

Address for Correspondence: Ali ZEYBEK MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Anatomy, Tekirdağ, Turkey
E-mail: azeybek@nku.edu.tr **ORCID ID:** orcid.org/0000-0002-9773-2739
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difficult to distinguish the effects that occur during their individual contractions, since they also affect the end point of the neighboring muscle during contraction[5].

There is a concept of force couple in rotator cuff biomechanics. The force couples are expressed as two opposite forces that help to rotate an object. In the studies, in terms of the shoulder joint, it has been reported that rotator cuff muscles form force couple with m. deltoideus in the coronal plane and m. subscapularis forms force couples with m. infraspinatus and m. teres minor in the transverse plane[6,7].

For a smooth shoulder abduction in the coronal plane, contraction with balanced force is needed between m. deltoideus and m. infraspinatus, m. teres minor and m. subscapularis. In cases where m. deltoideus is much stronger, m. latissimus dorsi and m. pectoralis major muscles also help the rotator cuff muscles. In the transverse plane, in order to keep the head of humerus in cavitas glenoidalis, the balance between m. infraspinatus and m. teres minor and m. subscapularis is important. Anterior or posterior dislocations can be seen in the force differences that may occur in the transverse plane[7].

Another situation that is anatomically and biomechanically important is the cable-crescent model formed by m. supraspinatus, m. infraspinatus and m. teres minor muscles at the points of attachment to the tuberculum majus. Before these muscles become tendon at the end points, they stretch in the form of a cable and then become thinner by forming a crescent-shaped structure and cover the tuberculum majus. The cable acts as a suspension, reducing the load while transferring it to the avascular thin crescent-shaped structure. This is a protective mechanism to prevent tear[8].

Formation Mechanism and Causes of Rotator Cuff Tears

Rotator cuff muscles, which we use frequently during daily activities, are exposed to many factors including traction, pressure, contusion, inflammation, and more importantly, degenerative changes due to aging because of some reasons such as subacromial loading and regional changes in blood supply. These factors change the normal biological structures of tissues by causing tendinitis over time. M. supraspinatus tendon is affected from this situation most commonly[9]. As a result of the changes occurring in the subacromial bursa that is affected secondarily, the subacromial region becomes narrower. With shoulder elevation movements, the tendons of the rotator cuff muscles are squeezed between the humerus head and the coracoacromial arch. If this situation continues, the destructive effects on the tendons may increase and cause tears[10].

Although there are many different views on the mechanism of rotator cuff tears, intrinsic and extrinsic factors are emphasized. Intrinsic causes include disorders in the vascular supply of the tendon, smoking, cholesterol, aging, and micro-structural collagen fiber abnormalities.

The vascular supply of the rotator cuff muscles begins to decrease especially at the age of forty years and over, the amount of fibrocartilage decreases in the tendon adhesion areas, vascularity deteriorates, cellular losses increase, tendon disintegration and separation in Sharpey fibers at the tendon-bone junction are seen. With the decrease in mobility at an advanced age, the possibility of tears in the tendons increases even with less force[11].

Lohr and Uhthoff[12] reported that rotator cuff blood supply was better on the bursal side, but less on the humeral side. However, Kim et al.[13] argued in their study that bursal sided rotator cuff tears were the most common partial tears, and they explained the reason as exposure of the anteromedial part of rotator cuff tendon and the acromion to repetitive trauma. Although it has been suggested that insufficient blood supply causes more degeneration in tendons and the formation of tears, the role of hypovascularity in tear formation is still not fully elucidated[12,13]. According to the results of a study conducted in 2010, it was observed that low density lipoprotein value was high in people with rotator cuff tears, while high density lipoprotein value remained at low levels, and it was reported that cholesterol level could be considered a risk factor in the formation of tears[14].

Extrinsic causes are factors related to the bone or soft tissue around the rotator cuff, which may cause tendon tears by narrowing the subacromial space. The subacromial space is the space between the coracoacromial arch, the anterior part of the acromion and the head of humerus. In publications on the subacromial space and rotator cuff, it is stated that conditions such as the acromion type, the shape of the anterior acromial spur, the acromial index, the features related to the coracoacromial ligament, the angle of the coracoid inclination, and the angle of the coracoacromial arch are associated with the formation of tears.

When we consider the acromion type, it is known that there are 4 types of acromion: flat type, curved type, hooked type and convex type. In the meta-analysis conducted by Morelli et al.[15], they stated that people with type 3 acromion had three times more rotator cuff tears than those with type 1 or type 2 acromion. According to another study, type 3 acromion causes subacromial compression by significantly narrowing the subacromial distance compared to type 1 or type 4 acromion[16]. However, another study does not support these findings and states that having a type 3 acromion does not pose a higher risk of rotator cuff tear than other acromion types[13]. The acromion inclination angle is found by measuring the angle between the lines formed by the intersection of the line passing through

the front and rear ends of the acromion at the highest point of the curvature. The angle of the acromion anterior inclination is much more effective than the acromion type in the formation of rotator cuff tears. Increasing this angle increases the angle of the coracoacromial arch and narrows the subacromial space[17].

Another aspect that supports the tear formation is the length of the anterior acromial spur. The anterior acromial spurs are grouped as small if they are less than 5 mm, medium if they are between 5-10 mm, and large if they are more than 10 mm according to their lengths. Considering their shapes, they can be grouped as straight and curved[18]. The larger the spur, the greater the likelihood of acromial inclination angle and the formation of rotator cuff tear. Spur size and acromial inclination angle increase with age[17].

Balke et al.[19] defined the acromial index as the ratio of the glenoid-acromion lateral edge distance to the glenoid-humeral lateral edge distance. Individuals with a large acromial index are more likely to have rotator cuff tears. This may be because of higher orientation of the head of humerus in the acromion and coracoacromial arch due to the force vector of the m. deltoideus. In individuals with larger acromial indices, the muscles may not function optimally and the humeral head may not be held in a centered position. This may reduce the subacromial area and cause compression of the rotator cuff tendons passing through it[15].

Coracoid inclination angle is the angle formed between the line drawn from the proc. coracoideus anterior cortex and the line drawn tangent to the glenoid surface from front to back. The reduction of this angle increases the angle of the coracoacromial arch, narrows the subacromial space and creates a risk for tear formation[20].

Treatment Approaches to Rotator Cuff Syndrome

Although written sources about the rotator cuff concept have been available since the 18th century, current approaches started to emerge mostly in the 20th century. The first rotator cuff repair in the world was performed by Coddman in 1909[21]. In 1944, Moseley classified tears and described the surgical treatment in detail. In 1972, Neer first described it using the term "impingement syndrome" and attributed the tear formation to mechanical compression under the coracoacromial arch at a rate of 95%. With anterior acromioplasty, he expanded the exit area of m. supraspinatus, smoothed the bone surface under the acromion and successfully repaired by reducing friction.

The treatment process for rotator cuff tears can be planned in two different ways. The decision of choosing a treatment is affected by some conditions such as the shape, location, and depth of the tear, the age range of the individual, his/her background and the level of recovery he/she expects to reach after treatment. Surgery is preferred for individuals with high activity levels or athletes, especially in younger ages and people with acute injuries. And, conservative treatment is preferred in a chronic picture[22].

Conservative Treatment

Neer states that the basis of conservative treatment is resting during exacerbation of symptoms, and a correct exercise program when symptoms disappear. The first aim is to reduce subacromial inflammation, prepare the ground for healing and restore functionality.

Exercise practices should aim at strengthening m. infraspinatus, m. teres minor and m. subscapularis, which are the muscles depressing the humeral head without increasing the dominance of m. deltoideus, and m. trapezius, m. levator scapulae and m. serratus anterior, which causes elevation of scapula[23].

Conservative treatment principles generally consist of protection, medical treatment, physiotherapy and rehabilitation stages. During the protection phase, it is recommended to rest by avoiding overhead activities that will cause compression in the rotator cuff muscles and subacromial bursa. If the pain is disturbing in daily life activities and is aggravated by movement, a shoulder brace may be preferred. The rest period should be kept as short as possible.

In medical treatment, non-steroidal anti-inflammatory drugs and steroid injection into the subacromial area reduce pain and allow exercise. However, it is not recommended after 2-3 repetitions because of damage to the tendon[24]. In recent years, it has been observed that platelet rich plasma (PRP) applications have a rapid and significant healing effect in rotator cuff cases, especially at the early stage. The plasma injected in PRP application is enriched in platelets and contains various proteins that support cell growth. In studies comparing corticosteroid injection with PRP application, it was found that PRP application in the early period was more effective, but the two methods were not superior to each other in the long term[25].

Physiotherapy and rehabilitation include training the individual about conditions and movement components that increase symptoms, physical modalities to reduce or heal symptoms, strengthening and stretching exercises for muscle strength deficiencies due to pain or weakness or muscle shortness, joint mobilization techniques, functionality or work- occupational activities. The goal is to reach normal range of motion, reduce pain and restore normal scapula-thoracic rhythm[26]. Due to the high probability of contracture formation, the sooner a personalized exercise program is applied, the faster the targeted and most effective results are achieved.

Neuromuscular control is also affected in the presence of unbalances between the forces related to the shoulder joint and related stability problems. Proprioceptive training plays an important role in the conservative treatment of this condition. Proprioceptive training ensures that the shoulder is protected and guided by appropriate muscle activity by sending returns to the central nervous system by the musculoskeletal system. Proprioceptive rehabilitation is at the forefront in increasing cognitive awareness related to position, movement and stabilization[27].

Strengthening the stabilizer muscles of the shoulder is a very effective method in treatment. Exercises known as closed kinetic chain exercises include movements that increase normal functions of the muscles that work systematically in a certain order. In a study conducted in 2007, the effects of open and closed kinetic chain exercises on problems with the rotator cuff were investigated and compared. In the study, it was stated that in exercises to be performed to strengthen the muscles stabilizing the shoulder circumference and scapula, it was more effective to continue with open kinetic chain exercises after the work done using closed kinetic chain exercises first, but the two types of exercises did not have superiority to each other[28].

Surgical Treatment

Individuals with acute traumatic rotator cuff tears require surgical repair in the first weeks after injury. In order to achieve more positive results in surgical application in full-thickness tears, it should be early stage and there should be no degeneration in the tissues[28]. While the success of surgery is higher in those who have not had previous injuries and at a young age, the prognosis is worse in elderly individuals and in long-term tears accompanied by loss of strength. Surgery should be considered as the primary treatment in young individuals with a rotator cuff tear or tuberculum majus displaced avulsion fracture following an acute trauma found radiological imaging methods, and as the secondary treatment in individuals who have received conservative treatment for six weeks or more but have not achieved results[29]. Nowadays, the success rate of rotator cuff surgeries is increasing with the trial of new devices and repair methods. For treatment, an arthroscopic-assisted mini-open repair has been observed instead of an open surgical method, and a change towards a full arthroscopic method has recently been observed due to the advantage of its being less invasive[30]. While open surgery is preferred as the gold standard in massive tears, the arthroscopic method is more preferred in small and medium-sized tears[31]. Although there are advantages such as preservation of m.deltoideus insertion, less soft tissue incision, less pain and rapid return to functionality in the full arthroscopic method, it is also stated that bone-tendon fixation with full arthroscopic technique is weaker, it takes a long time to learn the technique, and it should be performed by experienced surgeons in case of possible complications[21,32].

Within arthroscopic methods, there are differences between full arthroscopy and mini open repair. While deciding between the two, if the patient's shoulder range of motion and muscle strength are better, but there is a surgical indication with pain, the full arthroscopic method is preferred. However, the mini open method is preferred in cases where the loss of strength is more important and the tear needs to be repaired more securely.

Bone or suture anchors are implants that are used in tendon therapy and connect tissue and bone, and they are frequently used in rotator cuff surgery. When determining the technique to be preferred in surgery, it is important that the bone tissue has the strength to hold the anchors. Conditions such as the long duration of the tear, the advanced age of the patient, and some metabolic diseases can affect the bone density and prevent anchor placement. In such cases, repair may be required through open surgery using bone tunnels. However, there is information showing that anchors have more holding abilities than bone tunnels[33].

Moosmayer et al.[34] evaluated the effect of physiotherapy with open or arthroscopic-assisted mini-open method in patients with symptomatic, full-thickness tears not exceeding 3 cm, as a result of a 10-year follow-up, and they stated that surgical treatment had more permanent and significant effects in functionality and pain scores compared to physiotherapy treatment in the long term. They reported that they have effects. Although physiotherapy alone provides improvement in the short term, it is thought that it causes complaints again in the long term. Therefore, physiotherapy is thought to be a more effective treatment after a successful surgery.

CONCLUSION

Rotator cuff syndrome is one of the most common causes of shoulder pain, which can cause significant losses in quality of life, requires a multi-component and demanding treatment program, and is in the third place in terms of incidence after back and neck pain. Conservative or surgical treatment processes are both difficult and expensive. For this reason, it is especially important to determine risk factors, to take precautions and to apply preventive treatment methods. Although there are studies showing that there are various risk factors, rotator cuff syndrome risks are an important issue that needs to be studied and clarified in order to explain the situations that are still not agreed or proven.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.T., A.Z., Analysis or Interpretation: D.T., A.Z., Literature Search: D.T., A.Z., Writing: D.T., A.Z.

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REVIEW

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What Has Changed in the Diagnosis and Treatment of Colorectal Cancer?

Geçmişe Göre Günümüzde, Kolorektal Kanseri Tanısı, Önlenmesi ve Tedavisinde Ne Değişti?

Fatin Rüştü POLAT[1], Yasin DURAN[1], İhsan GÜNDÜZ[2]

[1]Tekirdağ Namık Kemal University Faculty of Medicine, Department of General Surgery, Tekirdağ, Turkey
[2]Tekirdağ State Hospital, Clinic of Surgical Gastroenterology, Tekirdağ, Turkey

ABSTRACT

Colorectal cancer (CRC); is the most common malignancy in the gastrointestinal tract. CRC is associated with significant morbidity and mortality in the worldwide. CRC is the third most common cancer-related death in both men and women globally. The overall 5-year survival rate is 50% last decade (1975). Currently this rate is over 75-80%. In this case; early diagnosis, prevention and effective treatment methods were the main factors. Nowadays, Genetic Analysis test, Fecal Occult Blood testing and colonoscopy methods are used in screening. Genetic Analysis testing is the best method for the lead time. In addition, polypectomy was performed in precarious patients and was classified as preventable disease.

Keywords: Colorectum, cancer, early diagnosis, lead time, prevention of cancer

ÖZ

Kolorektal kanser (KRK), dünya çapında önemli morbidite ve mortalitesi olan bir hastalıktır. KRK, dünya genelinde hem erkeklerde hem de kadınlarda kansere bağlı üçüncü en yaygın ölüm nedenidir. Geçmiş yıllarda (1975) beş yıllık hayatta kalma %50 iken günümüzde bu oran %75-80'dir. Bu duruma; erken evrede tanı, prevansiyon ve etkili tedavi yöntemleri temel etken olmuştur. Günümüzde taramada Genetik Analiz testi, Gaita Gizli Kan testi ve kolonoskopi yöntemleri kullanılmaktadır. Lead time en iyi yöntem Genetik Analiz testidir. Ayrıca günümüzde riskli olgulara polipektomi yapılarak önlenebilir bir hastalık kategorisine alınmıştır.

Anahtar Kelimeler: Kolorektum, kanser, erken tanı, lead time, kanserde korunma

INTRODUCTION

Cancer is a non-lethal genetic disorder in the cell, more simply defined as uncontrolled cell proliferation. The activation of oncogenes, inactivation of tumor suppressor genes, impairment of DNA repair ability, inability to perform apoptosis, reprogramming the cell energy metabolism that has been recently studied, and the protection of the tumor cell from the immune system constitute the basic physiopathology[1-3]. One or more physiopathological conditions is caused by hereditary, physical, chemical and/or biological (bacteria, virus) factors[1,2].

Colon is the approximately 150 cm part of the gastrointestinal system between the ileocecal valve and the rectosigmoid corner[3,4]. It consists of the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon[3,4]. The rectum is considered as a separate organ today. The nutrition of the colon is provided by the branches originating from the two main arteries of the aorta. The upper mesenteric artery is the midgut artery, it supplies the right half of the colon (a. ileocolic, right colic and middle colic artery). The lower mesenteric artery is the artery of the hindgut, it supplies the left half of the colon (left colic artery, sigmoid artery). These two networks are connected to each other by the arc of riolan. The venous anatomy of the colon is generally similar to the anatomy of the artery. The right colon drains into the portal system through the vena mesenterica superior, the left colon

Address for Correspondence: Fatin Rüştü POLAT MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of General Surgery, Tekirdağ, Turkey
E-mail: frpolat@nku.edu.tr **ORCID ID:** orcid.org/0000-0001-6628-2109
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through the vena mesenterica inferior. Likewise, the drainage of the lymphatic system takes place along the arteries and occurs in four main stages; epicolic, intermediate, paracolic and prespinal (paraaortic) lymph node[3].

Its Epidemiology and Distribution

It is the most common malignancy in the gastrointestinal tract[4]. In terms of mortality, it is among the third most common causes of death after lung and prostate cancer. It shows geographic differences throughout the world and its incidence in undeveloped regions is 6.5/7.7 per 100,000 women/men and around 50.9/60.8 in developed regions[5]. The distribution of colon tumors is often seen in the sigmoid colon and then in the cecum[6,7].

Etiology

Its etiology is not known for certain, but genetic and environmental factors that affect the colon mucosa play a role[6]. In terms of genetic factors, colon cancer is more common in those with familial polyposis or familial adenoma (>90%). It is also known that colon cancer develops without the presence of polyposis [hereditary non-polyposis colorectal cancer (CRC) or Lynch syndrome 1, 2][8]. It has been suggested that one or more of the *adenomatous polyposis coli (APC), p53,* delaeted in *colorectal cancer (DCC), MCC* and *K-ras* genes play a role[5,8]. When examined in terms of diet, it is known that excessive amounts of meat and fat ingested change the colon flora and establish a ground for cancer[3-8]. Studies suggesting an increased incidence of colon cancer after cholecystectomy or ureterosigmoidostomy have been conducted, but their accuracy has not been proven[9]. It is known that there is a relationship between inflammatory bowel diseases and colon cancer[10]. In addition, age is an important risk factor for colon cancers[11]. It increases significantly after the age of 50 years[11]. Correct determination of risk factors is important for effective results of community monitoring and screening programs.

Genetics in CRC screening: Somatic mutation in adenoma plays a role in the majority of colon cancers and hereditary (germline) mutation in some colon cancers. When mutations occur in more than one gene, it results in cancer. It takes a long time, such as 10-15 years, for a mutation in a normal cell to result in cancer (Sojourn time). Therefore, lead time can be kept much shorter with screening programs. *K-, N-, H-ras* (especially *K-ras*) activation of proto-oncogenes, APC which are tumor suppressor genes, *DCC* and *p53* mutation, *mutation of mismatch repair (MMR)* genes, especially the *hMSH2* gene among the *MMRs* play a major role in the cancerization of colon cells (50%). In addition, *hMSH3*, 6 and *hPMS2* and 3, of the *MMR* genes, also play a role. Multiple gene mutations are detected by DNA analysis.

Fecal Occult Blood test (FOBT) in CRC screening: With the formation of cancer tissue or adenomas reaching a certain size, bleeding occurs into the lumen. In this case, the diagnosis of cancer becomes meaningful after a certain period of time to occur cancer[2,3].

Colonoscopy in CRC screening: In 20% of cases, it may give false negative results due to insufficient bowel cleansing or inability to visualize the mass.

Lead time in early diagnosis: Genetic analysis test > FOBT > colonoscopy.

Pathogenesis: The majority of these tumors originate from the glandular epithelium and are adenocarcinoma[8]. It originates in the mucosal epithelium and spreads in the lumen and/or intramural region[8].

Classification in CRC: Two types of cancer are macroscopically seen in the colon[6]. a) "Cauliflower" is often seen on the right side of the colon, b) "ring-structure" is seen on the left side of the colon.

Clinical Symptoms and Signs

It is an inapparent disease and gives late symptoms. Initially, it starts with anemia and lower gastrointestinal system bleeding, then progresses as a change in bowel habit (diarrhea, constipation, change in stool characteristics). Non-specific symptoms such as abdominal pain, nausea, tenesmus, and weight loss are observed. Obstruction signs are observed in patients with more advanced stage. In other words, the clinical picture varies depending on the location, macroscopic structure, stage and complications of the tumor[3]. Tumors located on the right side of the colon present with anemia, and those located on the left side with signs of obstruction. In developed countries, while 87.9% of the cases were admitted to the emergency service with obstruction in the 1925s (stage 4)[6], today there has been a decrease in admission to the emergency services with obstruction (76-80%). This has been achieved with the effective use of diagnostic methods and conscious society[7]. However, a significant decrease is not observed in undeveloped societies.

Screening and Diagnosis

Cancer screenings are for detecting diseases at an early stage, thus reducing the incidence of advanced stage patients and reducing mortality[11]. The delay in diagnosis of colon cancer is still an important problem in today's underdeveloped societies. The biggest factor in this situation is the education and social status of the patients. Tests for colon cancer screening include FOBT, genetic analysis test and structural examination [colonoscopy, capsule endoscopy, double contrast barium graphy, computed tomographic (CT) colonography or

virtual colonoscopy] tests. The screening program should be performed at the age of 50 years in normal individuals, and around the age of 40 years in individuals at risk (family history or inflammatory bowel disease).

Prevention and Treatment

Cancer prevention is considered as primary and secondary[11]. Primary prevention is based on the elimination of biological, genetic and environmental factors, and secondary prevention is based on the early diagnosis and treatment of premalignant lesions. Chemoprevention; there are studies showing that regular aspirin or non-steroidal anti-inflammatory drugs use reduces colon cancers by 30-50%[12].

The main treatment method in patients diagnosed with cancer is surgery. First of all, it is evaluated whether the tumor is local, regional or systemic (positron emission tomography-CT, CT).

For patients with local tumors: With conventional, laparoscopic or robotic methods, the resection of the primary tumor with lymphatics that it drains (R_0, radical resection) and anastomosis for intestinal continuity are applied. Today, endoscopic muco-submucosal resection method is used in developed countries for early stage tumors.

For cases with regional tumors: If the tumor has invaded neighboring organs, the tumor mass is resected en-bloc after neoadjuvant chemoradiotherapy.

For patients with systemic disease: If the tumor cannot be removed surgically, a proximal diverting ostomy is performed and palliative treatment is applied[1-3,11]. If metastasis is present, in these cases, metastasis often occurs in the liver (70-80%)[1]. Partial hepatectomy, metastasectomy, radiofrequency ablation, embolization, transarterial chemoembolization, transarterial radioembolization, and chemotherapy are applied.

Prognosis: In developed countries, while the five-year survival rate was 50% in the past years (1975), this rate is 75-80% today[13]. In developing countries, patients are still diagnosed at a late stage, which decreases the patient's five-year survival rate[12,13].

CONCLUSION

CRC is the third most common cause of death from cancer worldwide[14]. Although colon cancer is more common in developed countries compared to underdeveloped countries[15,16], today, it can be prevented by screening programs in developed countries. While cure can be achieved with early diagnosis and effective surgery, unfortunately it is still an important health problem in undeveloped countries. In undeveloped countries, the disease can be brought to a preventable level with the education of individuals and effective implementation of screening programs.

Ethics

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.R.P., Concept: F.R.P., Design: F.R.P., Data Collection or Processing: F.R.P., Analysis or Interpretation: F.R.P., Y.D., İ.G., Literature Search: F.R.P., Y.D., İ.G., Writing: F.R.P.

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The Effect of Seasonal Temperature Changes on Gestational Diabetes Mellitus Prevalence

Mevsimsel Sıcaklık Değişikliklerinin Gestasyonel Diabetes Mellitus Prevalansı Üzerine Etkisi

Sedat AKGÖL[1], Bekir KAHVECİ[2], Mehmet OBUT[2], Özge KAHRAMANOĞLU[2], İlker KAHRAMANOĞLU[2], Cengiz ANDAN[2], Mehmet Şükrü BUDAK[3]

[1]*University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey*
[2]*Çukurova University Faculty of Medicine, Department of Obstetrics and Gynecology, Adana, Turkey*
[3]*Dicle University Faculty of Medicine, Department of Obstetrics and Gynecology, Diyarbakır, Turkey*

ABSTRACT

Aim: The aim of this study was to investigate the effect of seasonal changes in ambient temperature on the prevalence of gestational diabetes mellitus (GDM).

Materials and Methods: A retrospective evaluation was performed on the results of patients at 24-28 weeks gestation who underwent a GDM screening at the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital in Diyarbakır, which is a city that is warm and dry in summer and cold and rainy in winter, between January 2017 and December 2017. Pregnant women were divided into four groups according to the season they were screened for GDM. A comparison was made in terms of the prevalence of GDM among pregnant women screened for diagnosis of GDM in different seasons.

Results: Of 3,618 pregnant women screened, 7.5% (n=272) were diagnosed with GDM. The seasonal distribution of the GDM cases was 6.4% (n=54) in winter, 8.3% (n=78) in spring, 9.2% (n=84) in summer, and 6.1% (n=56) in autumn. A significant difference was observed in terms of seasonal distribution ($p<0.05$).

Conclusion: The results of this study have demonstrated that seasonal temperature changes have a significant effect on GDM prevalence. However, further studies are needed to better demonstrate this relationship.

Keywords: Gestational diabetes mellitus, seasonal temperature, prevalence

ÖZ

Amaç: Bu çalışmada, ortam sıcaklığındaki mevsimsel değişikliklerin gestasyonel diabetes mellitus (GDM) prevalansı üzerine etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Ocak 2017-Aralık 2017 tarihleri arasında, yazları sıcak ve kurak, kışın soğuk ve yağışlı bir şehir olan Diyarbakır'da Sağlık Bilimleri Üniversitesi, Gazi Yaşargil Eğitim ve Araştırma Hastanesi'nde GDM taraması yapılan 24.-28. haftalarında olan gebelerin sonuçları retrospektif olarak değerlendirildi. GDM taraması yapılan hamile kadınlar mevsimlere göre dört gruba ayrıldı. Farklı mevsimlerde GDM tanısı konulan gebelerde GDM prevalansı açısından bir karşılaştırma yapıldı.

Bulgular: Taranan 3.618 gebe arasından %7,5'i (n=272) GDM tanısı aldı. GDM olgularının mevsimsel dağılımı kışın %6,4 (n=54), ilkbaharda %8,3 (n=78), yaz aylarında %9,2 (n=84) ve sonbaharda %6,1 (n=56) olmuştur. Mevsimsel dağılım açısından anlamlı bir fark gözlendi ($p<0,05$).

Sonuç: Bu çalışmanın sonuçları, mevsimsel sıcaklık değişimlerinin GDM prevalansı üzerinde anlamlı bir etkisi olduğunu göstermiştir. Ancak, bu ilişkiyi daha iyi göstermek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, mevsimsel sıcaklık, prevalans

Address for Correspondence: Bekir KAHVECİ MD, Çukurova University Faculty of Medicine, Department of Obstetrics and Gynecology, Adana, Turkey
Phone: +90 506 418 66 28 **E-mail:** drbekirkahveci@hotmail.com **ORCID ID:** orcid.org/0000-0002-8729-1669
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INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of varying degrees beginning during pregnancy or first diagnosed during pregnancy[1,2]. It affects approximately 7% of pregnancies, and varies widely between 2.4% and 21%[3-5]. Despite a clinically asymptomatic evolution, there is an increased risk of type 2 diabetes (T2D) mellitus in the long term as well as increased pregnancy and delivery complications[6-8].

Despite the increase in GDM frequency over the years, the pathophysiology is still not fully understood[9,10]. Nevertheless, risk factors such as maternal overweight and obesity, low maternal birth weight, race, increased maternal age, family history of T2D, fetal death history, a macrosomic infant history, high saturated fat consumption, high ambient temperature and low D vitamin level have been revealed[11-13].

Brown fat tissue has an irreplaceable role in assisting the body to adapt to cold weather by producing adenosine triphosphate via the cellular mitochondrial system[14,15]. Based on evidence from animal and human studies, it has been shown that brown fat tissue is effective in body thermogenesis by altering the whole body's metabolism[16,17]. In some animal experiments, the reduction of the thermostat temperature from 24 °C to 19 °C resulted in a 30-40% increase of activity in brown fat and an increase in insulin sensitivity[17-19]. GDM is a metabolic disease, characterized by changes in the glucose and lipid metabolism as a result of insulin resistance[20]. Environmental temperature, which has been shown to cause changes in insulin resistance, has increased globally over the past century and this has also raised concerns related to human health[17,21,22]. From a review of literature, it can be seen that very few studies have examined the seasonal variation of the prevalence of GDM, due to seasonal changes in ambient temperature during the year and the effects of these changes on insulin sensitivity[10,23-26].

The aim of this study was to investigate the effect of seasonal temperature variations on GDM prevalence.

MATERIALS AND METHODS

The study were approved by the Ankara Numune Training and Research Hospital of Local Ethics Committee (protocol number: E-19-2669, date: 18.04.2019). The study included patients with one-step GDM result in a 75 g oral glucose tolerance test (OGTT) or a two-step GDM result in a 100 g OGTT following a 50 g oral glucose challenge test (OGCT) applied to pregnant women at 24-28 weeks, as defined by the last menstrual period and the first trimester obstetric ultrasound in the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital in Diyarbakır, between January 1, 2017 and December 31, 2017. This city has a climate that is warm and dry in summer and cold and rainy in winter. The GDM screening results of these pregnant women were evaluated retrospectively through the hospital automation system. GDM diagnosis was established when one or more of the three blood sugar values (fasting: ≥92 mg/dL, 1st hour ≥180 mg/dL and 2nd hour ≥153 mg/dL) screened in a single step scan with 75 g OGTT were high[27]. In the two-step scan, 24-28-week pregnant women with a 1-hour blood sugar level lower than 140 mg/dL following a 50 g OGCT were considered normal, while pregnant women with a 1-hour blood sugar level between 140 and 199 mg/dL were subjected to a 100 g OGTT. For the patients subjected to 100 g OGTT, according to the Carpenter-Coustan Conversion criteria, GDM diagnosis was established when two or more of the four blood sugar values (Fasting blood glucose: 95 mg/dL, 1st hour 180 mg/dL, 2nd hour 155 mg/dL and 3rd hour 140 mg/dL) were high after 100 g OGTT and 1st hour blood sugar value after a 50 OGCT was 200 mg/dL or more[27,28]. The seasons were determined by calendar (winter; December-January-February, spring; March-April-May, summer; June-July-August, autumn; September-October-November). The seasonal temperature values of the province of Diyarbakır in 2017 were obtained from the link of the temperature analysis given on the website of the General Directorate of Meteorology of the Ministry of Forestry and Water Affairs of the Republic of Turkey[29]. A comparison was made in terms of mean age, mean gravida and GDM prevalence among pregnant women screened for the diagnosis of GDM in the different seasons.

Statistical Analysis

Descriptive statistics (mean, standard deviation, frequency, percentage) were used to define continuous variables. The chi-square test was used to examine the relationship between categorical variables. A value of $p<0.05$ was accepted as statistically significant. The analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org).

RESULTS

The study included 3,618 pregnant women subjected to GDM screening at 24-28 gestational weeks between January 1, 2017 and December 31, 2017. Of these, 1358 (37.53%) were scanned with 75 g OGTT, as a single-step scan, and 2,262 (62.52%) were scanned using a two-step scan with 50 g OGCT, followed by 100 g OGTT. As a result of the two screening models, the overall rate of cases diagnosed as GDM was 7.5% (n=272), with the following distribution: 6.4% (n=54) in winter, 8.3% (n=78) in spring, 9.2% (n=84) in summer and 6.1% (n=56) in autumn. The seasonal average temperatures were 3.6 °C in winter, 13.5 °C in spring, 27.9 °C in summer and 17.4 °C in autumn (Figure 1). The mean age, gravida, average temperatures and GDM

prevalence according to seasons are shown in Table 1. There were no statistically significant differences in the mean age and mean gravida of pregnant women who were screened for the diagnosis of GDM in different seasons (Table 1). There was a statistically significant difference in the prevalence of GDM in pregnant women who were screened for the diagnosis of GDM in different seasons (Table 1).

DISCUSSION

The results of this study showed that the prevalence of GDM was seasonally different and this difference was found to be statistically significant. While Booth et al.[22], Chiefari et al.[23] and Vasileiou et al.[26] found results similar to those of the current study, Moses et al.[24] reported no significant difference in the seasonal distribution of GDM prevalence. However, the study of Moses et al.[24] was conducted in Wollongong, Australia, where the average temperature difference between the warmest and coldest seasons is 9.3 °C[30]. In the current study, this difference is 24.3 °C. In the study by Booth et al.[22], which showed a significant difference between seasonal frequencies of GDM prevalence similar to the current study, the average temperature difference between the coldest and warmest seasons was 24.13 °C, whereas it was 13.5 °C in the study of Chiefari et al.[23]. It can therefore be suggested that the result found by Moses et al.[24] for seasonal variation in the prevalence of GDM is different from the results of the current study and previous research[22,23] because of this low temperature difference between the coldest and warmest seasons[22,23,29].

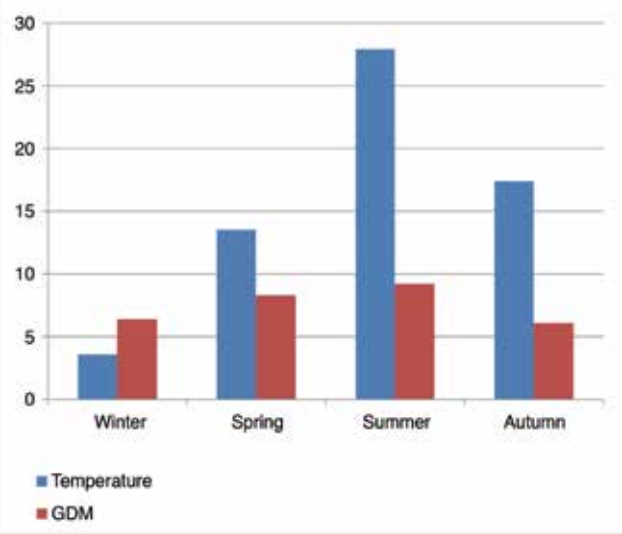

Figure 1. The distribution of seasonal temperature averages and gestational diabetes mellitus rates

GDM: Gestational diabetes mellitus

In the current study, the GDM prevalence increased with increasing temperature and reached the highest value in the summer. Other recent studies have also reported that the GDM prevalence increases with temperature and the highest prevalence is seen in summer[22-24]. Booth et al.[22] reported the rate of increase in GDM frequency as a 6-9% increase in the risk of the development of GDM for every 10 °C temperature increase. It has been shown in several studies that a decrease in temperature is accompanied by an increase in brown fat tissue activity for thermoregulation and this is associated with an increase in insulin sensitivity[17]. In the current study, the increase in GDM prevalence with the increase in temperature may be related to increased insulin resistance as a result of reduced insulin sensitivity, related to the increase in temperature, which is known to have an effect on insulin sensitivity and because insulin resistance has an important place in GDM pathophysiology[20].

Study Limitations

The main limitation of this study is its retrospective design. However, the large sample can be considered to render the results of value.

CONCLUSION

Seasonal temperature changes were found to have a statistically significant effect on GDM prevalence. Therefore, women at increased risk of GDM should consider the effect of seasonal temperature increases on the prevalence of GDM when they plan a pregnancy. In particular, it should be attempted to avoid the summer months coinciding with the second trimester of the pregnancy. However, further studies are needed to better demonstrate this relationship.

Table 1. Seasonal distribution of gestational diabetes mellitus pregnancies

	Winter (n=848)	Spring (n=939)	Summer (n=915)	Autumn (n=916)	Overall (n=3,618)	p
Age (years), (mean ± SD)	27.6±6.0	27.75±6.1	27.66±6.2	27.71±6.2	27.68±6.1	0.931
Gravida, (mean ± SD)	2.59±1.72	2.59±1.71	2.57±1.69	2.58±1.71	2.59±1.71	0.998
Average temperatures, °C	3.6	13.5	27.9	17.4	15.6	-
GDM, n (%)	54 (6.4%)	78 (8.3%)	84 (9.2%)	56 (6.1%)	272 (7.5%)	0.033

*Chi-square p<0.05.

GDM: Gestational diabetes mellitus, SD: Standard deviation, °C: Celsius

Ethics

Ethics Committee Approval: The study were approved by the Ankara Numune Training and Research Hospital of Local Ethics Committee (protocol number: E-19-2669, date: 18.04.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., B.K., M.O., Ö.K., İ.K., C.A., M.Ş.B., Concept: B.K., M.Ş.B., Design: B.K., M.Ş.B., Data Collection or Processing: S.A., M.O., C.A., Analysis or Interpretation: B.K., M.Ş.B., Literature Search: S.A., Ö.K., İ.K., Writing: B.K., M.Ş.B.

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Association of *Actinomyces* with Allergic Rhinitis, Adenotonsillar Hypertrophy and Chronic Recurrent Tonsillitis and Its Histopathological Findings

Actinomyces'in Alerjik Rinit, Adenotonsiller Hipertrofi ve Kronik Rekürren Tonsillit İlişkisi ve Histopatolojik Bulguları

İlke Evrim SEÇİNTİ

Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Pathology, Hatay, Turkey

ABSTRACT

Aim: To evaluate the prevalence of adenotonsillar *Actinomyces* with histopathological findings and to determine the relationship of *Actinomyces* with allergic rhinitis (AR), adenotonsillar hypertrophy (ATH) and chronic recurrent tonsillitis (CRT).

Materials and Methods: Histopathological sections were retrospectively analyzed in 228 patients who underwent adenoidectomy, bilateral tonsillectomy, and adenotonsillectomy. The presence of *Actinomyces*, cryptitis, and severity of inflammation were determined. Data were analyzed with the Statistical Package for the Social v.21.0 package software. The statistical significance level was accepted as $p<0.05$.

Results: *Actinomyces* was detected in 39 (17.1%) patients. *Actinomyces* was seen at a similar rate in ATH and CRT (p=0.08) (14.6% and 24.6%, respectively). The diameter of the tonsils with *Actinomyces* were larger than those without *Actinomyces* ($p<0.01$). The frequency of cryptitis in tonsils with *Actinomyces* histopathologically (p=0.03) and the degree of inflammation in the surface epithelium ($p<0.01$) were increased. *Actinomyces* was found more frequently in patients with AR than in patients without AR (p=0.02) (25.7% and 13%, respectively).

Conclusion: Our study shows that adenotonsillar *Actinomyces* colonization may cause ATH, CRT and AR, and AR may be one of the factors in the etiology of ATH.

Keywords: *Actinomyces*, adenotonsillar hypertrophy, allergic rhinitis, recurrent tonsillitis

ÖZ

Amaç: Adenotonsiller *Actinomyces* prevalansını histopatolojik bulgularla değerlendirmek ve *Actinomyces*'in alerjik rinit (AR), adenotonsiller hipertrofi (ATH) ve kronik tekrarlayan tonsillit (CRT) ile ilişkisini belirlemektir.

Gereç ve Yöntem: Adenoidektomi, bilateral tonsillektomi ve adenotonsillektomi uygulanan 228 hastanın histopatolojik kesitleri retrospektif olarak incelendi. *Actinomyces* varlığı, kriptit ve enflamasyonun şiddeti belirlendi. Veriler Statistical Package for the Social v.21.0 programı ile analiz edildi. İstatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edildi.

Bulgular: Otuz dokuz (%17,1) hastada *Actinomyces* saptandı. *Actinomyces* ATH ve CRT'de benzer bir oranda (p=0,08), sırasıyla %14,6 ve %24,6 olarak görüldü. *Actinomyces* görülen tonsillerin çapı, olmayanlardan daha büyüktü ($p<0,01$). Histopatolojik olarak *Actinomyces*'in görüldüğü tonsillerde kriptit sıklığı (p=0,03) ve yüzey epitelindeki enflamasyon şiddeti ($p<0,01$) artmıştı. *Actinomyces*, AR'li hastalarda AR olmayanlara göre daha sık bulunmuştur (p=0,02) (sırasıyla %25,7 ve %13).

Sonuç: Çalışmamız, adenotonsiller *Actinomyces* kolonizasyonunun ATH'ye, CRT ve AR'ye neden olabileceğini ve AR'nin ATH'nin etiyolojik faktörlerinden biri olabileceğini göstermektedir.

Anahtar Kelimeler: *Actinomyces*, adenotonsiller hipertrofi, alerjik rinit, rekürren tonsillit

Address for Correspondence: İlke Evrim SEÇİNTİ MD, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Pathology, Hatay, Turkey
Phone: +90 506 689 96 26 **E-mail:** ilkevrim@gmail.com **ORCID ID:** orcid.org/0000-0002-8614-3971
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INTRODUCTION

Palatine, tubal, pharyngeal (adenoid) and lingual tonsils form Waldeyer ring, which is an important lymphatic structure of the upper airway[1]. Adenoidectomy and tonsillectomy are the most common surgical procedures in both pediatric and adult patients. The most common indications for surgery are adenotonsillar hypertrophy (ATH) and chronic recurrent tonsillitis (CRT), which may cause obstructive sleep-related breathing disorders[2,3]. Although the causes of ATH are still unclear, there are studies in the literature showing that allergy may be a risk factor[4].

Actinomyces are Gram-positive, anaerobic, immobile, filamentous and rod-shaped commensal bacteria in the normal flora of the oropharyngeal, genitourinary and gastrointestinal tract[5]. They can resemble fungi because of their filamentous structure. In the literature, the incidence of *Actinomyces* in tonsil and adenoid has been reported in very variable rates, ranging from 0.3% to 40.7%[2,5-9]. There are different opinions on the role of *Actinomyces* in the etiology of tonsil/adenoid hypertrophy and CRT. In addition to the studies suggesting that *Actinomyces* plays a role as an etiologic agent in these pathologies[7,9-12], there are also studies suggesting that it is only a saprophyte agent[13]. However, few studies have examined the histopathological effects of *Actinomyces* on tonsil and adenoid tissues[14,15]. Allergic rhinitis (AR) is an inflammatory disease caused by IgE-mediated type 1 hypersensitivity reaction. AR has many factors in etiopathogenesis, including various fungi[16]. To date, no studies have investigated the relationship between AR and the presence of adenotonsillar *Actinomyces* in the literature. However, it is known that *Actinomyces* plays a role in the etiology of hypersensitivity pneumonia (extrinsic allergic alveolitis)[17].

This study aims to determine the prevalence of *Actinomyces* in adenoidectomy, tonsillectomy and adenotonsillectomy materials, to investigate the relationship of *Actinomyces* with AR, ATH and CRT, and to discuss all findings in the light of literature. This is the first study in the literature to investigate the relationship between AR and adenotonsillar *Actinomyces*.

MATERIALS AND METHODS

Patient Selection

This retrospective study included 228 patients who underwent adenoidectomy (n=143), bilateral tonsillectomy (n=29), and adenotonsillectomy (n=56) at Silifke State Hospital between January 2013 and December 2015. The study were approved by the Hatay Mustafa Kemal University of Local Ethics Committee (protocol number: 10, date: 16.01.2020). Unilateral tonsillectomies were excluded because of different surgery indications. Data on age, sex, diagnosis of AR, indications for operation, the largest diameters of tonsils and adenoids were obtained from the patient files and pathology reports.

Histopathological Evaluation

Hematoxylin-eosin stained histopathological sections of a total of 369 tissue materials taken from 228 patients were re-evaluated on the Olympus BX53 (Olympus, Tokyo, Japan) light microscope and photographed with the Olympus DP20 digital imaging system (Olympus, Tokyo, Japan). Tonsillar *Actinomycosis* diagnosis is made either by the presence of sulfur granules in the form of a basophilic mass with a granular center and the radial fringes around it or by the presence of a unique *Actinomyces* filament in the tonsillar tissue and/or crypt[15] (Figure 1).

The presence of *Actinomyces*, cryptitis (evaluated only in palatine tonsils because there was no crypt in adenoid tissue), inflammation in the surface epithelium and lymphoid hyperplasia were re-evaluated. Inflammation in the surface epithelium was scored semiquantitatively as 0: none, 1: mild, 2: moderate, and 3: severe. Lymphoid hyperplasia was classified as follicular hyperplasia, paracortical hyperplasia and mixed hyperplasia (follicular + paracortical).

Statistical Analysis

All clinical, histopathological and demographic data obtained from this study were analyzed with Statistical Package for the Social (SPSS) v.21.0 software package program (SPSS Inc, Armonk, NY, US). The Pearson chi-square test was used for the analysis of qualitative data. For quantitative data that were not normally distributed were statistically analyzed with the Kolmogorov-Smirnov and the Mann-Whitney U tests. Correlation analyses were performed with the Spearsman's rank correlation test. Statistical significance was accepted as $p<0.05$ in all analyses.

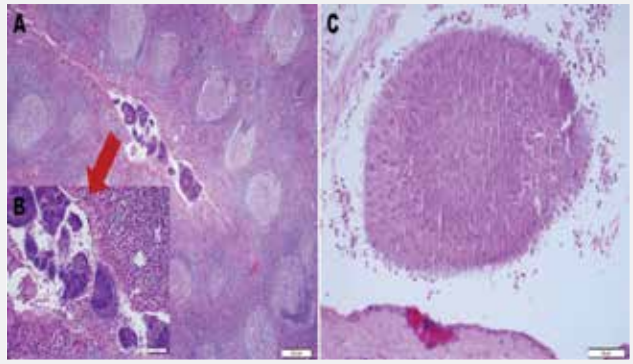

Figure 1. A) Irregularly shaped *Actinomyces* colonies in the tonsil crypt (hematoxylin-eosin, x200). B) On higher power, characteristic sulfur granules of *Actinomyces* (hematoxylin-eosin, x400). C) Filamentous branching of the bacteria at the periphery of the colonies (hematoxylin-eosin, x400)

RESULTS

The median age of all patients (n=228) was 8±5.06 years (minimum: 4, maximum: 39). 132 of them were male (57.9%) and 96 were female (42.1%). *Actinomyces* was detected in 39 patients (17.1%). *Actinomyces* was seen in 29 (34.1%) of 85 patients with tonsillectomy when adenoidectomy was excluded. The incidence of *Actinomyces* was similar in both sexes (p=0.20). The median age of the patients with *Actinomyces* was higher than that of those without *Actinomyces* (p<0.01). The median age of the patients with *Actinomyces* was 11±7.8 years and the median age of the patients without *Actinomyces* was 8±3.6 years. *Actinomyces* was seen in 25 (14.6%) of 171 patients who underwent surgery for ATH and in 14 (24.6%) of 57 patients who had surgery for CRT, and no significant difference was observed (p=0.08). The diameters of the tonsils (palatine + pharyngeal) with *Actinomyces* were larger than those without *Actinomyces* (p<0.01). Histopathologically, cryptitis was observed more frequently in tonsils with *Actinomyces* (p=0.03) and the degree of inflammation in the surface epithelium was increased (p<0.01). There was no difference in lymphoid hyperplasia types (p=0.45). Follicular hyperplasia was high in both groups. Comparison of the presence of *Actinomyces* with other data and statistical test results are summarized in Table 1. *Actinomyces* was localized only in the right tonsil in 11 (28.8%) of 39 patients with *Actinomyces*. Other localizations of *Actinomyces* are shown in Table 2.

Actinomyces was observed in 19 (25.7%) of 74 patients with AR, while 20 (13%) of 154 patients without AR had *Actinomyces*, and the difference was statistically significant (p=0.02). The diagnosis of AR was higher in patients operated for ATH than in patients operated for CRT (p=0.013). Adenoid diameters of patients with AR were larger than those without AR (p=0.046).

Table 1. Presence of *Actinomyces* and comparison of other data

	***Actinomyces* (-)** **n (%)**	***Actinomyces* (+)** **n (%)**	**p value**
Gender			
Male	113 (85.6)	19 (14.4)	0.20
Female	76 (79.2)	20 (20.8)	
Age (median)	8	11	<0.01
Allergic rhinitis			
No	134 (87)	20 (13)	0.02
Yes	55 (74.3)	19 (25.7)	
Indication for surgery			
Adenotonsillar hypertrophy	146 (85.4)	25 (14.6)	0.08
Chronic recurrent tonsillitis	43 (75.4)	14 (24.6)	
Type of surgery			
Adenoidectomy	133 (93)	10 (7)	
Tonsillectomy	15 (51.7)	14 (48.3)	<0.01
Adenotonsillectomy	41 (73.2)	15 (26.8)	
The largest diameter of the right tonsil (cm-median)	3	4	<0.01
The largest diameter of the left tonsil (cm-median)	2.5	4	<0.01
The largest diameter of the adenoid (cm-median)	2.5	4	<0.01
Histopathological findings			
Presence of cryptitis			
(-)	23 (82.1)	5 (17.9)	0.03
(+)	33 (57.9)	24 (42.1)	
The intensity of inflammation in the surface epithelium			
None	56 (91.8)	5 (8.2)	
Mild	65 (87.8)	9 (12.2)	<0.01
Moderate	58 (76.3)	18 (23.7)	
Severe	10 (58.8)	7 (41.2)	
Types of lymphoid hyperplasia			
Follicular hyperplasia	124 (84.9)	22 (15.1)	
Paracortical hyperplasia	20 (83.3)	4 (16.7)	0.45
Mixed hyperplasia	45 (77.6)	13 (22.4)	
Total	**189 (82.9)**	**39 (17.1)**	**228**

Table 2. *Actinomyces* localizations	
***Actinomyces* localization**	**n (%)**
Right tonsil	11 (28.2)
Left tonsil	7 (17.9)
Pharyngeal tonsil (adenoid)	10 (25.6)
Both tonsils	5 (12.8)
Right tonsil + adenoid	2 (5.1)
Left tonsil + adenoid	2 (5.1)
Both tonsils + adenoid	2 (5.1)

DISCUSSION

Actinomyces spp. are found in normal flora of the oropharyngeal, genitourinary and gastrointestinal tract[5]. Histopathological examination is more valuable than microbiological culture in the diagnosis of *Actinomyces*[18]. There is a wide range in the literature regarding the frequency of tonsillar *Actinomycosis* ranging from 0.3% to 40.7%. We wanted to investigate the incidence of *Actinomyces* in our series. Coban et al.[2] found only 3 (0.3%) *Actinomyces* in 1,078 tonsillectomy cases. Riffat and Walker[6] found 221 (18.2%) *Actinomyces* of 1,213 tonsillectomy cases. Ashraf et al.[5] found 83 (40.7%) *Actinomyces* of 204 tonsillectomy cases. We found *Actinomyces* at the rate of 17.1% (n=36) in our series. Since *Actinomyces* is found as saprophyte in oral flora, the general opinion is that it is also found as saprophyte in tonsils. Therefore, there may be different attitudes among pathologists to specify tonsillar *Actinomyces* in the report and this may lead to differences in the results of retrospective studies using the archive of reports. In fact, if only pathology reports were taken as the basis in our study, *Actinomyces* was reported in 11 (4.8%) of 228 patients, but when preparations were re-evaluated, the number of patients with *Actinomyces* was revised to 39 (17.1%). In some studies, it was reported that tonsillar *Actinomycosis* was seen more frequently in adults than in children[5,11,12,19,20], particularly in older children[5,21]. Some studies have shown that *Actinomycosis* is not age-related[15,22]. In this study, the median age value (median age: 11) of those with *Actinomyces* colony was greater than that of those without *Actinomyces* (median age: 8 years) (p<0.01).

In most of the studies in the literature, the rate of tonsillar *Actinomycosis* was found to be similar in both sexes[5,15,21,22]. Similar findings were obtained in this study, which is consistent with the literature.

The role of *Actinomyces* in the etiology of ATH and CRT remains unclear. In addition to the studies suggesting that *Actinomyces* has a role in the etiology of hypertrophy and recurrent tonsillitis[7,10-12,23], there are also studies suggesting that it is not associated with these diseases[5,11,13,24]. In the study of Kutluhan et al.[15], *Actinomyces* was found in 33.3% of tonsils and it was revealed that *Actinomyces* was more common in tonsillar hypertrophy (61.5%) than in recurrent tonsillitis (21.9%). Besides, they found that the volume of tonsils found in *Actinomyces* was larger than in those without *Actinomyces*. Similarly, Daneshmandan et al.[22] found that tonsil volumes with *Actinomyces* (mean 8.65 mL) were larger than in those without *Actinomyces* (mean 4.48 mL). In contrast to these studies, Jones et al.[25] found a negative correlation between tonsillar *Actinomyces* colonization and hypertrophy and found a higher rate of *Actinomyces* in patients with recurrent tonsillitis compared to hypertrophy patients. Toh et al.[11] reported that *Actinomyces* did not affect the tonsillar size. In this study, a similar rate of actinomyces was detected in patients operated for hypertrophy and recurrent tonsillitis (p=0.08). The diameters of the tonsils (palatine and pharyngeal tonsils) with *Actinomyces* were larger than in those without *Actinomyces* (p<0.01), suggesting that *Actinomyces* plays a role in the etiology of ATH. Tonsils with *Actinomyces* showed more cryptitis (p=0.03) and inflammation in the surface epithelium was more severe (p<0.01). This suggests that *Actinomyces* may be an effective pathogen in the etiology of recurrent tonsillitis.

AR is one of the most common chronic diseases in children[26]. Few studies have investigated the relationship between AR and AH and there is no consensus between these studies. Sadeghi-Shabestari et al.[27] found a significant correlation between positive skin prick test and high serum IgE levels with ATH. Modrzynski and Zawisza[28] also reported that AR might cause AH. Similarly, Bozkurt et al.[29] found that adenoid volumes of patients with AR were higher than those of patients without AR. In contrast to these studies argueing that AR causes AH or exacerbates existing AH, Ameli et al.[30] found that patients with AR had smaller adenoid volumes than those without AR, suggesting that anterior nasal obstruction stopped adenoid growth. In our study, the adenoid size was higher in patients with AR (p=0.046) and there was a positive correlation between them (p=0.04). Our findings support the view that AR may cause or increase existing AH, as in the studies of Sadeghi-Shabestari et al.[27] and Modrzynski and Zawisza[28]. Some fungi have been reported to play a role in the etiology of AR in the literature. In their study, Namyslowski et al.[16] found *Candida albicans* in 3.8%, *Aspergillus fumigatus* in 11.5%, *Alternaria alternata* in 3.8%, *Mucor racemosus* in 7.6% and *Cladosporum herbarum* in 7.6% in patients with AR. *Actinomyces* is also known to be similar to fungi because of their filamentous structure, and *Actinomyces* like *Aspergillus* have been shown to act as active pathogens in allergic diseases such as hypersensitivity pneumonia[17]. In our study, *Actinomyces* was found to be more frequent in patients with AR (25.7% and 13%, respectively) than in those without AR, and there was a positive correlation between them (p=0.02).

Study Limitations

Our study's retrospective design and therefore, the lack of access to drug history and laboratory values of all patients constitute the limitations of our study.

CONCLUSION

ATH and recurrent tonsillitis, which can cause obstructive sleep-related respiratory disorders, are the most common diseases and adenotonsillectomy is one of the most common surgical procedures in the treatment of these diseases. However, the etiologic cause of ATH is still unclear. Our study shows that adenotonsillar *Actinomyces* colonization may cause ATH, recurrent tonsillitis, and AR. It also suggests that AR may be involved in the etiology of ATH. Establishing causal relationships will contribute to the development of both preventive and therapeutic approaches. Our study is the first study to investigate the relationship between AR and *Actinomyces*.

Ethics

Ethics Committee Approval: The study were approved by the Hatay Mustafa Kemal University of Local Ethics Committee (protocol number: 10, date: 16.01.2020).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

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Affective Temperaments May Predict Postpartum Depression: A Preliminary Study

Afektif Mizaçlar Postpartum Depresyonu Öngörebilir: Bir Ön Çalışma

Erson AKSU[1], Elmas BEYAZYÜZ[2],

[1]Rumeli University Faculty of Health Services, İstanbul, Turkey
[2]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Psychiatry, Tekirdağ, Turkey

ABSTRACT

Aim: Postpartum depression (PPD) is a serious clinical condition, which affects both mother and baby as well as partners. Although PPD is accepted as a mood disorder, there have been limited numbers of studies that investigated affective temperaments in PPD and pregnancy. Moreover, no study has been carried out on the subject of whether affective temperaments assessed during pregnancy can predict PPD.

Materials and Methods: One hundred-fourteen pregnant women were included in present study considering specific criteria. Patients were assessed with the Temperament Evaluation of Memphis, Pisa, Paris and San Diego auto-questionnaire and socio-demographic forms during the third trimester of pregnancy. In the following four weeks of delivery, patients were assessed with the Edinburgh Postpartum Depression Scale for evaluating the presence of tendency to PPD.

Results: The patients who had a tendency to PPD had significantly higher scores on all affective temperament scores except hyperthymic temperament. In logistic regression analysis, it was found that higher scores of cyclothymic temperament and anxious temperament (AT) were associated with tendency to PPD (Odds ratio: 1.26 and 1.47).

Conclusion: Cyclothymic and anxious temperaments are candidates for predicting tendency to PPD. Pregnant women, who have higher scores specifically for cyclothymic and ATs should be considered in terms of affective disorders.

Keywords: Postpartum, depression, affective, temperament

ÖZ

Amaç: Postpartum depresyon (PPD) anne, bebek ve eşleri etkileyen ciddi bir klinik durumdur. PPD, duygudurum bozukluğu olarak kabul edilmekle birlikte, PPD ve gebelikte afektif mizaçları araştıran sınırlı sayıda çalışma vardır. Ayrıca, gebelikte afektif mizaçların PPD'yi yordayıp yordayamayacağını araştıran herhangi bir çalışma bulunmamaktadır.

Gereç ve Yöntem: Alınma ve dışlanma kriterlerine göre 114 gebe çalışmaya dahil edildi. Hastalar, gebeliğin üçüncü trimesterinde Memphis, Pisa, Paris ve San Diego'nun Mizaç Değerlendirmesi anketi ile ve sosyo-demografik formlarla değerlendirildi. Doğumu takip eden ilk dört haftada, hastaların PPD'ye eğilimi olup olmadığını değerlendirmek için Edinburgh Doğum Sonrası Depresyon Ölçeği uygulandı.

Bulgular: PPD eğilimi olan hastaların hipertimik mizaç dışındaki tüm afektif mizaç puanlarında anlamlı olarak daha yüksek puanları vardı. Lojistik regresyon analizinde, yüksek siklotimik mizaç ve anksiyete mizaç (AT) puanlarının doğum sonrası depresyona yatkınlıkla ilişkili olduğu bulunmuştur (Odds oranı: 1,26 ve 1,47).

Sonuç: Siklotimik ve AT, doğum sonrası depresyon eğilimini yordamak için aday olabilirler. Özellikle siklotimik ve AT puanları yüksek olan gebeler afektif bozukluklar açısından değerlendirilmelidir.

Anahtar Kelimeler: Postpartum, depresyon, afektif, mizaç

Address for Correspondence: Elmas BEYAZYÜZ MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Psychiatry, Tekirdağ, Turkey
Phone: +90 282 250 72 34 **E-mail:** elmasbeyazyuz@yahoo.com **ORCID ID:** orcid.org/0000-0001-5680-0101
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INTRODUCTION

Depressive disorder is one of the most common cause of disability in women in the whole World and the prevalence of depression is twice the number in women compared to men[1]. Postpartum phase is also an important time interval for developing depression among women. The Diagnostic and Statistical Manual of Mental Disorders-5th Edition (APA 20013) describes the postpartum depression (PPD) as a depressive state that has symptoms ranging from moderate to severe, which begins during four weeks after delivery[2-4].

Postpartum psychiatric disorders consist of PPD, postpartum blues and postpartum psychosis[5]. PPD causes severe social and occupational functional impairments and is closely associated with problems in interactions with partner, family and baby[6-8]. The strongest risk factors for PPD have been identified as antenatal depression or anxiety, history of major depressive disorder, problems in marriage, poor social support and stressing life events[9,10]. Furthermore patients with a history of PPD have been reported to have higher percentages of PPD subsequent to deliveries[11,12].

Currently, affective temperaments are considered to be predictors of some mood disorders[13]. Depressive temperament (DT) was reported to be related to depressive disorder, and irritable temperament (IT), hyperthymic temperament (HT) were considered to be associated with bipolar 1 disorder, and cyclothymic temperament (CT) was regarded as a tendency to bipolar 2 disorder[13,14]. However, there have been limited numbers of studies that investigated affective temperaments during pregnancy and postpartum period. Yazici et al.[15] reported that affective temperament scores of pregnant women were different from those of healthy control group. Another current study reported that pregnancy and postpartum periods correlated with HT in women without psychiatric diagnosis[15]. There has been only one study that assessed affective temperaments in patients with PPD[16]. However, no study assessing whether affective temperaments evaluated during pregnancy may predict PPD has been carried out.

In the present study, we aimed to investigate whether there would be associations between affective temperaments assessed during pregnancy and PPD. We hypothesized that some affective temperaments could predict PPD.

MATERIALS AND METHODS

The present study was conducted at Tekirdağ Namık Kemal University Faculty of Medicine, Departments of Gynecology and Obstetrics and Psychiatry. It was approved by Tekirdağ Namık Kemal University Non-Invasive Clinic Research Ethical Committee (date and approval number: 2018/124/08/15).

Inclusion criteria were defined as being at the third period of pregnancy, having no previous or current psychiatric diagnosis, having enough education for being able to complete the self-assessment tests that were used in the present study, and being willing to be participate in the study. Patients who had previous or current psychiatric diagnosis, who had insufficient knowledge for understanding the aim of the study as well as tests that were used in the study, and who were unwilling to participate in the study were excluded. According to inclusion and exclusion criteria, 170 female patients, who were at the 3rd trimester of their pregnancy, were initially involved in the present study. All of the patients completed the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto-questionnaire (TEMPS-A) form and socio-demographic form during pregnancy. After delivery, all patients, who completed TEMPS-A, were evaluated by the Edinburgh Postpartum Depression Scale (EPDS) at the routine controls in the four weeks after delivery. As 114 patients completed the second round, 114 patients were finally included in the study. All patients signed written informed consent form before participating in the study.

Assessment Tools

Socio-demographic Form

This form was created by authors in the light of the literature. This form consists of the data on age, duration of marriage, having a child, education and occupation status, family structure, income rate, place of birth, status of cigarette, and alcohol use.

Temperament evaluation of Memphis, Pisa, Paris and San Diego Auto-questionnaire

The TEMPS-A is a scale that was originally designed by Vahip et al.[17] and then adopted into Turkish by Vahip et al.[17]. In the present study, this scale was used to evaluate the scores of subdimensions. It is a self-assessment scale, involving "true" or "false" indications that ask about mood and temperament properties of the entire life of the individual. The subdimensions consist of depressive, cyclothymic, hyperthymic, irritable (DT, CT, HT, IT), and anxious temperaments (AT).

The Edinburgh Postpartum Depression Scale

EPDS was created by Cox et al., and translated and adapted to Turkish by Engindeniz et al.[18] (1997). The purpose of the scale is to evaluate women's PPD levels and it consists of ten items rated on a four-point Likert scale ranging from 0 to 3. The lowest total score that can be obtained is 0, and the highest is 30. Individuals, who score 13 or more, are considered to be at risk of depression.

Statistical Analysis

Statistical analyses were conducted with R 3.5.3, SPSS 23.0., STATA 14.0 and G * Power 3.1. Power analysis was performed to determine the power of the study. We defined a new variable by using EPSD score with its cut-off point. According to that, we

tried to predict the redefined EPSD variable by using the Binary Outcome Logistic Regression. This new variable was also used to determine whether the mean of EPDS dimensions differed. For the assumptions of parametric tests, the Kolmogorov-Smirnov test was used to test for data normality and the box plot was also used. The Levine test was used for the variance homogeneity.

Power Analysis

The Mann-Whitney U test statistic with allocation ratio 0.29 was used as a test statistic. A sample size of 20 achieves 70% power to detect an effect size (d) of 1.3978 using the Mann-Whitney U test with a significance level (alpha) of 0.05. When the sample size is n=45, the power of the test has already achieved 95%. However, the sample size of the study was determined as 114. For the given parameters, for an alpha of 0.05 and a sample size of 114 observations, the type 2 error is 0.0003 and the power is ≅ 1.0 (Figure 1).

RESULTS

One hundred fourteen patients were included in the present study. The mean age of participants was 29.72±5.73 years. The median scores of DT, CT, HT, IT and AT were 4, 6, 10, 2 and 7, respectively. The numbers of patients, who scored 13 and higher on EPDS, were 26 (22.8%). The data of demographical and clinical variables of patients were demonstrated in Table 1.

The Kolmogorov-Smirnov test was used to examine the normality of the presence-absence of tendency to PPD distributions. None of them distributed normally. Both the Kolmogorov-Smirnov test and the box-plots showed that presence- absence of tendency to PPD distributions were skewed (Figure 2). For two independent samples comparison, the Mann-Whitney U test was applied when the assumption of normal distribution did not fit. According to the presence- absence of tendency to PPD based on EPDS, there were statistically significant differences between DT scores (absence: 4.34±2.83, presence: 6.35±2.91), CT scores (absence: 6.64±5.16, presence: 8.96±4.86), IT scores (absence: 2.80±2.85, presence: 5.27±4.31) and AT scores (absence: 6.12±6.00, presence: 14.35±5.76) (Table 2).

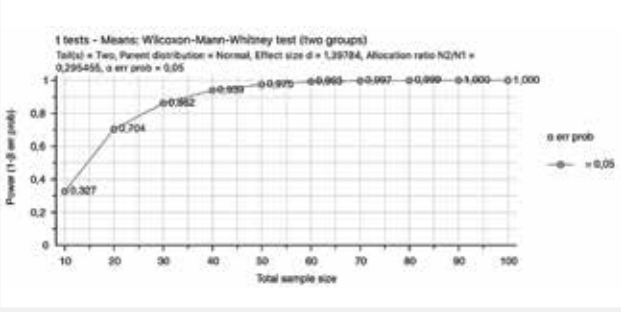

Figure 1. Power analysis of study

The general form of the logistic regression model is:

$$logit(P)=a+b_1x_1+b_2x_2+b_3x_3+...+b_kx_k$$

where logit(P)=Y is a dependent variable and $x_1,x_2,x_3,...,x_k$ are independent variables.

The parameters of $b_1,b_2,b_3,...,b_k$ are the logistic regression coefficients. The binary response variable is taken as 0 or 1. The value 1 means the presence of PPD and value 0 indicates the absence of PPD. The *P* is denoted as the probability of presences of tendency to PPD. A pseudo R^2 greater than 2 indicates a relatively good fit; equals to 1 indicates a perfect fit and equal to 0 means no relationship. According to the Table 3, the model has a relatively good fit (pseudo R^2=0.48). The Cox and Snell's R^2 and Nagelkerke R^2 indicates that the independent variables can explain the dependent variables with the values of approximately 40% and 61%. For all that, the predicted accuracy was 94% for the absence of depression, the predicted accuracy was 73% for the presence of tendency to PPD and the overall predicted accuracy was 89%. The model was significant at 5% significance level. CT, AT, having a child, and place of birth had a statistically significant effect on the presence of tendency to PPD (Table 3).

DISCUSSION

In the present study, our main findings were as follows; except HT, all subdimensions of TEMPS-A were significantly higher in the patient group who scored ≥13 at the EPDS, which reflects tendency to PPD. Moreover, we found that higher scores of CT and AT were associated with tendency to PPD.

PPD is a severe mental disorder which affects both mother and child[19-21]. The exact etiology of PPD is considered unclear;

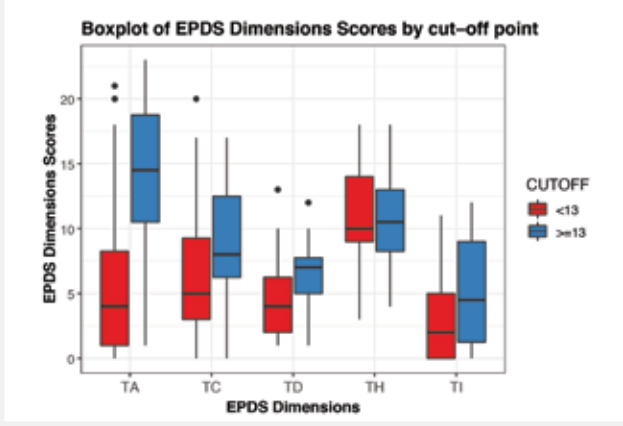

Figure 2. Demonstration of Boxplot of Edinburg Postpartum Depression Scale dimensions by cut-off point

EPDS: Edinburg Postpartum Depression Scale

The blue color indicated depression group, red color indicated non-depressed group

however, biological factors such as ovarian steroids, oxytocin and glucocorticoids as well as other neurotransmitters, which are also associated with mood disorders, have been reported to be etiological factors[6]. Affective temperaments are among well-established factors for the development of affective disorders[22,23]. Akiskal ve Akiskal[24] created the modern concept of affective temperaments for identifying all spectrum of affective situations from healthy reactions to major affective disorders.

There have been two studies that investigated affective temperaments in pregnant women. In the first study, Yazici et al.[15] compared affective temperaments between pregnant women and healthy women and reported that cyclothymic, irritable and AT scores of the pregnant women were significantly lower in pregnant women, and they concluded that differences of affective temperaments could be associated with trimesters of pregnancy. Yazici et al.[16] investigated affective temperaments between pregnant women in different trimesters, women who were at prenatal period and postpartum period, and age-matched healthy women. The researchers concluded that pregnancy and postpartum periods correlated with HT characteristics in women without active psychiatric diagnosis.

In our study, we compared affective temperaments, which were obtained at third trimester between pregnant women with and without tendency to PPD, based on EPDS. We found that except HT, all subdimensions of TEMPS-A were significantly higher in the patient group who scored ≥13 at the EPDS. These temperaments were reported more frequently in affective patients with mixed episodes indicating a relationship between mixed affective episodes and simultaneous presence of inverse temperamental types[25].

From this perspective, we can say that affective temperaments differed in pregnant women with and without the risk for postpartum depressive disorder. However, our main purpose was to provide predictive roles of affective temperaments for developing postpartum depressive disorder. We performed

Table 1. Socio-demographical and clinical characteristics of participants

		n	%	±	Median	Standard deviation	Minimum	Maximum
Age		114		29.72	30.00	5.731	16.0	41.0
Period of marriage		114		7.33	6.50	5.111	1.0	20.0
Have a child	**Yes**	88	77.2	-	1.00	-	1.0	2.0
	No	26	22.8	-		-		
Education	**Primary**	19	16.7	-	2.00	-	1.0	3.0
	Middle/high	73	64.0	-		-		
	Higher	22	19.3	-		-		
Occupation	**No**	82	71.9	-	1.00	-	1.0	2.0
	Yes	32	28.1	-		-		
Family Structure	**Core**	88	77.2	-	1.00	-	1.0	2.0
	Broad	26	22.8	-		-		
Income Rate	**High**	2	1.8	-	2.00	-	1.0	3.0
	Mid	95	83.3	-		-		
	Low	17	14.9	-		-		
Place of birth	**Metropolis**	11	9.6	-	2.00	-	1.0	3.0
	Other city	69	60.5	-		-		
	Village/town	34	29.8	-		-		
Use of alcohol substance	**No**	114	100.0	-	1.00	-	1.0	1.0
Use of cigarette	**Yes**	14	12.3	-	2.00	-	1.0	2.0
	No	100	87.7	-		-		
EPDS		114	-	7.28	5.00	6.507	1.0	24.0
DT		114	-	4.79	4.00	2.957	1.0	13.0
CT		114	-	7.17	6.00	5.166	0.0	20.0
HT		114	-	10.91	10.00	4.088	3.0	18.0
IT		114	-	3.36	2.00	3.387	0.0	12.0
AT		114	-	8.00	7.00	6.864	0.0	23.0
EPDS	**Cut-off <13**	88	77.2	-	1.00	-	1.0	2.0
	Cut-off ≥13	26	22.8	-		-		

EPDS: Edinburgh Postpartum Depression Scale, AT: Anxious temperament, CT: Cyclothymic temperament, DT: Depressive temperament, HT: Hyperthymic temperament, IT: Irritable temperament

logistic regression analysis and found that higher scores of CT and AT were associated with tendency to PPD (respectively Odds ratio; 1.26 and 1.47). There has been only one study that investigated affective temperaments in patients, who were diagnosed with PPD. In this study, affective temperament and the presence of postpartum depressive disorder were assessed simultaneously and it was reported that cyclothymic and AT were among the significant risk factors independently from psychosocial factors[17]. The methodology of our study differed from Masmoudi et al.'s[26] research. Firstly, we assessed affective temperaments in women at third trimester of pregnancy, who had no present or previous psychiatric disorder. Secondly, our study is a follow-up study that investigated the patients in both pregnancy and postpartum periods. Our results are first to show cyclothymic and AT as candidates for developing tendency for postpartum depressive disorder. Additionally,

Table 2. Comparison of affective temperaments between the groups that were separated according to the Edinburg Postpartum Depression Scale

EDSDO		n	Mean rank	Sum of ranks	Mann-Whitney U	p value
DT	**Cut-off <13**	88	52.28	4600.50	684.500	0.002
	Cut-off ≥13	26	75.17	1954.50		
CT	**Cut-off <13**	88	53.60	4716.50	800.500	**0.020**
	Cut-off ≥13	26	70.71	1838.50		
HT	**Cut-off <13**	88	58.20	5121.50	1082.500	0.676
	Cut-off ≥13	26	55.13	1433.50		
IT	**Cut-off <13**	88	53.13	4675.00	759.000	**0.008**
	Cut-off ≥13	26	72.31	1880.00		
AT	**Cut-off <13**	88	48.85	4298.50	382.500	**p<0.001**
	Cut-off ≥13	26	86.79	2256.50		
Age	**Cut-off <13**	88	57.52	5062.00	1142.000	0.989
	Cut-off ≥13	26	57,42	1493,00		

AT: Anxious temperament, CT: Cyclothymic temperament, DT: Depressive temperament, HT: Hyperthymic temperament, IT: Irritable temperament

Table 3. The predictors of tendency to postpartum depression according to the Edinburg Postpartum Depression Scale

Model	B	Standard deviation	Wald	df	p value	Exp (B)	95% CI for Exp (B)
DT	-0.006	0.166	0.002	1	0.969	0.994	0.716-1.376
CT	-0.261	0.128	4.144	1	**0.042**	**1.264**	0.599-0.990
HT	-0.127	0.110	1.338	1	0.247	0.881	0.710-1.092
IT	0.235	0.157	2.230	1	0.135	0.771	0.929-1.720
AT	0.385	0.092	17.658	1	**p<0.001**	**1.470**	1.228-1.759
Age	0.046	0.069	0.438	1	0.508	1.047	0.914-1.197
Period of marriage	-0.129	0.108	1.409	1	0.235	0.879	0.710-1.087
Have a child	3.401	1.517	5.025	1	**0.025**	**2.990**	1.533-5.55
Education	0.177	0.660	0.072	1	0.788	1.194	0.327-4.349
Occupation	-0.861	0.898	0.920	1	0.337	0.423	0.072-2.455
Family structure	-2.474	1.170	4.474	1	0.054	0.084	0.008-0.833
Income rate	-0.590	0.861	0.469	1	0.493	0.555	0.102-2.997
Place of birth	1.797	0.721	6.217	1	**0.013**	**6.033**	1.468-24.78
Constant	-8.947	4.232	4.469	1	0.035	0.000	0.000-0.520
Pseudo R^2	0.479						
Cox and Snell's R^2	0.402						
Nagelkerke R^2	0.611						
x^2	**58.66**						
p value							**p<0.001**

Binary outcome logistic-regression.

EPDS: Edinburgh Postpartum Depression Scale, AT: Anxious temperament, CT: Cyclothymic temperament, DT: Depressive temperament, HT: Hyperthymic temperament, IT: Irritable temperament, CI: Confidence interval

having a child and place of birth were found to be other risk factors for postpartum depressive disorder.

Study Limitations

Although we performed power analysis for the present study, the numbers of patients can be considered small for making a general conclusion in terms of identifying predictors for postpartum depressive disorder. This is the major limitation of our study. Including the pregnant women without psychiatric disorder, assessing the patients at the same trimester, evaluating the PPD in the first four weeks and prospective design of our study can be regarded as the strengths of our study.

CONCLUSION

In conclusion, we argue that cyclothymic and AT can be considered candidates for predicting tendency to PPD beside other risk factors. Pregnant women who have higher scores specifically for cyclothymic and AT should be evaluated in terms of affective disorders.

Ethics

Ethics Committee Approval: It was approved by Tekirdağ Namık Kemal University Non-Invasive Clinic Research Ethical Committee (date and approval number: 2018/124/08/15).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Ambulance Diversion: A Solution or Problem?

Ambulans Diversiyonu: Çözüm mü Yoksa Problem mi?

Mehmet Ali CEYHAN[1], Gültekin Günhan DEMİR[2]

[1]University of Health Sciences Turkey, Ankara City Hospital, Clinic of Emergency Medicine, Ankara, Turkey
[2]İstanbul Medipol University Faculty of Medicine, Department of Cardiology, İstanbul, Turkey

ABSTRACT

Aim: Ambulance diversion (AD) is defined as redirection of ambulance to an emergency department (ED) different from the initially intended ED with the purpose of both appropriate use of hospital sources for selected patients and relief of ED overcrowding. In the present study, the authors sought to perform a comprehensive analysis of ADs in Ankara, the capital city of Turkey.

Materials and Methods: In this retrospective study, a comprehensive analysis of reasons for AD and the disposition data in the receiving hospital of patients diverted by ambulances of Ankara 112 Emergency Medical Service throughout 2014 (01 January-31 December 2014) was performed.

Results: A total of 174.669 patients were transferred by ambulance to EDs and of those 1.300 ADs (0.74%) occured. The causes of AD were respectively lack of bed in intensive care unit (ICU), inpatient care ward or EDs (639 AD, 49.1%), shortage of on-call specialist doctors (242 AD, 18.6%), and insufficent radiology, laboratory equipment and other resources (174 AD, 13.3%).

Conclusion: Unavailability of patient beds in EDs, ICUs or inpatient clinics are the most common causes of AD.

Keywords: Ambulance diversion, emergency medicine services, emergency department overcrowding, emergency department

ÖZ

Amaç: Ambulans diversiyonu (AD) acil servislerin (AS) aşırı yoğunluğunu hafifletmek ve hastane kaynaklarının en uygun şekilde kullanılması amacıyla ambulansla alandan nakledilen seçilmiş bazı hastaların başlangıçta götürülmesi planlanan hastane AS'den farklı bir hastanenin AS'e yeniden yönlendirilmesi olarak tanımlanır. Bu çalışmada Türkiye'nin Başkenti Ankara'da hastanelerin AS'lerinden yapılan AD'larının kapsamlı analizi yapıldı.

Gereç ve Yöntem: Bu retrospektif çalışmada 1Ocak 2014-31 Aralık 2014 tarihleri arasında Ankara 112 Acil Sağlık Hizmetleri Ambulansları'yla başka hastane acil servisine yönlendirilen hastaları alan hastane sonuçları, AD nedenleri, tanı ve demografik özellikleri araştırıldı.

Bulgular: Toplam 174.669 hasta ambulanslarla hastane AS'lerine nakledildi ve 1.300 (%0,74) AD'u yapıldı. Kadın hastaların sayısı 692 idi (%53,2). Başlıca hasta AD sebepleri yoğun bakımlarda, hastane servislerinde ve AS'lerinde yer olmaması (639 AD, %49,1), nöbetçi uzman doktorun olmaması (242 AD, %18,6), ve radyoloji, laboratuvar tetkikleri ve diğer kaynakların yetersizliğiydi (174 AD, %13,3).

Sonuç: AS'lerde, yoğun bakımlarda ve hastane servislerinde yer olmaması AD'nun en sık nedenidir.

Anahtar Kelimeler: Ambulans diversiyon, acil sağlık hizmetleri, acil servis aşırı yoğunluğu, acil servis

INTRODUCTION

Ambulance diversion (AD) is defined as the redirection of ambulance to an emergency department (ED) different from the initially intended ED[1]. Lagoe and Jastremski[2] initially used AD in patients with minor injuries with the purpose of both appropriate use of hospital sources for selected patients and relief of overcrowding in EDs. Actually, AD is supposed to be used in cases of disasters or overcrowding in EDs for ED surge capacity and redistribution of patients among regional EDs in

Address for Correspondence: Mehmet Ali CEYHAN MD, University of Health Sciences Turkey, Ankara City Hospital, Clinic of Emergency Medicine, Ankara, Turkey
Phone: +90 538 627 38 72 **E-mail:** maceyhan@hotmail.com.tr **ORCID ID:** orcid.org/0000-0003-0000-0177
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the health service network[2,3]. Although initial utilization of ADs targeted improved health care to overcome conditions such as insufficient hospital resources [computed tomography scanner, blood bank, operating room, intensive care unit (ICU)], staff shortage (trauma team, on-call specialists etc.) and ED overcrowding, inappropriate overuse of AD turned out to be a daily practice and led to increased patient transport time, delays in emergency medical care and negative outcomes in patient health care[1,3-6].

Determination of frequency, causes and consequences of AD might provide useful information for relevant arrangement and regulations. AD has not been subject to investigation in Turkey so far. The present study aimed to perform a comprehensive and comparative analysis on causes, prevalence, disposition and outcomes of ADs in Ankara, the capital city of Turkey.

MATERIALS AND METHODS

Management of ED and Emergency Medical Service (EMS) in Turkey is executed according to Emergency Medical Services Regulations (EMSR)[7]. EMSR dictates that all hospitals with emergency healthcare services have to admit and perform necessary interventions to patients transferred by ambulance regardless of the ability to pay or presence of insurance. Temporary interruption of emergency healthcare or AD for patients transferred by ambulance are prohibited. However, if emergency treatment of the patient is not possible in the first admitting hospital and requires transfer to another hospital, transfer to another healthcare facility is permitted after the establishment of required transferred conditions via 112 Ambulance Command Control Center (ACCC) coordination[7]. In practical aspect, EMSR was not largely followed in the management of patients transferred by ambulance to ED and their transfer to another hospital after AD.

The study was conducted in the assigned work area of Ankara Provincial Directorate of Health (PDH). EMS in Ankara is provided by the Directorate of Emergency Medical Services Department located in the structure of PDH. Stations of 112 Ambulance Services were settled in previously assigned critical points. A crew consisting of paramedic, emergency medicine technician and ambulance driver are on duty basis of 24/7. A few numbers of ambulances include doctor employment and are reserved for complicated cases. Ambulance crew have been trained for Basic Life Support and Advanced Life Support for pediatric and adult population. When 112 emergency line is dialed for emergency medical help, 112 ACCC assigns the nearest ambulance crew to the scene. Patients collected from the scene are transferred to the nearest hospital ED by the discretion of the ambulance crew. AD practice of EDs in Ankara is quite different from the one defined in the literature. After the transfer of the patient collected from the scene to the nearest hospital ED by the discretion of the ambulance crew, patient is evaluated by ED physician without being unloaded from ambulance stretcher and diverted to another hospital after the declaration of reason for not admitting the patient. Following decision for AD, the selection of the next hospital is decided by ambulance crew, in some occasions, two or more hospitals are visited for admission to hospital. The most convenient destination is generally found after the ambulation of EDs with the patient.

Ambulance run-sheets include patient name, surname, gender, initial diagnosis, treatment content during transport, the name of the receiving hospital and staff. If AD is decided for the case from the first ED, the name of the physician deciding AD and the reason for AD are recorded.

Ambulance run-sheets are collected towards the end of each month in the Committee of Emergency Health Services Coordination (CEHSC) office embodied in Ankara PDH. The data are extracted from ambulance run-sheets as a summary including demographics of the patient, date, the name of the hospital and the physician deciding AD, the reason for AD and the name of the receiving hospital after AD. A written form with the information of extracted data is sent to hospitals involved in ADs of the last month by CEHSC. Evaluation Committee of Ambulance Diversion (ECAD) consists of three physicians one of whom is ED staff and evaluates AD by collecting information from the hospital deciding AD. ECAD of the receiving hospital evaluates the characteristics, final diagnosis and the disposition of the admitted AD patients. Reports from both hospitals involved in the AD process are sent to CEHSC in hardcopy and digital format. A commission in PDH is gathered each month to interprete ADs performed in the past month.

The present study comprised patients loaded to EMS ground ambulances from scene and diverted by EDs of the first hospital they were transported to another hospital in Ankara in the year 2014 (01 January-31 December 2014). Required data were obtained from CEHSC embodied in Ankara PDH and analyzed in a retrospective fashion. The prevalence and causes of AD, patient demographics, final diagnoses, characteristics of the diverting and receiving hospitals, disposition features in the receiving hospital and deaths were investigated.

This study was approved by the Ethical Board of University of Health Sciences Turkey, Ankara Numune Health Training and Research Hospital (Ankara, Turkey; 18.4.2019, decision number: Ethics Committee-19-2669).

Statistical Analysis

Descriptive statistics were used to summarize clinical characteristics. Median and range were used for expressing

continuous variables which had abnormal distribution. Normal distribution was tested by the Kolmogorov-Smirnov test. Statistical Package for the Social Sciences (SPSS version 11.0, SPSS Inc., Chicago, IL, USA) was used for analysis.

RESULTS

Ankara had a population of 5.150.072 in year 2014[8]. A total of 174,699 patients were transferred to ED of hospitals in Ankara. A total of 1300 (0.74%) ADs took place. AD was most frequently used in weekends and out of working hours (974, 74.9%).

Six-hundred ninety-two patients (53.2%) were female and the number of patients younger than 18 years was 178 (13.6%). The number of patients between the ages of 18 and 65 years was 662 (50.9%). The median age of the study population was 49 years (100-1).

ADs due to internal medical conditions (974 ADs, 74.9%) were greater than ADs due to surgical conditions (326 ADs, 25%). The most common causes of medical conditions included shortness of breath (95 ADs, 7.3%), chest pain (61 ADs, 4.6%) and cerebrovascular diseases (57 ADs, 4.3%) (Table 1). Furthermore, the most common surgical conditions

Table 1. Medical complaints of ambulance diversion patients

	n (%)		n (%)
Shortness of breath	95 (7.3)	Schizophrenia	6 (0.4)
Chest pain	61 (4.6)	Burns	6 (0.4)
Cerebrovascular diseases	57 (4.3)	Palpitations	6 (0.4)
General condition disorder	53 (4.0)	Febrile seizure	6 (0.4)
Abdominal and pelvic pain	47 (3.6)	Allergic reactions	5 (0.3)
Preterm birth	46 (3.5)	Epistaxis	5 (0.3)
Fever	45 (3.4)	Gas poisoning	5 (0.3)
Syncope	44 (3.3)	Lung cancer	5 (0.3)
COPD exacerbation	37 (2.8)	Imminent abortion	4 (0.3)
Nausea and vomiting	35 (2.6)	Renal colic	4 (0.3)
Seizure	33 (2.5)	Post-operative complications	3 (0.2)
Drug poisoning	28 (2.1)	Hematuria	3 (0.2)
Non-specific medical complaints	25 (1.9)	Hemorrhage from dialysis access sites	3 (0.2)
Normal delivery	25 (1.9)	UTI	3 (0.2)
Agitation/anxiety	18 (1.3)	CKD	3 (0.2)
Hypertension	17 (1.3)	Caustics ıngestion	3 (0.2)
Acute pain	15 (1.1)	Prostate cancer	3 (0.2)
Toxic alcohol consumption	15 (1.1)	Tear gases exposure	2 (0.1)
Gastrointestinal bleeding	14 (1.0)	Asthma exacerbations	2 (0.1)
Dizziness	13 (1.0)	Brain cancer	2 (0.1)
Hypoglycemia	13 (1.0)	Ectopic pregnancy	2 (0.1)
Substance abuse	13 (1.0)	Pulmonary edema	2 (0.1)
Pneumonia	11 (0.8)	Normal pregnancy	2 (0.1)
Low back pain	9 (0.6)	Intrauterine death	2 (0.1)
Hypotension	9 (0.6)	Food poisoning	2 (0.1)
Carbon monoxide poisoning	9 (0.6)	Foreign body in the eye	2 (0.1)
Airway foreign body aspiration	8 (0.6)	Conversion disorder	2 (0.1)
Headaches	7 (0.5)	Methyl alcohol consumptions	2 (0.1)
Mood disorders	7 (0.5)	Senile disorders	2 (0.1)
Congestive heart failure	7 (0.5)	Bipolar disorder	2 (0.1)
Diarrhea	6 (0.4)	Urinary retention	2 (0.1)
Hyperglycemia	6 (0.4)	Other complaintsa[a]	45 (3.4)
Total			**974 (74.9)**

[a]Medical conditions recorded for once.

COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, UTI: Urinary tract infection

included road accidents (151 ADs, 11.6%), fall-related injury (95 ADs, 7.3%) and fight injury (22 ADs, 1.6%) (Table 2).

The most common cause of AD was unavailability of beds in EDs, ICUs, and inpatient services (622 ADs, 47.8%) (Table 3).

Unavailability of on-call specialist or a certain clinic with relevant specialization led to 290 (22.3%) ADs. Neurology (30 ADs 2.3%), neurosurgery (28 ADs, 2.1%) and physchiatry (16 ADs, 1.2%) were the main branches causing AD, respectively (Table 3).

Unavailability of imaging devices, laboratory tests or other hospital resources led to 176 (13.5%) ADs. The most common reason among those was broken status or absence of computed tomography (69 ADs, 5.3%). The number of ADs with undetermined cause or missing data was 114 (8.7%) (Table 3).

Sociological factors led to 62 ADs (4.7%). The most common sociological factor leading to AD was patient's will to be treated in the ED of hospital in which his/her previous treatment was followed (25 ADs, 1.9%).

The presence of multiple factors such as unavailability of ICU bed, relevant specialist, laboratory tests or other hospital resources was detected in 26 ADs (2%). Employment of the required surgeon in another surgical operation caused 10 ADs (0.7%).

A total of 15 (1.1%) AD patients died. Three of them died during ambulance transport, and four died right after arrival to the

Table 2. Surgical complaints of ambulance diversion patients

	n (%)
Road accidents	151 (11.6)
Fall-related injury	95 (7.3)
Fight injury	22 (1.6)
Superficial lacerations (except scalp and tendon)	20 (1.5)
Soft-tissue injury	9 (0.6)
Head trauma	5 (0.3)
Fracture	5 (0.3)
Superficial scalp lacerations	4 (0.3)
Hand finger amputations	3 (0.2)
Gunshot injury	2 (0.1)
Bike accidents	2 (0.1)
Tendon lacerations	2 (0.1)
Eye trauma	1 (0.07)
Dog bites	1 (0.07)
Blunt thoracic injuries	1 (0.07)
Shoulder dislocation	1 (0.07)
Ring tourniquet syndrome	1 (0.07)
Scrotal trauma	1 (0.07)
Total	**326 (25)**

Table 3. Causes of ambulance diversions

	n=1,300 (100%)
Unavailability of beds in EDs, intensive care units, inpatient services	**622 (47.8)**
Unavailability of beds in EDs	385 (29.6)
Unavailability of beds in ICUs or lack of ICU	205 (15.7)
Unavailability of beds in inpatient services	32 (2.4)
Unavailability of on-call specialist or a certain clinic with relevant specialization	**290 (22.3)**
Neurologist or neurology department not available	30 (2.3)
Neurosurgeon or neurosurgeon department not available	28 (2.1)
Psychiatrist or psychiatry department not available	16 (1.2)
Cardiologist or cardiology department not available	15 (1.1)
Child neurologist not available	14 (1.0)
Neonatal ICU specialist or neonatal ICU not available	14 (1.0)
Thoracic surgeon specialist or thoracic surgeon department not available	14 (1.09)
Pulmonologist or pulmonary diseases service not available	12 (0.9)
Orthopedist not available	10 (0.7)
Other shortage of on-call specialists[a]	137 (10.5)
Unavailability of imaging devices, laboratory tests or other hospital resources	**176 (13.5)**
Broken status or absence of computed tomography	69 (5.3)
Turning away for multidisciplinary and multidepartmental hospital	40 (3.0)
Patient registration and automatic control systems break down	21 (1.6)
Insufficient other resources[a]	46 (3.5)
Undetermined cause or missing data	**114 (8.7)**
Sociological factors	**62 (4.7)**
Patient's will to be treated in the ED of hospital in which his/her previous treatment was followed	25 (1.9)
Transfer of patient to wrong hospital by ambulance	9 (0.6)
Physical plant breakdown	8 (0.6)
Diversion requested by a patient or family member	7 (0.5)
Insurance issues	6 (0.4)
Admission of two hostile sides in a fight to the same hospital	3 (0.2)
Other social causes[b]	4 (0.3)
Presence of multiple factors such as unavailability of intensive care bed, relevant specialist, laboratory tests or other hospital resources	**26 (2)**
Employment of the required surgeon in another surgical operation caused	**10 (0.7)**

[a]Number of causes less than,

[b]Causes recorded for once.

ICU: Intensive care unit, ED: Emergency department

receiving hospital ED (Table 4). One of the patients died after road accident while the others died from medical conditions.

Five hundred three patients (38.6%) were discharged from the receiving hospital ED and 187 patients (14.3%) were admitted to inpatient clinics of the receiving hospital. Admissions to ICUs were made in 76 patients (5.8%); 54 of those (4.1%) were admitted to ICUs of the receiving hospital while 22 of those (1.6%) were admitted to ICUs of another hospital due to unavailability of ICU bed in the receiving hospital. The disposition of 496 patients (38.1%) in the receiving hospital could not be determined (Table 4). A small portion of ambulances (52 ADs, 4%) were diverted for more than once by hospital EDs.

The most common institutions using AD were Community-General Hospitals (475 ADs, 36.5%) and University Hospitals (371 ADs, 28.5%), respectively. The most common institutions receiving ADs were education and research hospitals (858 ADs, 66%) and university hospitals (207 ADs, 15.9%), respectively (Table 5).

Table 4. The disposition of patients in the receiving hospital

	n=1,300 (100%)
Discharged from the admitting ED	503 (38.6)
Receiving hospital could not be determined	496 (38.1)
Admitted to inpatient clinics of the receiving hospital	187 (14.3)
Admitted to ICUs of the receiving hospital	54 (4.1)
Admitted to ICUs of another hospital due to unavailability of ICU bed	22 (1.6)
Left hospital with refusal of treatment	19 (1.4)
Died in the receiving hospitals and during ambulance transport	15 (1.1)
Transferred to inpatient clinics of other hospitals due to bed unavailability	3 (0.2)
Transferred to the hospital with previous follow-up records	1 (0.07)

ED: Emergency department, ICU: Intensive care unit

Table 5. The institutions using ambulance diversion and the institutions receiving ambulance diversions

	Institutions performing ADs n=1,300 (100%)	Institutions receiving ADs n=1,300 (100%)
Community-general hospitals	475 (36.5)	119 (9.1)
University hospitals	371 (28.5)	207 (15.9)
Private hospitals	227 (17.4)	80 (6.1)
Education and research hospitals	149 (11.4)	858 (66)
Private university hospitals	26 (2)	36 (2.7)
Multiple ADs	52 (4)	

AD: Ambulance diversion

When reports of CEHSC committee assessing appropriate use of ADs were taken into account, 507 ADs (39%) were deemed appropriate while 365 ADs (28%) were deemed inappropriate. Appropriate use could not be determined in 428 ADs (32.9%) due to missing response from hospitals.

DISCUSSION

The number of patients transferred by ambulance in the study period was greater than the number reported in previous studies; however, AD rates were less than those in the literature[1,3,4,9]. Prohibition of AD in Turkey is the main reason for this finding. Although AD is forbidden in Turkey, inadequate hospital resources mandated the use of AD. Furthermore, this appears to reflect serious problems within the hospital system and a failure on the part of local health regulatory agencies to assure access to care as described by law or regulation.

The present study showed that AD was most commonly used in weekends and out of working hours. Similarly, previous studies reported increased use of AD in the evening hours[1,3,4]. The leading cause might be unavailability of many routine health services and on-call specialists in the off-hour time periods.

In consistence with previous reports, the number of patients older than 18 years involved in ADs were greater than the number of pediatric patients[1,4]. Thus, reorganization of EDs providing healthcare service to adult patients might be useful to prevent future ADs.

In countries where AD is legal, eligible conditions and patients for AD are prespecified by AD policies[4,7,10,11]. Since AD is prohibited in Turkey and there is no health policy for AD, patients with conditions such as road accident or pregnancy which should not be diverted (even in countries where AD is legal) underwent AD. It was also noticed that this situation turned out to be a variable practice of AD between hospitals regardless of the magnitude or severity of the injury. An AD policy with a better and clear definition of cases which should not be diverted might be developed.

In consistence with previous AD reports, unavailability of beds in EDs, ICUs and inpatient clinics were detected as the most common cause for AD[3-5,9,12]. Patients have no restrictions for ED admissions in Turkey and each patient in the ED can seek medical care regardless of the ability to pay. Therefore, there is a sheer amount of admissions to EDs resulting in overcrowding. So, adjustments to increase the number of beds in ICUs and inpatient services are needed to prevent overcrowding of ED and also AD.

Death rates were quite lower than the rates reported in previous studies[1,3]. The main underlying reason of this result

might be less diversion of unstable patients and lower AD rates when compared to those in the literature.

In this study, it was noticed that a portion of ambulances encountered multiple diversions in hospital EDs. Previous studies also reported the involvement of more than one hospital in AD period in the same time frame[4]. Selection of the most suitable destination hospital by ambulance crew is a result of lack of a healthy communication among 112 ACCC, ambulance crew and hospital ED directors. Previous studies in the literature pointed out limited coordination among hospital and EMS providers as a contributing factor to diversion problem, thus reconstitution of an effective communication and monitoring infrastructure would establish an effective transport and accurate ED destination of the patient[3,13].

The majority of ADs were made by community-general hospitals in consistence with previous reports[6]. Unavailability of on-call specialists for 24 hours and limited hospital resources in those hospitals might have played a key role in this setting.

When reports of CEHSC committee assessing appropriate use of ADs were taken into account, only 39% of ADs were deemed appropriate. Meanwhile, previous reports defined AD as being supposed to be used in cases of disasters or overcrowding in EDs for ED surge capacity and redistribution of patients among regional EDs in the health service network[2,3]. Besides, it is clear that hospitals receiving AD have the capacity to overcome this extra patient burden. However, the main problem might be related to lack of contact (radio or telephone) between the prehospital personnel and hospital EDs. This is not within the standard for almost all EMS systems. Therefore, we believe that constitution of an AD policy with an effective and controllable coordination among 112 ACCC, EMS crew and hospitals is crucial in patient transportation from scene to the most appropriate destination.

Another specific finding reported in our study is the discrepancy of patients supposed to be admitted in ICUs. A total of 205 ADs were done due to unavailability of ICU beds; however, only 76 patients of those were admitted to ICUs in the receiving hospitals. This finding suggests decreased accuracy rate of triage made by the ED physician who diverted the patient or lower decision threshold for ICU admission ending with AD.

Study Limitations

Although sample size is one of the largest data in this particular topic, retrospective analysis is a limitation. Some of the data including causes of AD, patient outcomes and disposition were missing. Similarly, patient demographics of patients transported by private ambulance services were missing. Besides, limitation of AD interpretation with 1 particular year might have diminished the yielding effect of data.

CONCLUSION

Unavailability of patient beds in EDs, ICUs or inpatient clinics are the most common causes of AD. Therefore, there is an obvious need for more hospital beds. Furthermore, improvement of communication among ACCC, EMS crew and EDs should be targeted for better patient outcomes and optimal management of resources.

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Ethics

Ethics Committee Approval: This study was approved by the Ethical Board of University of Health Sciences Turkey, Ankara Numune Health Training and Research Hospital (Ankara, Turkey; 18.4.2019, decision number: Ethics Committee-19-2669).

Informed Consent: Retrospective study.

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Authorship Contributions

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

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ORIGINAL ARTICLE

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Predictability of Atrial Fibrillation in Patients having Coronary Artery Bypass Graft Surgery, Based on Selvester Score

Selvester Skoruna Göre Koroner Arter Baypas Greft Cerrahisi Geçiren Hastalarda Atriyal Fibrilasyonun Tahmin Edilebilirliği

Dinçer UYSAL[1], Mevlüt Serdar KUYUMCU[2]

[1]Süleyman Demirel University Faculty of Medicine, Department of Cardiovascular Surgery, Isparta, Turkey
[2]Süleyman Demirel University Faculty of Medicine, Department of Cardiology, Isparta, Turkey

ABSTRACT

Aim: Patients having coronary artery bypass graft (CABG) surgery are influenced mostly by atrial fibrillation (AF), with the peak incidence of 16-44%. Due to post-operative AF (POAF), patients may be hospitalized for longer periods, require intensive care unit care again, necessitate more healthcare resources and even undergo congestive heart failure or stroke. Recent studies have shown that the size of the ventricular scar might be used as an indicator in the pathophysiology of AF. Selvester score was developed for the measurement of myocardial scar volume in patients with abnormal ventricular conduction, reporting its prognostic value in AF. Thus, we aim to investigate a likely relationship of POAF and the Selvester scoring system.

Materials and Methods: This retrospective study included 180 patients with CABG from 2017 August to 2018 September. The obtained data had been analyzed in separate cohort of patients with POAF (n=50) and with post-operative sinus rhythm (PSR) (n=130). Intergroup comparisons were made using Selvester scores in particular.

Results: The POAF group had higher Selvester scores (p<0.001), score of SYNTAX (p=0.039), serum high-sensitivity C-reactive protein levels (p=0.026), mean age (p<0.001), hypertrophy of left ventricul (LVH) (p=0.019) and hypertension (p=0.007) and decrased ejection fraction (LVEF) (p<0.001) than the PSR group. Logistic multivariable regression analyses showed that there were an independent association of LVH (p=0.041), LVEF (p=0.004), older age (p=0.008) and higher Selvester score (p<0.001) with POAF.

Conclusion: Higher scores in Selvester scoring system are closely related to POAF, and Selvester score is a potential indicator for POAF.

Keywords: Post-operative atrial fibrillation, Selvester score, coronary artery bypass graft surgery

ÖZ

Amaç: Koroner arter baypas grefti (KABG) ameliyatı geçiren hastalar, %16-44 oranında atriyal fibrilasyondan (AF) etkilenmektedirler. Ameliyat sonrası post-operatif AF (POAF) nedeniyle hastalar daha uzun süre hastanede kalabilir, uzamış yoğun bakım hizmetine ihtiyaç duyabilir, daha fazla sağlık kaynağı harcanmasına yol açabilir ve konjestif kalp yetmezliği veya inme geçirebilirler. Son çalışmalar, ventriküler skar boyutunun AF patofizyolojisinde prediktör olarak kullanılabileceğini göstermiştir. Selvester skoru, anormal ventriküler iletisi olan hastalarda miyokardiyal skar hacminin ölçümü için geliştirilmiş ve AF'de prognostik değerini bildirmiştir. Bu nedenle çalışmamızda, POAF ve Selvester puanlama sisteminin olası bir ilişkisini araştırmayı hedefledik.

Gereç ve Yöntem: Bu retrospektif çalışma, Ağustos 2017'den Eylül 2018'e kadar KABG uygulanan 180 hastayı içermektedir. Elde edilen veriler, post-operatif sinüs ritmi (PSR) (n=130) ve POAF (n=50) olan iki ayrı hasta grubunda analiz edilmiştir. Gruplar arası parametreler ve Selvester puanları kıyaslanmıştır.

Bulgular: POAF grubunda Selvester skoru (p<0,001), SYNTAX skoru (p=0,039), serum yüksek sensitif C-reaktif protein düzeyleri (p=0,026), ortalama yaş (p<0,001), elektrokardiyografik sol ventrikül hipertrofisi (SVH) oranı daha yüksek (p=0,019); hipertansiyon (p=0,007) ve ortalama sol ventrikül ejeksiyon fraksiyonunda (SVEF) PSR grubuna göre daha düşük (p<0,001) saptanmıştır. Çok değişkenli lojistik regresyon analizinde SVEF (p=0,004), SVH (p=0,041), ileri yaş (p=0,008) ve daha yüksek Selvester skoru (p<0,001), POAF için bağımsız risk faktörü olarak saptanmıştır.

Sonuç: Selvester puanlama sistemindeki yüksek puanlar POAF ile yakından ilişkilidir ve Selvester skoru POAF için potansiyel bir gösterge olabilir.

Anahtar Kelimeler: Post-operatif atriyal fibrilasyon, Selvester skoru, koroner arter baypas greft ameliyatı

Address for Correspondence: Dinçer UYSAL MD, Süleyman Demirel University Faculty of Medicine, Department of Cardiovascular Surgery, Isparta, Turkey
E-mail: drdinceruysal@hotmail.com **ORCID ID:** orcid.org/0000-0002-8498-9076
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INTRODUCTION

Patients having coronary artery bypass graft (CABG) surgery are influenced mostly from atrial fibrillation (AF), with the peak incidence of 16-44%[1,2]. Due to post-operative AF (POAF), patients may be longer hospitalized, require intensive care unit again, necessitate more healthcare resources and even undergo congestive heart failure or stroke[3-6]. In order to lower the morbidity and mortality rates from such a frequent complication, preoperative risk factors should essentially be identified along with the development of clinical predictive models and prophylactic strategies[7,8]. In patients under 70 years of age, who undergo CABG, the incidence of AF in the first post-operative year is higher, indicating its association with higher renal dysfunction and infection[9-13].

For cardiac examination, the twelve-lead electrocardiogram (ECG) is commonly used because of its cost-efficiency, non-invasiveness, reproducibility, quickness, and portability. There are several predictors for the prognosis of AF considering abnormalities on ECG including fragmented QRS or bundle branch block and longer duration of QRS[14,15]. The Selvester model became a novel scoring system of QRS in 1980s, consisting of 32 points corresponding to the sections of left ventricular (LV) mass, about 3% each (Figure 1)[16]. Additionally, the Selvester score was developed for measurement of myocardial scar volume in patients with abnormal ventricular conduction, reporting its prognostic value in AF. A research has recently shown that ventricular scar size may have a part in the pathophysiology of AF[17].

In the light of these findings, we aim in this study to investigate a likely association between POAF and Selvester scoring system.

MATERIALS AND METHODS

We first retrospectively evaluated a total of 208 patients with a history of on-pump isolated CABG at Süleyman Demirel University, Faculty of Medicine Research and Training Hospital. The exclusion criteria were identified as several risk factors including chronic obstructive pulmonary disease (n=2), valvular heart diseases (n=5), preoperative AF or flutter (n=8), additional surgical intervention (n=4), renal insufficiency (n=3), preoperative inotropic or mechanical support (n=2), and recurrent surgery or emergency coronary surgery (n=4) considering that these could develop AF.

Hypertension was diagnosed immediately for a patient using anti-hypertensive drugs, or after three different measurements at least for a patient with a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg. Again, for the diagnosis of diabetes mellitus, we considered anti-diabetic medication, or if not, a fasting blood glucose level of ≥126 mg/dL. A patient having used statin three months ago was diagnosed with hyperlipidemia, or for total cholesterol levels of ≥200 mg/dL. Patients who used to smoke were recorded as smokers even if they quitted following hospitalization.

The Local Ethics Committee approved our study protocol Süleyman Demirel University Faculty of Medicine Clinical Research and Ethics Committee (decision date: 22.10.2020, number: 323), and the patients provided written informed consent individually. We designed and conducted this study in accordance with the Declaration of Helsinki, Good Clinical Practice and International Conference on Harmonization guidelines.

Echocardiography

Echocardiography was performed in all patients before surgery. Echocardiographic assessment was performed using a VIVID 7 dimension cardiovascular ultrasound system (Vingmed-General Electric, Horten, Norway) with a 3.5 MHz transducer. The echocardiographic examination was performed in the left lateral decubitus position. Parasternal long- and short-axis views and apical views were used as standard imaging windows. Left ventricular ejection fraction (LVEF) was calculated by using a modified Simpson method. All echocardiographic images were analyzed by an experienced cardiologist.

Lead	Criterion	QRS points
I 2p	Q ≥ 30ms	1
	R/Q ≤ 1	1
	R ≤ 0.2mV	1
II 2p	Q ≥ 40ms	2
	Q ≥ 30ms	1
aVL 2p	Q ≥ 30ms	1
	R/Q ≤ 1	1
aVF 5p	Q ≥ 50ms	3
	Q ≥ 40ms	2
	Q ≥ 30ms	1
	R/Q ≤ 1	2
	R/Q ≤ 2	1
V1 (ant) 1p	Any Q	1
V1 (lat) 4p	R/S ≥ 1	1
	R ≥ 50ms	2
	R ≥ 1mV	2
	R ≥ 40ms	1
	R ≥ 0.6mV	1
	QandSs0.3mV	1
V2 (ant) 1p	Any Q	1
	R < RV1	1
	R ≤ 10ms	1
	R ≤ 0.1mV	1

Lead	Criterion	QRS points
V2 (lat) 4p	R/S ≥ 1.5	1
	R ≥ 60ms	2
	R ≥ 2mV	2
	R ≥ 50ms	1
	R ≥ 1mV	1
	QandS ≤ 0.4mV	1
V3 1p	Any Q	1
	R ≤ 20ms	1
	R ≤ 0.2mV	1
V4 3p	Q ≥ 20ms	1
	R/Q ≤ 0.5	2
	R/S ≤ 0.5	2
	R/Q ≤ 1	1
	R/S ≤ 1	1
	R ≤ 0.7mV	1
V5 3p	Q ≥ 30ms	1
	R/Q ≤ 1	2
	R/S ≤ 1	2
	R/Q ≤ 2	1
	R/S ≤ 2	1
	R ≤ 0.7mV	1
V6 3p	Q ≥ 30ms	1
	R/Q ≤ 1	2
	R/S ≤ 1	2
	R/Q ≤ 3	1
	R/S ≤ 3	1
	R ≤ 0.6mV	1

Figure 1. Selvester score chart

Selvester QRS Score

Prior to hospitalization, twelve-lead ECG records were taken using an electrocardiograph (FCP-7541; Fukuda Denshi Co. Ltd, Tokyo, Japan). The 12-lead ECG was recorded at a paper speed of 50 mm/s in the supine position. All of the ECGs were scanned and transferred to a personal computer to decrease the error measurements, and then used for x400% magnification by Adobe Photoshop software. An average value of three readings was calculated for each lead. An experienced cardiologist manually calculated the 32-point Selvester QRS score, based on an algorithm reported in literature (Figure 1)[18].

Medication, Anesthesia and Surgical Procedure

Acetylsalicylic acid and clopidogrel were routinely discontinued 5 days before the procedure in all patients. Enoxaparin treatment was started instead. Only beta blockers were preoperatively continued even on the morning of surgery. Angiotensin-converting enzyme (ACE) inhibitors were discontinued from preoperative admission to avoid vasoplegic syndrome. Calcium channel blockers were also stopped preoperatively and the beta-blocker was started or the dose was increased according to blood pressure and heart rate. If only with beta-blocker it was normotensive, no other drug was started. With the recommendation of the guidelines, patients were not given statins before the operation. If there was no drainage in the first 6 hours, acetylsalicylic acid was started, and if there was drainage, it was waited for 24 hours. Beta blocker was given as the first dose at 06:00 in the morning after surgery. Statin started after discharge.

A radial artery catheter was inserted to monitor all patients on whom midazolam (0.05-0.1 mg/kg) (Zolamid®; Defarma, Tekirdağ, Turkey) was intravenously administered. We induced anesthesia in the patients, using fentanyl by 1-2 µg/kg (Talinat®; Vem, İstanbul, Turkey) pentothal by 5-7 mg/kg (Pental® Sodium, İstanbul, Turkey) and intravenous rocuronium bromide of 0.6 mg/kg (Curon®, Mustafa Nevzat, İstanbul, Turkey). The Primus® (Draeger Medical, Lübeck, Germany) was utilized to maintain intraoperative mechanical ventilation. Midazolam, fentanyl, and rocuronium were used for the patients to maintain the continuance of anesthesia. We performed standard CABG sternotomy made from medial postion and mild grade hypothermia (32 °C). With the administration of heparin (300 IU/kg), an activated coagulation time higher than 400 sec. was achieved. The CABG was carried out through cannulation of aortovenous with two-stage. We first placed an X-clamp on the ascending aorta and then induced cardiac arrest using cold cardioplegia (10 to 15 mL/kg) and high level of potassium. To maintain arrest of heart, blood cardioplegia had provided every 15 to 20 min. We established CABG with the help of a roller pump with a membrane oxygenator (Maquet, Getinge group, Restalt, Germany) and an arterial line filter at pump flow rates of 2 to 2.4 L/min/m^2. Following the preparation of internal thoracic artery and saphenous vein, we constructed distal anastomoses during a single period of total X-clamp and partially clamped the aorta to establish proximal anastomoses. Hot blood shot cardioplegia was released, and the X-clamp was instantly removed. The patients having undergone cardiovascular surgery were transported to the related intensive care unit. Standard procedure for post-operative care was implemented in each patient. Extubation was performed as soon as hemodynamic stability was observed. For a new onset of AF, the first-choice anti-arrhythmic agent was amiodarone for use in the patient.

Post-operative Atrial Fibrillation Assessment

POAF was defined when AF lasted for at least 30 minutes according to the ECG report[19-21]. The patients were periodically monitored to make an assessment of AF in the first four post-operative days. Subsequently, 12-lead ECG measurement was carried out 3 times a day until discharge. The patients were also monitored for AF with a 12-lead ECG whenever they described palpitations.

Statistical Analysis

Utilizing SPSS for Windows version 21.0 (SPSS, Chicago, IL, USA), the mean, standard deviation, rate, and frequency values were used for the statistical analyses. Number of each group was adjusted as more than 25 patients because we calculated the minimum number of individuals that should be sampled with 90% power and 0.05 type 1 error as at least 46 (R 3.0.1. open source program). The primary effect variable was determined as one point of Selvester score chart. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Parametric data were analyzed with the Student's t-test, and non-parametric data were analyzed with the Mann-Whitney U test. Intergroup comparative analysis was carried out using the chi-square test for categorical variables. Logistic regression model was established to explain the linearity between relevant variables. We used standardized beta coefficients and 95% confidence intervals, and statistical significance was accepted as a p value of <0.05.

RESULTS

The baseline clinical and demographic characteristics of the study population are shown in Table 1. There was no difference between the groups in terms of their body mass index, gender, diabetes mellitus, smoking, peripheral vascular disease and cerebrovascular event history status. The mean age ($p<0.001$) and rate of hypertension ($p=0.007$) were higher in the POAF group. There was no difference in the use of calcium channel blockers ($p=0.168$), beta blockers ($p=0.196$), ACE ($p=0.506$) and anti-aggregates ($p=0.723$), which are potential drugs that can prevent the development of POAF.

Electrocardiographic, echocardiographic and surgical characteristics of the groups are shown in Table 2. The POAF group had significantly higher mean SYNTAX scores (p=0.039) and significantly lower mean LVEF (p<0.001). When the left atrium diameter was examined, the diameter was found to be higher in the POAF group, but not statistically significant (p=0.056), The POAF group had significantly higher frequency of ECG-detected left ventricular hypertrophy (p=0.019) as well as higher mean Selvester score (p<0.001). Normal sinus rhythm was found to be lower in the POAF group. However, it was not statistically significant (p=0.076). When post-operative complications were examined, there was no difference between the groups in terms of pacemaker need (p=0.900), perioperative death (p=0.8282), and ischemic cerebrovascular event (p=0.504). Out of the laboratory parameters, only the high-sensitivity C-reactive protein level had a statistically significant difference between the groups (p=0.026) (Table 3).

The predictors (Table 1-3) of POAF were determined through univariate and multiple linear regression analyses, and the results are shown in Table 4. In the univariate regression analysis, older age [odds ratio (OR): 1.081; 95% confidence interval (CI): 1.040-1.124; p<0.001], hypertension (OR: 3.717; 95% CI: 1.370-10.087; p=0.010), lower LVEF (OR: 0.939; 95% CI: 0.908-0.971; p<0.001), higher high-sensitivity C-reactive protein levels (OR: 1.025; 95% CI: 1.002-1.049; p=0.032), higher Selvester score (OR: 1.524; 95% CI: 1.305-1.780; p<0.001) and left ventricular hypertrophy detected on ECG (OR: 4.295; 95% CI: 1.158-15.934; p=0.029) were significantly associated with POAF. Multiple linear regression analysis demonstrated that older age (OR: 1.068; 95% CI: 1.017-1.122; p=0.008), lower LVEF (OR: 0.939; 95% CI: 0.900-0.981; p=0.004), higher Selvester score (OR: 1.602; 95% CI: 1.337-1.921; p<0.001) and left ventricular hypertrophy detected on ECG (OR: 8.368; 95% CI: 1.657-42.255; p=0.041) were independent predictors of POAF.

There was a statistically significant negative correlation between ejection fraction and Selvester score (p=0.048, r=-0.521).

DISCUSSION

In this study, a high Selvester score was significantly associated with POAF, suggesting that along with classical risk factors such as EF and age, Selvester score may be predictive of POAF. Up to 50% of patients undergoing CABG have post-operative new arrhythmias[22]. The most common arrhythmias after CABG are AF, which is associated with a higher rate of adverse events and cost of care. POAF may occur in between 16% and 25% of patients and is associated with an increased mortality risk, stroke and prolonged hospitalization[23]. In a study carried out with 16,169 patients who were followed up for a mean duration of 6 year, El-Chami et al.[24] reported that the incidence of POAF could predict long-term mortality. Therefore, to ensure favorable outcomes, strategies should be formulated to prevent POAF after cardiac surgery[25].

The strongest predictors for POAF are age, longer ventilation requirement (not less than 24 hours), utilization of cardiopulmonary bypass and preoperative arrhythmias[26,27]. Kalman et al.[28-30] reported that the POAF arm of a study on patients who underwent CABG surgery showed elevated norepinephrine levels, which suggested sympathetic activation.

ECG is essential to detect arrhythmias and ischemic changes. Understanding ischemic changes is important for early detection of cardiac malfunctions. Thanks to the Selvester

Table 1. Baseline characteristics of the study groups

Variables	Post-operative sinus rhythm (n=130)	Post-operative atrial fibrillation (n=50)	p value
Age, years	59.87±12.45	68.10±8.83	**<0.001**
Female, n (%)	41 (31.5%)	10 (20.0%)	0.124
BMI, kg/m^2	29.01±5.35	27.97±4.60	0.227
Diabetes mellitus, n (%)	54 (41.5%)	26 (52.0%)	0.206
Hypertension, n (%)	92 (70.8%)	45 (90.0%)	**0.007**
Smoking, n (%)	43 (33.1%)	23 (46.0%)	0.107
NYHA class	1.31±0.23	1.40±0.31	0.567
Cerebrovascular event history, n (%)	18 (13.8%)	7 (14.0%)	0.979
Peripheral vascular disease, n (%)	13 (10.0%)	5 (10.0%)	0.998
Beta blocker usage, n (%)	118 (90.8%)	42 (84.0%)	0.196
Calcium channel blocker usage, n (%)	22 (16.9%)	13 (26.0%)	0.168
ACE/ARB usage, n (%)	63 (48.5%)	27 (54.0%)	0.506
Acetylsalicylic/clopidogrel usage, n (%)	56 (43.1%)	23 (46.0%)	0.723

Data are given as mean ± SD, n, or median (interquartile range).

BMI: Body mass index, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, SD: Standard deviation

Table 2. Electrocardiographic, echocardiographic and surgical features of the groups

Variables	Post-operative sinus rhythm (n=130)	Post-operative atrial fibrillation (n=50)	p value
In-hospital mortality, n (%)	4 (3.1%)	2 (4.0%)	0.757
SYNTAX score	29.98±8.45	34.74±5.27	**0.039**
Graft number	2.56±0.81	2.74±0.72	0.174
Cardiopulmonary bypass time, minute	78.84±27.41	83.76±34.71	0.321
Aortic cross clamp time, minute	47.61±19.09	46.31±16.86	0.674
Positive inotropic time, hours	23.12±0.49	23.59±0.31	0.768
Aortic balloon pump usage	2 (1.5%)	1 (2.0%)	0.828
Pacemaker usage	3 (2.1%)	1 (2.0%)	0.900
Perioperative death	2 (1.5%)	1 (2.0%)	0.828
Ischemic cerebrovascular accident	1 (0.8%)	1 (2.0%)	0.504
Left ventricular ejection fraction, %	56.54±9.46	49.27±11.94	**<0.001**
Left ventricular diastolic diameter, mm	45.80±5.47	47.29±8.46	0.168
Left ventricular systolic diameter, mm	29.67±6.85	31.42±5.86	0.120
Interventricular septum diameter, mm	11.05±3.24	11.30±3.51	0.652
Posterior wall thickness, mm	10.47±2.28	0.97±2.28	0.590
Left atrial diameter, mm	39.09±6.20	41.26±7.85	0.056
Systolic pulmonary artery pressure, mmHg	26.65±9.08	28.26±6.68	0.257
Selvester score	4.75±2.20	7.36±2.54	**< 0.001**
Normal sinus rhythm	84 (64.6%)	50 (18.2%)	0.072
Left bundle branch block	5 (3.8%)	4 (8.0%)	0.252
Left anterior fascicular block	24 (18.2%)	13 (26.0%)	0.265
Left posterior fascicular block	0	0	-
Right bundle branch block	12 (9.2%)	2 (4.0%)	0.241
Right bundle branch block + left anterior fascicular block	1 (0.8%)	1 (2.0%)	0.480
Left ventricular hypertrophy	4 (3.1%)	6 (12.0%)	**0.019**

Data are given as mean ± SD, n or median (interquartile range).
SD: Standard deviation

Table 3. Laboratory parameters of the study groups

Variables	Post-operative sinus rhythm (n=130)	Post-operative atrial fibrillation (n=50)	p value
Glucose, mg/dL	142.54±67.23	161.46±80.35	0.121
Creatinine, mg/dL	1.09±0.33	1.14±0.29	0.318
WBC, $10^3/mm^3$	8.89±4.27	8.46±2.44	0.419
Hemoglobin, g/dL	13.77±1.85	13.74±1.77	0.922
Platelet, $10^3/mm^3$	232.34±63.08	227.64±72.84	0.669
Hs-CRP, mg/L	6.24±4.85	11.24±7.54	**0.026**
Total cholesterol, mg/dL	196.33±48.11	196.8±45.54	0.798
LDL-C, mg/dL	129.58±51.06	126.26±38.45	0.749
HDL-C, mg/dL	42.14±10.72	41.22±9.45	0.675
Triglyceride, mg/dL	147.30±59.66	150.50±62.10	0.798
Potassium, mmol/L	4.43±0.65	4.57±0.45	0.747
Magnesium, mmol/L	0.81±0.15	0.82±0.21	0.805

Data are given as mean ± SD, n, or median (interquartile range).
HDL: High density lipoprotein, Hs-CRP: High-sensitivity C-reactive protein, LDL: Low-density lipoprotein, WBC: White blood cells, SD: Standard deviation

Table 4. Multivariate logistic regression analysis to predict post-operative atrial fibrillation

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Age	1.081 (1.040-1.124)	**<0.001**	1.068 (1.017-1.122)	**0.008**
Hypertension	3.717 (1.370-10.087)	**0.010**	1.156 (0.970-1.376)	0.064
SYNTAX score	1.290 (1.001-1.579)	0.066	-	-
Left ventricular ejection fraction	0.939 (0.908-0.971)	**<0.001**	0.939 (0.900-0.981)	**0.004**
Hs-CRP, mg/L	1.025 (1.002-1.049)	**0.032**	1.016 (0.983-1.050)	0.341
Selvester score	1.524 (1.305-1.780)	**<0.001**	1.602 (1.337-1.921)	**<0.001**
Left ventricular hypertrophy	4.295 (1.158-15.934)	**0.029**	8.368 (1.657-42.255)	**0.041**

CI: Confidence interval, OR: Odds ratio, Hs-CRP: High-sensitivity C-reactive protein

QRS scoring system, we can place myocardial scar location and detect its size. The highly complex Selvester QRS scoring system was simplified afterwards[31]. This simplified Selvester scoring system is based on the duration of Q and R waves and the ratios of the R/Q and R/S amplitudes in each of 10 leads (I, II, aVL, aVF, and V1-V6). We took the original and developed systems to compare them in terms of the severity of myocardial injury[32]. However, Selvester scoring could not be used in the presence of right or left bundle-branch-block and left anterior fascicular block. In 2009, the new version of the QRS scoring system was published to measure myocardial scar in the presence of particular abnormalities of interventricular conduction. It was shown that the QRS scoring system was usable with any type of ventricular conduction and applicable to patients with both ischemic and non-ischemic cardiomyopathy[33]. Moreover, Rosengarten et al.[34] reported that the QRS scoring was very useful to quantify transmural scar and display its association with medium-term mortality risk.

In "the PRIMERI study", Tiffany Win et al.[35] reported that AF-free patients with structural heart disease (Selvester score ≥5 on ECG) showed abnormal P-terminal force in V1, which was associated with a higher risk of stroke and AF. AF is generally seen more frequently in patient populations with heart failure with a reported incidence rate of 13-27%[36]. Post-myocardial infarction scarring was shown to be a strong predictor of low EF and higher LV volume[37]. Neilan et al.[38] evaluated the effects of myocardial scarring on AF in hypertrophic cardiomyopathy. This pathology is frequently accompanied by scar formation. Analyses of late-gadolinium enhancement cardiovascular magnetic resonance images showed that AF patients had more extensive LV scarring[39]. Therefore, the Selvester scoring algorithm needs to be evaluated for its association with AF. The Selvester score, therefore, may be used to predict the occurrence of post-operative arrhythmias in patients who have had a recent myocardial infarction and have undergone CABG.

The Selvester score shows excellent correlation with ventricular scar tissue size[40]. Several factors like tissue damage and infection, which may cause injury physiologically, stimulate inflammation as a defense mechanism. Damaging stimuli may only be eliminated when inflammation occurs on time and in an adequate intensity. Otherwise, the trigger would be persistent with insufficiency of inflammation as a body response. Tissues may more easily heal when injury can actively induce inflammation resolution. Otherwise, any failure may lead to chronic inflammation and prolong the duration of tissue destruction and progressive fibrosis[41]. More research has reported that inflammation has a role in the pathophysiology of AF, indicating that the inflammatory process may be a potential therapeutic target[42]. Both electrical and structural remodelings of the atria are the primary pathophysiological mechanisms contributing to AF development and progression. Moreover, AF itself may induce inflammation during atrial remodeling, which maintains the arrhythmia-the so-called "AF begets AF" phenomenon[43]. Ventricular inflammatory activity, measured by ^{18}F-fluorodeoxyglucose positron emission tomography, was reported to be higher by 35% in 21 patients with AF in comparison to other 21 matched control cases with no AF[17]. The close relationship between fibrosis and AF may be one of the explanations of why the Selvester score is predictive of POAF.

Study Limitations

In this study, we utilized a cross-sectional design and sampled a relatively small number of cases. Unfortunately, we had no data on major adverse cardiovascular events during the follow-up for the patient population that was studied. Therefore, the results of this study need to be confirmed in multi-center prospective longitudinal studies including a greater sample size. The study had a retrospective design. There were no repetitive Sylvester score measurements. Long-term ECG data of the patients were not available. Echocardiograms were performed by different doctors in patients, and the rate of variation might be high. These limitations could have possibly affected the study results.

CONCLUSION

In this study, the Selvester score was found to be a predictor for POAF. Our study has the potential to predict new risk scores for POAF and be a preliminary step for possible treatments.

Further studies with multi-center prospective longitudinal designs and larger sample sizes may well-establish the potential relationship of POAF and the Selvester scoring system.

Ethics

Ethics Committee Approval: The Local Ethics Committee approved our study protocol Süleyman Demirel University Faculty of Medicine Clinical Research and Ethics Committee (decision date: 22.10.2020, number: 323).

Informed Consent: The patients provided written informed consent individually.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Hematological Side Effects of Valproate Used for the Treatment of Epilepsy

Epilepsi Tedavisinde Kullanılan Valproatın Hematolojik Yan Etkileri

Pınar YILMAZBAŞ[1], Nesrin ŞENBİL[2]

[1]University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital, Clinic of Child Health and Pediatric Diseases, İstanbul, Turkey
[2]Kırıkkale University Faculty of Medicine, Department of Pediatric Neurology, Kırıkkale, Turkey

ABSTRACT

Aim: Valproate is a commonly used antiepileptic drug with hematologic and non-hematologic side effects at therapeutic doses. The aim of this study was to investigate the relationship between the known hematological side effects of valproate and duration, dose and serum levels of this drug.

Materials and Methods: The study population consisted of patients with epilepsy followed by pediatric neurology outpatient clinic, who had been using valproate for at least 3 months. Duration of treatment, valproate doses, hemogram and serum valproate levels of patients were recorded from their files. Patients with other systemic and/or hematological diseases and those who were taking drugs other than valproate were not included in the study.

Results: Serum valproate levels and complete blood count results were obtained in 80 of 112 patients who met the criteria. Thirty of them (37.5%) were female. The mean age was 8.2±4.8 years (1-16 years) and the mean duration of treatment was 19.93±16.4 months (3 months-10 years). Valproate use dose ranged from 20 to 60 mg/kg day. At least one hematologic side effect was detected in 34 (42%) patients. These side effects were macrocytosis (18.7%), thrombocytopenia (17.5%), leukopenia (12.5%) and anemia (7.5%). There was no correlation between thrombocytopenia and valproate using time, but a significant correlation was found between dose and serum levels. There was a relationship between macrocytosis and serum valproate level only. No correlation was found between leukopenia and anemia and duration of treatment, dose and serum levels.

Conclusion: Hematological side effects of valproate used in the treatment of epilepsy are not uncommon, and these side effects are unpredictable. Therefore, it was concluded that complete blood counts should be sufficient in the follow-up of the patients and families should be informed about the side effects.

Keywords: Valproate, epilepsy, thrombocytopenia, anemia

ÖZ

Amaç: Valproat yaygın olarak kullanılan, tedavi dozlarında hematolojik ve hematolojik olmayan yan etkilere sahip antiepileptik bir ilaçtır. Bu çalışmada; tedavi dozunda kullanılan valproatın bilinen hematolojik yan etkilerinin (trombositopeni, lökopeni, anemi, makrositoz) ilaç kullanım süresi, dozu ve serum seviyesi ile ilişkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Çocuk nöroloji polikliniği tarafından epilepsi tanısı ile takip edilen ve en az 3 aydır valproat kullanmakta olan hastalar çalışma evrenini oluşturmuştur. Hastaların tedavi alma süreleri, kullandıkları valproat dozları, tam kan sayımı ve serum valproat düzeyleri dosyalarından kaydedilmiştir. Valproat dışında ilaç kullanan, başka bir sistemik ve/veya hematolojik hastalığı olan hastalar çalışmaya dahil edilmemiştir.

Bulgular: Çalışma kriterlerini karşılayan 112 hastadan 80'inin serum valproat düzeyi ve hemogram sonuçlarına ulaşılabildi. Hastaların 30'u (%37,5) kız idi. Yaş ortalamaları 8,2±4,8 yıl (1-16 yıl), tedavi süreleri ortalaması 19,93±16,4 ay (3 ay-10 yıl) idi. Valproat kullanım dozu 20-60 mg/kg/gün arasında değişmekte idi. Hastaların 34'ünde (%42) en az bir hematolojik yan etki geliştiği saptandı. Bu yan etkiler makrositoz (%18,7), trombositopeni (%17,5), lökopeni (%12,5) ve anemi (%7,5) idi. Trombositopeni ile valproat kullanım süresi arasında ilişki yok iken, ilaç kullanım dozu ve serum seviyesi ile anlamlı ilişki saptandı. Makrositoz ile sadece serum valproat seviyesi arasında ilişki saptandı. Lökopeni ve anemi ile valproat kullanım süresi, dozu ve serum seviyesi arasında ilişki saptanmadı.

Sonuç: Epilepsi tedavisinde kullanılan valproatın hematolojik yan etkilerinin nadir olmadığı, bu yan etkilerin önceden tahmin edilemeyeceği görülmektedir. Bu nedenle hastaların takibinde tam kan sayımının değerlendirilmesinin yeterli olacağı ve yan etkiler açısından ailelerin bilgilendirilmesi gerektiği sonucuna varılmıştır.

Anahtar Kelimeler: Valproat, epilepsi, trombositopeni, anemi

Address for Correspondence: Pınar YILMAZBAŞ MD, University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital, Clinic of Child Health and Pediatric Diseases, İstanbul, Turkey
E-mail: drpinary@yahoo.com **ORCID ID:** orcid.org/0000-0002-1283-1712
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INTRODUCTION

Valproate is an antiepileptic drug that is frequently used and effective in many seizure types[1]. Hematological and non-hematological side effects are observed in the treatment doses of valproate[2]. Hematological side effects include thrombocytopenia, leukopenia, anemia, bone marrow suppression, macrocytosis, prolonged bleeding time, platelet dysfunction, hypofibrinogenenia, factor XIII deficiency, myelodysplastic syndrome and increased hemoglobin (Hb) F levels[3,4]. Thrombocytopenia is the most common hematological side effect, usually dose dependent and transient. There is a correlation between high valproate plasma levels and thrombocytopenia. Thrombocytopenia begins to resolve within a few days with dose reduction[5]. In different studies, the incidence of thrombocytopenia due to valproate has been reported to be between 5% and 40%[5-8]. Macrocytosis is a side effect that can be seen in those receiving valproate therapy and is thought to be not dose dependent. Recovery of macrocytosis may take months after drug discontinuation[9,10]. In addition, valproate can cause bone marrow depression and myelodysplasia, affecting a single cell or whole cell series. The suppressive effect of valproate on the bone marrow regresses with the withdrawal of the drug, but supportive treatment may be required during the recovery period[11,12]. Transient leukopenia can be seen during valproate therapy and has been shown to develop at a rate of 15-26% in studies[10,13].

In this study, we aimed to investigate the relationship between the dose, serum level and duration of use of valproate and hematological side effects.

MATERIALS AND METHODS

Our study is a retrospective study. Patients who were diagnosed with epilepsy by the Pediatric Neurology Outpatient Clinic of Dr. Sami Ulus Child Health and Diseases Training and Research Hospital and who had been using valproate for at least 3 months constituted the study population.

Valproate usage doses, duration of treatment, Hb level, white blood cell count, platelet count, mean corpuscular volume (MCV) and serum valproate levels were recorded from the patients' files. Patients who used drugs other than valproate and had any other systemic and/or hematological diseases were not included in the study. The lower bound for platelet count was taken as 150,000/mm^3, normal Hb values were accepted as 10.5-15 g/dL, white blood cell counts between 5,100 and 15,000 cells/uL and MCV counts between 76 and 90.1 micro mm^3 values were considered as normal.

The follow-up of the hematological values (thrombocytopenia, anemia, macrocytosis, leukopenia) at the pathological margin and the times to return to normal were recorded from the patients' files. Our study was carried out according to the Declaration of Helsinki protocol. This study is the article of pediatrics speciality thesis, and it was made with the necessary permission taken from the Education Planning Board in November 2003 (10.021.2003). The relationship between the duration of valproate use, the dose of valproate and serum valproate levels of the patients and thrombocytopenia, anemia, leukopenia and macrocytosis were investigated.

Statistical Analysis

IBM SPSS Statistics 12 for statistical analysis (SPSS IBM, Turkey) program was used for evaluating the data obtained in the study. The Mann-Whitney U test was used to investigate the relationship between valproate duration, dose, serum level and anemia, leukopenia, thrombocytopenia and macrocytosis, and $p<0.05$ values were considered as statistically significant. Non-parametric tests were used for age and gender.

RESULTS

Of 112 patients meeting the study criteria, 80 patients who used only valproate as treatment and whose serum valproate level and hemogram results could be obtained were included in the study.

Thirty (37.5%) of the patients were girls. The mean age was 8.2±4.8 years (1-16 years), the mean duration of treatment was 19.93±16.4 months (3 months-10 years). Valproate usage dose varied between 20 and 60 mg/kg/day. Serum valproate levels of patients varied between 33 and 194 µ/mL. Normal valproate serum levels were between 50 and 100 µ/mL, 6 patients' serum valproate levels were under normal. Five patients' serum valproate levels were above normal, two of which were very high as 187 and 194 µ/mL.

At least one hematological side effect was found in 34 (42%) of the patients. These side effects were macrocytosis (18.7%), thrombocytopenia (17.5%), leukopenia (12.5%) and anemia (7.5%). Thrombocytopenia was detected in 14 (17.5%) of the patients. While there was no relationship between thrombocytopenia and the duration of valproate use, a significant relationship was found with the usage dose, serum valproate level and thrombocytopenia (Table 1).

Fifteen (18.7%) of the patients had macrocytosis and a relationship was found between macrocytosis and only serum valproate level (Table 2).

Leukopenia (12%) was found in 10 patients and anemia (7.5%) in 6 patients. No relationship was found between leukopenia and anemia and the duration, dose, and serum level of valproate.

DISCUSSION

In this study, it was found that at least one hematological side effect developed in 42% of 80 patients who used valproate as a single antiepileptic drug, and hematological side effects related to valproate were not uncommon. On the other hand, it was observed that these side effects did not cause serious clinical problems. Consistent with other studies, the most common hematological side effect was macrocytosis[10,14]. A significant relationship was found between macrocytosis and serum valproate level, but the dose was not decreased due to macrocytosis. Thrombocytopenia, the second most common side effect, was detected at a rate of 17.5%, and the lowest platelet count was measured as 33,000/mm^3. None of the patients with thrombocytopenia developed bleeding diathesis and no platelet suspension was required. The dose of valproate was found to be very high in 2 of the patients (194 and 187 µ/mL) and the treatment of these patients was continued with another drug apart from valproate. Twenty percent reduction was made in the treatment doses of the other 12 patients.

It was observed that the platelet counts returned to normal 1 week later in 7 patients, 2 weeks later in 5 patients. Since there was no seizure recurrence in patients with reduced valproate doses, their treatment was continued with reduced doses. Since there is no relationship between thrombocytopenia and the duration of treatment, it seems that patients can develop at any time during treatment and this cannot be predicted. Consistent with other studies, a significant relationship was found between valproate dose and serum level and thrombocytopenia[8,10,15].

In patients with leukopenia, this side effect was observed to be independent of the duration of treatment, dose and serum level. It has been shown in previous studies that leukopenia is transient[15,16]. In our patients, leukopenia was not found to be life threatening, and the drug dose of the patients was not changed. The patients were followed up until the white blood cell count increased and the leukopenia was found to be transient.

Anemia developing due to valproate, occurs due to the toxic effect of valproate on DNA metabolism and cannot be predicted as stated in previous studies[13,17,18]. In our study, no relationship was found between anemia and the duration, dose and serum level of valproate. However, a patient who developed deep anemia was hospitalized for supportive treatment and her treatment was changed with another antiepileptic drug.

There is no consensus on the path to follow when hematological side effects develop during the use of valproate. General approach is to make small reductions (10-25%) in treatment doses when thrombocytopenia develops, to continue at the same dose if the seizure is under control, and if there is no seizure control, to increase the dose gradually[10]. In patients with severe anemia, close follow-up of the patient, and if there is bone marrow suppression, continuing treatment with another drug is recommended. Dose reduction was sufficient when thrombocytopenia developed in our patients. In one patient who developed deep bone marrow suppression, treatment was continued with another antiepileptic.

There are different opinions about how often the patients should be tested during valproate treatment[10,19,20]. Since the hematological side effects cannot be predicted during valproate treatment, we think that it is important to follow up the patients and to inform families about the side effects of valproate, especially considering that there may be patients with mental motor retardation. It is thought that contacting the doctor may prevent the development of life-threatening complications when these side effects develop.

Study Limitations

Our study was a retrospective study and we could not investigate all hematological side effects like platelet

Table 1. Relationship between platelet count and valproate dose, duration, serum level

	Number of patients	Average duration of valproate usage (months)	Valroate dose (mg/kg/day)	Valproate serum level (µ/mL)
Platelet count <150,000/mm^3	14	20.6	29.6	99.3
Platelet count >150,000/mm^3	66	19.8	22.5	65.9
p	-	0.176	<0.001	<0.001

Table 2. Relationship between macrocytosis and valproate dose, duration, serum level

	Number of patients	Average duration of valproate usage (months)	Valproate dose (mg/kg/day)	Valproate serum level (µ/mL)
MCV <90 micro mm^3	65	19.7	23.8	67
MCV >90 micro mm^3	15	21	23.7	92.4
p	-	0.532	0.587	<0.001

MCV: Mean corpuscular volume

dysfunction, hypofibrinogenenia, and factor XIII deficiency, which was a limitation.

CONCLUSION

It is seen that the hematological side effects of valproate used in the treatment of epilepsy are not uncommon and these side effects cannot be predicted. Therefore, evaluation of complete blood count would be sufficient in the follow-up of these patients, and families should be informed about the side effects.

Ethics

Ethics Committee Approval: The study was the Pediatrics Speciality Thesis of Pınar Yılmazbaş and was approved by Dr. Sami Ulus Obstetrics and Gynecology, Child Health and Diseases Training and Research Hospital (73799008-799).

Informed Consent: Consent form was filled out by all participants.

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Authorship Contributions

Surgical and Medical Practices: N.Ş., P.Y., Concept: P.Y., N.Ş., Design: P.Y., N.Ş., Data Collection or Processing: P.Y., Analysis or Interpretation: P.Y., Literature Search: N.Ş., P.Y., Writing: P.Y.

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Evaluation of the Effectiveness of Physical Therapy in Patients with Chronic Cervical Disc Hernia Associated with Fibromyalgia

Fibromiyaljinin Eşlik Ettiği Kronik Servikal Disk Hernisi Tanısı Alan Hastalarda Fizik Tedavi Etkinliğinin Araştırılması

Fatma USTABAŞIOĞLU

Edirne Sultan 1st Murat State Hospital, Clinic of Physical Medicine and Rehabilitation, Edirne, Turkey

ABSTRACT

Aim: Fibromyalgia is a disease that is characterized by chronic widespread musculoskeletal pain, sleep disorders, fatigue and decreased pain threshold. The purpose of our study was to investigate the effect of physiotherapy on pain, depression and neck functions in patients with chronic cervical disc hernia accompanied by fibromyalgia.

Materials and Methods: In total, 20 chronic cervical disc hernia patients who were diagnosed with fibromyalgia according to the 2010 American College of Rheumatology diagnostic criteria and 20 chronic cervical disc hernia patients without fibromyalgia were included in our study. Visual analogue scale (VAS), Beck depression inventory (BDI), and neck disability index (NDI) were performed to evaluate pain, depression and neck functions respectively. Patients were evaluated before therapy, immediately after therapy, and at 1-month control follow-up.

Results: In both groups, VAS, BDI and NDI scores were significantly decreased in the period after therapy and at 1-month control follow-up compared to the pre-treatment period. No statistical difference was observed between two groups in terms of VAS, BDI and NDI scores before and after treatment. However, we found that VAS, BDI and NDI scores of cervical disc hernia patients with fibromyalgia were significantly higher than cervical disc hernia patients without fibromyalgia before treatment, after treatment and at 1-month control follow-up.

Conclusion: We demonstrated that the effect of physical therapy on pain, depression, and neck function was the same in the group with fibromyalgia compared to the group without fibromyalgia.

Keywords: Fibromyalgia, cervical pain, depression

ÖZ

Amaç: Fibromiyalji kronik yaygın kas-iskelet ağrısı, uyku bozuklukları, yorgunluk ve ağrı eşiğinin azalması ile karakterize bir hastalıktır. Çalışmamızın amacı, fibromiyaljinin eşlik ettiği kronik servikal disk hernisi olan hastalarda fizik tedavinin ağrı, depresyon ve boyun fonksiyonları üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Çalışmamıza 2010 Amerikan Romatoloji Derneği tanı kriterlerine göre fibromiyalji tanısı alan 20 kronik servikal disk herni hastası ve fibromiyaljisi olmayan 20 kronik servikal disk herni hastası dahil edildi. Ağrı, depresyon ve boyun fonksiyonlarını değerlendirmek için sırasıyla görsel analog skalası (VAS), Beck depresyon ölçeği (BDÖ), boyun özürlülük indeksi (BÖİ) yapıldı. Hastalar bu veriler için tedavi öncesi, tedavinin hemen sonrası ve 1. ay kontrolü olmak üzere 3 kez değerlendirildi.

Bulgular: Her iki grupta da VAS, BDÖ ve BÖİ skorları tedavi sonrası dönemde ve 1 aylık kontrolde, tedavi öncesi döneme göre anlamlı derecede azaldı. Tedavi öncesi ve sonrası iki grup arasında VAS, BDÖ ve BÖİ skorları açısından istatistiksel bir fark gözlenmedi. Bununla birlikte, fibromiyaljisi olan servikal disk hernili hastaların VAS, BDÖ ve BÖİ skorlarının tedaviden önce, tedaviden sonra ve 1 aylık kontrolde fibromiyaljisi olmayan servikal disk hernisi olan hastalardan anlamlı derecede yüksek olduğu saptandı.

Sonuç: Fibromiyaljili grupta fizik tedavinin ağrı, depresyon ve boyun fonksiyonu üzerindeki etkisinin fibromiyaljisi olmayan gruba göre aynı olduğu bulundu.

Anahtar Kelimeler: Fibromiyalji, servikal ağrı, depresyon

Address for Correspondence: Fatma USTABAŞIOĞLU MD, Edirne Sultan 1st Murat State Hospital, Clinic of Physical Medicine and Rehabilitation, Edirne, Turkey
Phone: +90 284 214 55 18 **E-mail:** fatmaustabasioglu@gmail.com **ORCID ID:** orcid.org/0000-0003-2049-3650
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INTRODUCTION

Fibromyalgia is a common chronic pain disorder and its cardinal features are generalized body pain and diffuse hyperalgesia. Fibromyalgia patients also commonly present a range of other problems, including persistent fatigue, dysregulated sleep, cognitive dysfunction, functional bowel disorder, paresthesias and mood disturbance[1].

Fibromyalgia is diagnosed clinically and there are no specific laboratory tests or radiological abnormalities for diagnosis. Diagnosis is established based on a common pain index and symptom score according to the 2010 American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia[2].

Cervical radiculopathy is a pathological process involving the neural root of the cervical spine, meaning paresthesia or numbness in a particular distribution of the nerve root and neck pain that includes girdle of the shoulder and/or arm pain[3-5]. Cervical disc herniation (CDH) is the most common cause of this process[4]. CDH can cause chronic neck pain and pain radiating to the arm, and may be associated with fibromyalgia.

Our objective in this study was to compare the differences in the functions of pain, depression and neck movement after physical therapy between the patients with chronic CDH accompanied by fibromyalgia and patients with chronic CDH not accompanied by fibromyalgia.

MATERIALS AND METHODS

Our study was conducted at İstanbul Training and Research Hospital Physical Medicine and Rehabilitation between June 2012 and July 2013. The Local Ethics Committee of İstanbul Training and Research Hospital approved the study protocol (approval no: 272, date: 07.06.2013). A written informed consent was obtained from each participant.

Patient Selection

Fourty patients (women) between the ages of 23 and 65 years, who were referred to the physical therapy unit after diagnosing chronic CDH, were included in our study. Patients were divided into two groups. The first group was formed with 20 patients who were diagnosed with fibromyalgia according to the 2010 ACR diagnostic criteria. The second group was formed as a control group with 20 patients without fibromyalgia. Patients with a history of cervical disc hernia operation were not included.

Method

The records of patients included in the study were analyzed retrospectively. In order to evaluate the treatments applied to the patients included in the research; visual analogue scale (VAS), Beck depression inventory (BDI), and neck disability index (NDI) measurements were used.

Patients were evaluated for three times in total: Pre-treatment, immediately after therapy and at the 1st month control follow-up.

Treatment

Hot pack (HP) was applied to both groups as a superficial heating agent for 20 minutes. Transcutaneous electrical neural stimulation (TENS) was applied as an electrotherapy agent. Conventional TENS were applied with a frequency of 100 Hz, 60 µsec current, 7x9 cm sized plate electrodes were used, and the application was made for 30 minutes. Electrodes were placed at the point or area where pain was felt and fixed with velcro.

Ultrasonography was applied for 8 minutes. Application Ati Medical Equipment C-Soundmaster GU-001 ultrasound device was applied with a soundhead of 5 cm^2 at a frequency of 1 MHz. Dosage was determined as 1-1.5 watts/cm^2 considering the width of the area to be treated. The application was carried out by moving the ultrasonography probe circular.

Neck isometric exercises and stretching exercises were included in the patients' exercise program, and the training of these exercises was given to the patients one to one. Patients were asked to do these exercises twice a day.

The treatment was arranged as 10 sessions within two weeks. Sessions continued for 5 days a week. The patients were evaluated for three times with the evaluation parameters mentioned above; before the first session, after the 10th session and at 1st month after the treatment.

Statistical Analysis

While evaluating the findings of the study, SPSS version 16 (Chicago, IL) was used for statistical analysis. Data were summarized as mean±standard deviation for continuous variables. Distribution of variables was measured by the Kolmogorov Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative data. The Wilcoxon test was used to analyze the measurements. In the analysis of qualitative data, the chi-square test was used, and when the chi-square test conditions were not met, the Fisher exact was used. Significance was evaluated at the level of $p<0.05$.

RESULTS

All 40 patients included in the study were women. The mean age of the group with fibromyalgia was 47.8 (range, 23-65) years and the mean age of the other group was 49.2 (range, 30-65) years. There was no significant difference ($p>0.05$) between the ages and occupations of the patients in both groups.

In both groups, VAS score was significantly lower (p<0.05) after the treatment and in the control period, compared to that before the treatment (Table 1). Compared to the pre-treatment period, the decrease in VAS score in the post-treatment and control periods did not differ significantly between the two groups (p>0.05). In the group with fibromyalgia, the VAS score in the pre-treatment, post-treatment and control period was significantly higher than in the group without fibromyalgia (p<0.05).

In both groups, BDI score was significantly lower (p<0.05) in the post-treatment and control period than in the pre-treatment period (Table 2). The decrease in BDI score in the post-treatment and control periods compared to the pre-treatment period did not differ significantly between the two groups (p>0.05). In the group with fibromyalgia, the BDI score before treatment, after treatment and in the control period was significantly higher than in the group without fibromyalgia (p<0.05).

Table 1. The change in visual analogue scale values of the patients before treatment. immediately after treatment and in the control period

	Without fibromyalgia mean ± SD median (min.-max.)			With fibromyalgia p value mean ± SD median (min.-max.)			
VAS							
Before treatment	6.6±2.0	7	2-9	8.7±1.09	-	7-10	**0.001[m]**
After treatment	3.3±2.4	3	0-9	5.6±1.85	-	1-8	**0.002[m]**
Control	3.1±2.7	2	0-8	4.6±3.04	-	0-9	**0.044[m]**
Change of before/after treatment	-3.3±2.3	-3	-8-0	-3.1±2.1	-3	-8-0	0.869[m]
Change p	**0.000[w]**	**-**	**-**	**0.000[w]**	**-**	**-**	**-**
Change of before treatment/control	**33.5±2.5**	**-3**	**-8-1**	**-4.1±3.4**	**-5**	**-10-1**	**0.653[m]**
Change p	**0.000[w]**			**0.000[w]**			

[m]: Mann-Whitney U test, [w]: Wilcoxon test, VAS: Visual analogue scale, SD: Standard deviation, min.: Minimum, max.: Maximum

Table 2. The change in the Back depression score values of the patients before treatment, immediately after treatment and in the control period

	Without fibromyalgia mean ± SD median (min.-max.)			With fibromyalgia p value mean ± SD median (min.-max.)			
Beck depression score							
Before treatment	13.8±7.8	16	0-28	20.8±11.2	21	5-60	**0.031[m]**
After treatment	10.4±7.9	11	0-25	16.4±12.6	14	2-60	**0.038[m]**
Control	9.6±8.0	11	0-25	14.9±12.9	14	0-60	**0.047[m]**
Change of before/after treatment	-3.4±5.3	-3	-16-6	-4.4±4.7	-4	-14-4	0.431[m]
Change p	**0.010[w]**	-	-	0.001[w]	-	-	-
Change of before treatment/control	**-4.3±6.5**	**-3**	**-21-5**	**-5.9±6.3**	**-4**	**-19-3**	**0.363[m]**
Change p	**0.006[w]**			**0.001[w]**			

[m]: Mann-Whitney U test, [w]: Wilcoxon test, SD: Standard deviation, min.: Minimum, max.: Maximum

Table 3. The change in the Neck disability score values of the patients before treatment, immediately after treatment and in the control period

	Without fibromyalgia mean ± SD median (min.-max.)			With fibromyalgia p value mean ± SD median (min.-max.)			
Neck disability score							
Before treatment	13.8±4.1	14	8-22	20.3±4.5	19	14-28	**0.000[m]**
After treatment	8.8±5.7	8	1-21	16.1±6.4	14	4-28	**0.000[m]**
Control	8.2±5.8	8	0-21	14.9±8.8	14	3-30	**0.015[m]**
Change of before/after treatment	-5.0±5.2	-5	-17-3	-4.2±4.2	-4	-12-4	0.714[m]
Change p	0.001[w]	-	-	0.001[w]	-	-	-
Change of before treatment/control	**-5.6±6.7**	**-5**	**-16-11**	**-5.4±6.6**	**-6**	**-16-6**	**0.871[m]**
Change p	**0.002[w]**			**0.005[w]**			

[m]: Mann-Whitney U test, [w]: Wilcoxon test, SD: Standard deviation, min.: Minimum, max.: Maximum

In both groups, the NDI score after treatment and in the control period was significantly lower ($p<0.05$) than before treatment (Table 3). The decrease in NDI score after treatment and in the control period compared to the pre-treatment did not differ significantly between the two groups ($p>0.05$). In the group with fibromyalgia, NDI score was significantly higher before the treatment, after the treatment and in the control period than in the group without fibromyalgia ($p<0.05$).

DISCUSSION

Fibromyalgia is a disease characterized by chronic widespread pain with additional symptoms, such as joint stiffness, fatigue, sleep disturbance, cognitive dysfunction, and depression[6]. Since there were no specific laboratory and imaging findings for the diagnosis, ACR published diagnostic criteria in 2010. These diagnostic criteria are based on questioning regional pain points and somatic symptoms.

CDH can cause chronic neck and arm pain, it may also be associated with fibromyalgia. The prevalence of fibromyalgia in patients with CDH in a pilot study conducted in Turkey was found to be higher than in the normal population[7].

In the literature, fibromyalgia is more common between the ages of 35 and 50 years[8]. The ages of the patients in our study are consistent with the literature. 92% of the patients in a study conducted by Castro-Sanchez et al.[9], 97% of the patients in a study carried out by Jones et al.[10] and 96% of the patients in another study conducted by Romeyke et al.[11] were female patients. In our study, since fibromyalgia was more common in women, we created the patient group only from female patients.

In our study, HP, TENS and US were applied to our patients as physical therapy agents. There are not many studies on the effectiveness of US in fibromyalgia in the literature, but positive results in fibromyalgia have been reported in studies conducted in our country[12].

In the study conducted by Carbonario et al.[13], 28 patients with fibromyalgia were divided into two groups and the first group was given TENS treatment; TENS treatment was not given to the second group. The same protocol was applied to both groups. Initially, it was stated that while both groups had the same VAS, tender point index, and fibromyalgia effect questionnaire, there was more improvement in the group receiving TENS after the treatment[13].

In the study conducted by Dailey et al.[14], patients with fibromyalgia were divided into three groups, the first group was given TENS and the second group was given placebo TENS. TENS was not applied to the third group. As a result, the VAS values in the movement of the group receiving active TENS decreased significantly compared to the others[14]. In our study, after applying physical therapy agents, the VAS, BDI and NDI values of both groups improved compared to the pre-treatment period. However, the change in VAS, BDI and NDI scores evaluated between the two groups before and after the treatment and in the control period did not differ.

In the study of Bello et al.[15], VAS score was higher in patients with spondyloarthritis accompanied by fibromyalgia than in patients with isolated spondyloarthritis. In a study by Lage-Hansen et al.[16] and also in another study by Levy et al.[17], if patients with rheumatoid arthritis were accompanied by fibromyalgia, their VAS values were higher than those who were not. In this study, we found that VAS values were higher in patients with CDH if fibromyalgia was accompanied by the other group. Even though no significant difference was found between the two groups in the reduction of VAS values after treatment, VAS values were higher in the CDH fibromyalgia group prior to treatment, post-treatment and during the control period. This suggests that when chronic pain is added to fibromyalgia, the severity of pain increases. However, the effectiveness of the treatment is the same as those without fibromyalgia.

In our study, NDI was found to be lower in both groups after treatment and in the control period than before treatment. In the fibromyalgia group, NDI was higher than in the non-fibromyalgia group in all periods. This clearly shows that when neck pain is treated in CDH patients with fibromyalgia, it cannot reach the same level as CDH patients without fibromyalgia, even if the neck functions improve. As a result, fibromyalgia patients need additional treatments, such as medical therapy, cognitive-behavioral therapy, and exercise.

There are many studies in the literature that state that fibromyalgia is associated with mood disorders. A study indicates that depression is a condition that accompanies fibromyalgia and it affect disability and quality of life very much in these patients[18]. Another study has noted that even if the risk of major depressive disorder is about three times higher in women with fibromyalgia than in healthy women, the lifetime risk of major depressive disorder is similar. In addition, it has been suggested that the relationship between major depressive disorder and fibromyalgia is more complex than expected and it indicates that high attention should be paid to depression accompanied by fibromyalgia[19]. Another study has reported that depression is the most common psychiatric disorder in fibromyalgia patients[20]. In a study by Gowans et al.[21] the BDI mean of fibromyalgia patients was reported as 20.6 ± 3.1[21]. In our study, the BDI mean was 20.8 ± 11.8, which was consistent with the literature. After treatment, there was a significant decrease in BDI in both groups, but there was no significant difference between the groups. However, in the CDH group with fibromyalgia, the BDI score was significantly

higher than in the group without fibromyalgia. This shows that the degree of depression increases when accompanied by fibromyalgia. On the other hand, after the physical therapy, the improvement in the degree of depression is similar in the two groups.

Study Limitations

Our study has some limitations. The first is that the number of patients was low. Secondly, the medical treatments of the patients were not taken into account while designing the study. This may be seen as an important deficiency of our study, especially since the use of drugs in fibromyalgia may affect the outcome of treatment.

CONCLUSION

As a result, we found that the effect of physical therapy on pain, depression and neck functions did not change in patients with CDH when fibromyalgia was accompanied. Improvement in patients with fibromyalgia after treatment was similar to that in patients without fibromyalgia. The only difference was that patients with CDH and fibromyalgia had worse pain, depression, and neck functions before, during and after treatment. From this point of view, while fibromyalgia patients benefit from treatment for CDH, we can conclude that they need additional treatment to reach the same level as patients without fibromyalgia. However, studies with more cases are needed to investigate the effects of fibromyalgia.

Ethics

Ethics Committee Approval: The Local Ethics Committee of İstanbul Training and Research Hospital approved the study protocol (approval no: 272, date: 07.06.2013).

Informed Consent: A written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

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The Preparation of Dye-Acrylamide/Itaconic Acid Gel Dosimeters for Process Validation of Medical Device Sterilization

Tıbbi Cihazların Sterilizasyonunun Proses Validasyonu için Hazırlanan Boya-Akrilamid/İtakonik Asit Jel Dozimetresi

Betül TAŞDELEN, Sarkis SÖZKES

Tekirdağ Namık Kemal University, Çorlu Faculty of Engineering, Department of Biomedical Engineering, Tekirdağ, Turkey

ABSTRACT

Aim: In this study, a new polymer gel dosimeter (PGD) was prepared using gamma rays for process validation of medical device sterilization. New polymeric systems were studied, consisting of itaconic acid, acrylamide, gelatin, different dyes [methylene blue, methyl orange and crystal violet (CV)] and N,N'-methylenebisacrylamide, with ascorbic acid as an oxygen scavenger.

Materials and Methods: The study investigated the effect of the different dyes in the newly prepared PGD dosimeter formulations on the dose rate constants and radiation chemical yields in the high dosage ranging from 7 to 28 kGy-typical for the sterilization of many medical devices, pharmaceutical products and biological tissue-by using a ultraviolet-visible spectrophotometer method.

Results: The sample spectrums of the prepared PGD dosimeters underwent a change following gamma irradiation, and bleaching of the blue gel color increased with the radiation dose. Even at the sterilization dose for medical devices (25 kGy), the dark blue color of the non-irradiated CV-PGD became almost colorless. The response of non-irradiated and irradiated PGD dosimeters remained stable during a storage period of 60 days.

Conclusion: The prepared dye-PGD dosimeters are therefore suitable for use in monitoring various high dose radiation-processing applications, which can be useful for many medical devices and healthcare products.

Keywords: Dosimeter, gamma ray, radiation, sterilization

ÖZ

Amaç: Bu çalışmada tıbbi cihazların sterilizasyonunun proses validasyonu için kullanılacak yeni bir polimer jel dozimetre (PGD), gama ışınları kullanılarak hazırlanmıştır. İtakonik asit, akrilamid, jelatin, farklı boyalar [metilen mavisi, metil turuncusu ve kristal mor (KM)] ve oksijen tutucu olarak N, N'-metilenbisakrilamid ve askorbik asitten oluşan yeni polimerik sistemler üzerinde çalışılmıştır.

Gereç ve Yöntem: Hazırlanan yeni PGD dozimetre formülasyonlarındaki farklı boyaların doz hız sabitleri ve radyasyon kimyasal verimleri üzerindeki etkisi, birçok tıbbi cihaz, farmasötik ürün ve biyolojik dokunun ultraviyole kullanılarak sterilizasyonu için tipik olan 7-28 kGy yüksek doz aralığında spektrofotometre yöntemi ile araştırılmıştır.

Bulgular: Hazırlanan PGD dozimetrelerinin spektrumu, numunelerin gama ışıması üzerine bir değişikliğe uğraması ve mavi jel renginin ağartılması, radyasyon dozu ile artar; tıbbi cihazın sterilizasyon dozunda (25 kGy) bile, ışınlanmamış KM-PGD'nin koyu mavi rengi neredeyse renksiz olana dönmüştür. Işınlanmamış ve ışınlanmış PGD dozimetrelerinin tepkisi, 60 günlük saklama süresi boyunca oldukça kararlıdır.

Sonuç: Hazırlanan boya-PGD dozimetrelerinin yüksek doz gerektiren radyasyon proses uygulamalarında, örneğin; tıbbi cihazlar ve sağlık bakım ürünlerinin sterilizasyonunun proses validasyonunda faydalı olacağı kanaatindeyiz.

Anahtar Kelimeler: Dozimetre, gama ışını, ışınlama, sterilizasyon

Address for Correspondence: Sarkis SÖZKES MD, Tekirdağ Namık Kemal University, Çorlu Faculty of Engineering, Department of Biomedical Engineering, Tekirdağ, Turkey
Phone: +90 282 250 23 47 **E-mail:** ssozkes@nku.edu.tr **ORCID ID:** orcid.org/0000-0003-1555-3591
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INTRODUCTION

In the medical sector, process validation of medical device sterilization is crucial. Unfortunately, surgical devices are not properly sterilized in many places across the world. Many patients die or are diagnosed with various infections after surgery because of improper sterilization.

Authorities require regular sterilization as a mandatory process for the most of the medical equipments and devices[1]. Sterilization is a process that ensures the medical device is without bacteria and any microorganisms. Medical devices are mostly reused for other patients after surgical operations, where they are contaminated by microorganisms. Therefore, effective sterilization is necessary in order to reuse such medical devices again. Ethylene oxide (ETO) sterilization, autoclaving as steam sterilization, radiation, hydrogen peroxide sterilization and chlorine dioxide sterilization are various methods of sterilization[1,2]. To sterilize the medical devices such as syringes, implants, medical dressings, blood-bags and artificial joints methods such as gamma radiation from cobalt-60 (^{60}Co), X-rays or electron beams were used for many years. Sterilization of homogeneous systems and heterogeneous systems such as solid materials, gas materials, liquid materials and also medical devices are done gamma rays[3]. Gamma irradiation has physical inhibation effect on bacterial division by breaking the DNA of bacteria for providing decontamination to kill bacteria[4]. Contamination is caused by the energy of gamma rays passing through the equipments which disrupts pathogens. The reproduction capability or life of organisims causing contamination is finished by molecular changes induced by photons. Irradiation by gamma creates no radioactivity for medical equipment. Comparing with other methods of sterilisation gamma irradiation have reasons for preferance. Comparing with aseptic process method and filtration method, no excess ETO residues, advantage of less temperature for processing and easy validation of the sterilisation can be counted as the advantages of gamma irradiation[5].

Eventhough dose is accepted as sterilisation standard parameter for validation of the sterilisation of medical equipment,to measure the dose is not an easy task. If the reponse to the dose of radiation is known and can be reproducibly achieved, then small blocks made of plastic, films, pellets or fluids may be used as dosimeters[6].

Polymer gel dosimeters (PGD) are prepared from radiation-sensitive chemicals. These chemicals polymerize depending on the absorbed radiation dose[7-10]. These gel dosimeters do not have recording limitations and maintain distribution in three-dimensions. They also have specific advantages when compared to one-dimensional dosimeters, such as ion chambers, and two-dimensional dosimeters, such as film.

Different PGD compositions and monomers in different types were studied. The aim was to create dosimetry system with temporal stability, spatial stability, dose-response exhibition in an optimal level, dose rate dependency and energy rate dependency for suitable and easy applications in clinic[11-13].

Tetrakis phosphonium chloride (THPC) or an oxygen inhibiter like ascorbic acid is homogenously used in these systems as an agent for crosslinking in an aqueous gel matrix. The changes in the physical properties of the material is produced by the reactions of crosslinking agents and monomers to initiate the polymerization and gel form from water radiolysis the formation of free radicals which are induced by ionizing radiation.

In this study, a new polymeric system consisting of itaconic acid (ITA)[14], acrylamide (AAm), gelatin, different dyes [methylene blue (MB), methyl orange (MO) and crystal violet (CV)] and N,N'-methylenebisacrylamide (BIS), with ascorbic acid as an oxygen scavenger was studied. The use of doses from 0 to 1000 Gy have been already studied for hydrogel formation with the monomers ITA and BIS in an aqueous gelatin solution with THPC as an oxygen scavenger[15]. The effects of the different dyes in the newly prepared PGD dosimeter formulations were investigated in a high dose range from 7 to 28 kGy, typical for syringe sterilization, using a ultraviolet (UV)-visible spectrophotometer method.

MATERIALS AND METHODS

Materials

AAm (99%), ITA (99%), BIS, ascorbic acid, MO and CV were obtained from the Sigma Aldrich Chemical Company. MB was supplied by Merck (cat no: 1,05045,0100). All the reagents mentioned above were used as received.

Method

All applicable international and national ethical guidelines were followed. No animal or human subject requiring ethics committee approval was included in the study. The optical absorbency of all irradiated samples was measured by a Shimadzu UV-visible spectrophotometer (Shimadzu UV-2401). The absorbencies of the PGDs were determined to be at wavelengths of 592, 664 and 462 nm before and 24 hours after their irradiation. These have been given as the ideal stabilization durationof the polymerization reactions within a PGD[16]. The optical absorbance of the irradiated sample (Ai) and its sample non-irradiated correspondence(Ao) difference is defined as Relative absorbance (ΔA). Then, ΔA fits to a linear function of the dose (D), and PGD sensitivity is represented by the slope(s)[12].

$$\Delta A: Ai - Ao = sD + n \qquad \textbf{Equation (1)}$$

The pH was measured using a pH meter (WTW pH 315i). The chemical characteristics of the PGD dosimeters were characterized using fourier transform infrared spectroscopy (Bruker VERTEX 70 ATR).

Preparation of the Polymer Gel Dosimeters

AAm-based gels were prepared based on the Venning method[16] using 89% w/w of ultrapure deionized water, 5% w/w of gelatin, 3% w/w of BIS, 3% w/w of AAm, 1% w/w of ITA, 0.1% w/w of three different dyes (MB, MO and CV) and 10 mM of ascorbic acid. The gelatin was mixed with 90% of the water in dosimeters for a duration of ten minutes at room temperature. Then, the temperature was set to 45 °C and constantly stirred to obtain the homogeneousity of the solution. Afterwards, BIS was added to the solution and mixed for 15 minutes at 45 °C. After that, the temperature was decreased to 37 °C and the AAm, IA and MB were added. The total solution was mixed at 37 °C for 30 minutes and ascorbic acid was mixed with the remaining 10% of the water at 35 °C. For two minutes the solution was kept in same condition. The prepared solutions were then put into glass tubes with stoppers[17]. For stabilization purposes, the dosimeters put in storage at 4 °C for 24 hours before irradiation. Irradiation of all solutions was performed with a Nordion-Canada model JS 9600 model gamma irradiator from Gamma-Pak Ind & Trade Inc under air at 25 °C. The PGD dosimeters were irradiated up to the maximum 25 kGy dose at a dose rate of 3 kGy/h.

Statistical Analysis

Equation 2 may be used to express the dye removal with gamma irradiation[18]. The constant of dose, k, is the natural logarithm (ln) of the slope of the compound concentration versus the absorbed dose.

$$\ln (C/C0) = kD \qquad \textbf{Equation (2)}$$

where C is the concentration after gamma irradiation (M), C0 is the initial concentration (M), k is the dose constant (Gy-1) and D is the absorbed dose (Gy).

Necessary doses for Degradation percentage 50%, 90% and 99% degradation of CV ($D_{0.5}$, $D_{0.9}$ and $D_{0.99}$ values) constants were calculated by using equations 3, 4 and 5, respectively[18].

$$D_{0.5} = \ln (2)/k \qquad \textbf{Equation (3)}$$

$$D_{0.9} = \ln (10)/k \qquad \textbf{Equation (4)}$$

$$D_{0.99} = \ln (100)/k \qquad \textbf{Equation (5)}$$

Table 1 shows the calculated k, and the $D_{0.5}$, $D_{0.9}$ and $D_{0.99}$ values for the different dye-PGD dosimeters prepared.

Absorbtion of 100 eV energy by degraded molecules is the definition of the G value[19].

RESULTS

The G value was calculated using equation 6.[20]

$$G=6.023x10^{23}\Delta R/6.24x10^{17} D \qquad \textbf{Equation (6)}$$

where D is the absorbed dose (Gy), the dye (M) concentration change is ΔR, the factor of conversion from Gy to 100 eV/L is $6.24x10^{16}$ and the constant of avogadro is $6.023x10^{23}$.

Table 2 shows the calculated G values for the different dye-PGD dosimeters prepared. The G values were observed to be in a continuously decreasing trend when the absorbed dose increased from 7000 to 28000 kGy for all different dye-PGD dosimeters.

The decrease in G values may have been related to the situation as the dye concentration decreases, where the dose absorbed increases (Figure 1)[21].

DISCUSSION

Gamma irradiation is the most popular form of radiation sterilization and is used when materials are sensitive to the high temperature of autoclaving but are compatible with ionizing radiation[22]. Exposure is achieved when the packages are transported around an exposed ^{60}Co source for a defined period of time.

The European standard (EN 522) for the use of gamma rays on medical devices at a minimum dose of 25 kGy ensures the sterility assurance level of 10^{-6}. The international and European standards for the validation and routine control of medical device sterilization using ionizing radiation requires that a sterilization dose of 25 kGy should be effective[23].

Table 1. The calculated k, $D_{0.5}$, $D_{0.9}$ and $D_{0.99}$ values for the different dye-polymer gel dosimeters prepared

	CV-PGD	MB-PGD	MO-PGD
k x10^6 (Gy^{-1})	4.00	1.00	4.00
$D_{0.5}$ (Gy)	0.173	0.693	0.173
$D_{0.9}$ (Gy)	0.576	2.303	0.576
$D_{0.99}$ (Gy)	1.151	4.605	1.151

PGD: Polymer gel dosimeter, CV: Crystal violet, MB: Methylene blue, MO: Methyl orange

Table 2. The calculated G values for the different dye-polymer gel dosimeters prepared

Absorbed dose (Gy)	G values (molecules/100 eV)		
	CV-PGD	MB-PGD	MO-PGD
7000	1.87	2.26	0.27
14000	1.04	1.24	0.17
21000	0.76	0.92	0.34
28000	0.62	0.74	0.14

PGD: Polymer gel dosimeter, CV: Crystal violet, MB: Methylene blue, MO: Methyl orange

PGD dosimeters were irradiated in a range from 7 kGy to 28 kGy. As shown in Figure 2, as the radiation dose increases, the color of the various PGD dosimeters is bleached. Even at a sterilization dose of 25 kGy, the dark blue color of the non-irradiated CV-PGD became almost colorless.

Three different PGD dosimeters containing different dyes (CV-PGD, MB-PGD and MO-PGD) were analyzed at their own absorbance peaks of 592, 664 and 462 nm wavelengths by an UV spectrophotometer. Figure 3 shows the calibration lines for CV, MB and MO, respectively. According to equation 1, the dose response of three different PGD dosimeters are summarized in Table 3 and Figure 4.

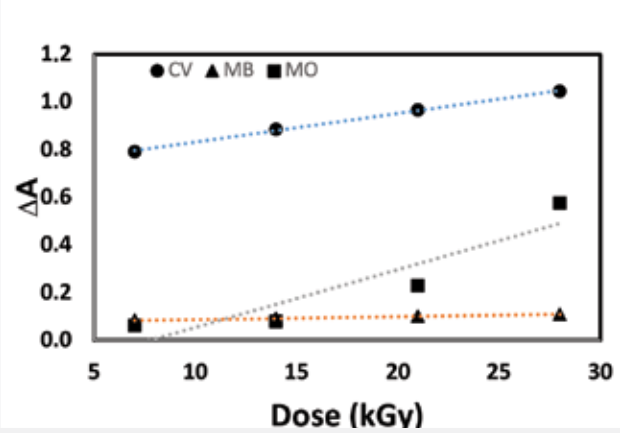

Figure 1. Linear dose response of the three different polimer jel dosimeters

ΔA: Relative absorbance, CV: Crystal violet, MB: Methylene blue, MO: Methyl orange

Study Limitations

The findings of this study should be evaluated considering some limitations. There is very little prior research on our specific topic, and we had to develop research typology. Dye-PGD dosimeters are suitable for use in monitoring various high dose radiation-processing applications and the usage in medical devices, pharmaceutical products and biological tissues should be supported with new studies for further development in this area.

CONCLUSION

Sterilization of medical devices is very important in medical sector. Many different health risks arise in the absence of sterilization for health care products and surgical materials. To keep patients safe during the surgical process, medical conditions are extremely important during surgery. Thus medical sterilization is vitally important. Radiation sterilization has been widely used worldwide for the sterilization of health care products.

In this study, a novel PGD based on ITA, AAm, gelatin and different dyes (MB, MO and CV) was prepared. The sample spectrums of the prepared PGD dosimeters underwent a change following gamma irradiation, and bleaching of the blue gel color increased with the radiation dose. Even at the normal sterilization dose for medical devices (25 kGy), the dark blue color of the non-irradiated CV-PGD became almost colorless. The response of non-irradiated and irradiated PGD dosimeters was stable during a storage period of 60 days. Therefore, the prepared dye-PGD dosimeters are suitable for use in monitoring various high dose radiation-processing applications, which can be useful for many medical devices, pharmaceutical products and biological tissues.

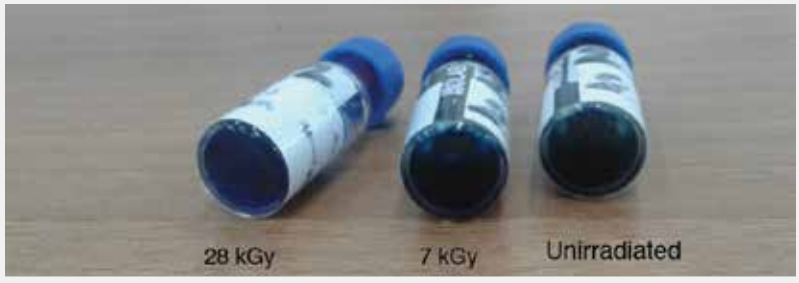

Figure 2. The resulting color change in methylene blue-polymer gel dosimeter following irradiation

Table 3. The dose response of the three different polimer jel dosimeters prepared

Dosimeter name	Ao (non-irradiated) (absorbance)	7 kGy A_i (abs)	14 kGy A_i (abs)	21 kGy A_i (abs)	28 kGy A_i (abs)
CV-PGD	1.111	0.318	0.226	0.144	0.065
MB-PGD	0.941	0.858	0.850	0.840	0.832
MO-PGD	0.965	0.904	0.886	0.737	0.388

PGD: Polymer gel dosimeter, CV: Crystal violet, MB: Methylene blue, MO: Methyl orange, abs: Absorbance, Ao: Non-irradiated sample, A_i: Irradiated sample

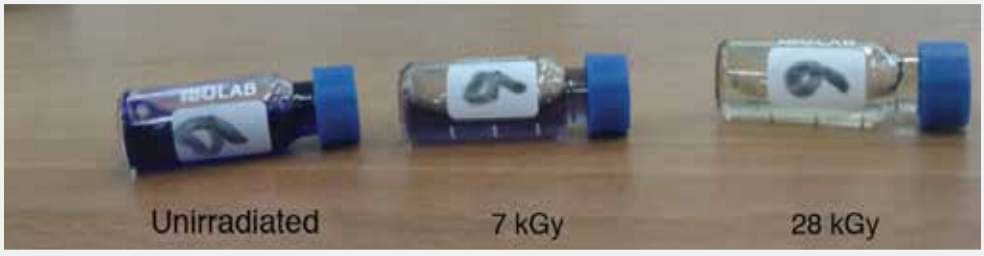

Figure 3. The resulting color change in crystal violet-polymer gel dosimeter following irradiation

Figure 4. The resulting color change in methyl orange-polymer gel dosimeter upon irradiation

Ethics

Ethics Committee Approval and Informed Consent: All applicable international and national ethical guidelines were followed. No animal or human subject requiring ethics committee approval was included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Evaluation of the Relationship Between Orthopedic Injuries and Attention Deficit Hyperactivity Disorder in Childhood and Adolescence

Çocukluk ve Ergenlikte Ortopedik Yaralanmalar ve Dikkat Eksikliği Hiperaktivite Bozukluğu Arasındaki İlişkinin Değerlendirilmesi

İsmail Gökhan ŞAHİN[1], Leyla BOZATLI[2], Zeynep Anıl ŞAHİN[3], Işık GÖRKER[2]

[1]*Muğla Sıtkı Koçman Training and Research Hospital, Clinic of Orthopedics and Traumatology, Muğla, Turkey*
[2]*Trakya University Medical Faculty Hospital, Department of Child and Adolescent Psychiatry, Edirne, Turkey*
[3]*Muğla Sıtkı Koçman Training and Research Hospital, Child and Adolescent Psychiatry Clinic, Muğla, Turkey*

ABSTRACT

Aim: Attention deficit hyperactivity disorder (ADHD) is the most neurodevelopmental disorder in childhood, which causes repetitive trauma and extremity injuries. Oppositional defiant disorder (ODD) and conduct disorder (CD) are the most comorbid conditions of ADHD. Our study investigated the correlation between extremity trauma and ADHD's subgroups in pediatric trauma patients and comparison with the control group. Our aim was to detect high-risk patients in pediatric extremity injuries and to prevent possible extremity injuries with early diagnosis.

Materials and Methods: Between September 2018 and February 2019, 60 pediatric patients with extremity injuries (group 1) and non-traumatic reasons (group 2) were included in this prospective study consecutively. Patients were evaluated with the Conner's Parent Rating Scale and Strength and Difficulties Questionnaire for ADHD subgroups, ODD and CD. Patients who received an initial diagnosis were evaluated by the Child and Adolescent Psychiatry Department of Trakya University Medical Hospital.

Results: Patients who were diagnosed as ADHD were significantly higher in the trauma group (p=0.042), but no statistical significance was found in any subgroups of ADHD, ODD and CD.

Conclusion: Our results were in accordance with the vast majority of current literature in which ADHD was found to be significantly higher in the trauma group. ADHD must be considered in pediatric trauma patients to prevent possible extremity injuries.

Keywords: Pediatric trauma, extremity injury, attention deficit hyperactivity disorder, inattentive, hyperactive, impulsivity

ÖZ

Amaç: Dikkat eksikliği hiperaktivite bozukluğu (DEHB), çocukluk çağında tekrarlayan travma ve ekstremite yaralanmalarına en fazla neden olan nörogelişimsel bozukluktur. Karşıt olma karşı gelme bozukluğu (KOKGB) ve davranım bozukluğu (DB) ise DEHB'ye en sık eşlik eden durumlar olarak bilinmektedir. Çalışmamızda pediatrik travma hastalarında, ekstremite travmaları ve DEHB alt grupları arasındaki korelasyon, kontrol grubu ile karşılaştırılarak araştırılmıştır. Amacımız pediatrik ekstremite travmaları açısından yüksek riskli olguların saptanması ve erken tanı ile olası ekstremite yaralanmalarının önlenmesidir.

Gereç ve Yöntem: Eylül 2018-Şubat 2019 tarihleri arasında ekstremite yaralanması bulunan (grup 1) ve travmatik olmayan nedenlerle başvuran (grup 2) toplam 60 çocuk ardışık olarak çalışmaya dahil edildi. Katılımcılar Conners Ebeveyn Değerlendirme Ölçeği ve Güçler Güçlükler Anketi kullanılarak ön değerlendirmeye tabi tutuldu. Riskli olarak saptanan olgular Trakya Üniversitesi Tıp Fakültesi Hastanesi, Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Kliniği'ne detaylı değerlendirme için yönlendirildi.

Bulgular: DEHB tanısı alan olguların sayısı travma grubunda anlamlı olarak daha yüksek saptandı (p=0,042), ancak DEHB alt grupları arasında ve KOKGB ve DB'yi karşılayan olgular arasında, pediatrik travma açısından anlamlı fark saptanmadı.

Sonuç: Bulgularımız, güncel literatürün büyük çoğunluğu ile uyumlu olup DEHB, travma grubunda anlamlı olarak daha yüksek saptanmıştır. Pediatrik travma hastalarında olası ekstremite yaralanmalarını önlemek için DEHB'ye dair semptomatoloji dikkate alınmalıdır.

Anahtar Kelimeler: Pediatrik travma, ekstremite yaralanması, dikkat eksikliği hiperaktivite bozukluğu, dikkatsizlik, hiperaktivite, dürtüsellik

Address for Correspondence: Leyla BOZATLI MD, Trakya University Medical Faculty Hospital, Department of Child and Adolescent Psychiatry, Edirne, Turkey
Phone: +90 505 758 93 68 **E-mail:** leylyabozatli@gmail.com **ORCID ID:** orcid.org/0000-0002-4701-4835
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INTRODUCTION

Extremity injuries are one of the most important hospitalization causes in childhood[1]. The causes of pediatric trauma are multiple and psycho-social problems are one of them. Coincidental accidents are seen 1.5 times more in children with behavioral disorders than in others[2]. In the literature, attention deficit hyperactivity disorder (ADHD) is stated as a type of behavioral disorder which is the most common comorbid disease of pediatric trauma[3].

ADHD is a neurodevelopmental disease, and it has three main symptoms including attention deficit, hyperactivity, and impulsivity[4]. Its prevalence is increasing and nearly genetic inheritance is seen in 79% of the patients, which has been determined as the main etiological factor[5]. ADHD is the most common neurodevelopmental disorder in childhood and adolescence, which affects 3-5% of this population[6]. ADHD has three main subgroups as inattentive type (type 1), hyperactive-impulsive type (type 2) and the combined type (type 3). Oppositional defiant disorder (ODD) and conduct disorder (CD) are the most common comorbid conditions of ADHD.

ADHD is a chronic condition. The first step, which is very important, should be to develop a shared-care approach with the parents and child or adolescent, based on a shared understanding of identified treatment goals and preferences and accurate information about underlying etiology[7]. ADHD is associated with increased risk of unintentional injuries[1-3,5,6]. Our aim was to detect high-risk patients in pediatric extremity injuries, to prevent possible extremity injuries with early diagnosis and to ensure access to appropriate treatment options for ADHD.

MATERIALS AND METHODS

This prospective study was carried out at the outpatient clinic of Orthopedics and Traumatology in Turkish Minister of Health, Edirne Sultan 1st Murat State Hospital from September 2018 to June 2019. The study was approved by the Institutional Medical Ethics Committee of the Medical Faculty Hospital of Trakya University (protocol no: TÜTF-BAEK 2018/226).

Patients between the ages of 6 and 15 years, who applied to the outpatient clinic of orthopedics and traumatology with their parents or legal representative, were included in the study. Patients were put into two groups as the trauma group (group 1) and the control (non-trauma) group (group 2) and they were questioned for their demographic data and medical histories (Table 1, 2). The trauma group consisted of patients who were directed by the emergency service and the non-trauma group consisted of patients who applied to the outpatient clinic for non-traumatic reasons (Table 3, 4). Thirty patients at each group, who had no history of psychiatric diagnosis and treatment, were consecutively included in the study. All patients were questioned and evaluated with the Conner's Parent Rating Scale (CPRS) and Strength and Difficulties Questionnaire (SDQ). The CPRS was developed by Conners et al.[8] to evaluate the behaviors of the child, and adaptation studies into Turkish were carried out by Kaner et al.[9]. It is seen that as the scores obtained from the scale increase, the severity of the symptoms increases. In our study, the scale was filled by the parent of the case. This scale was used to screen ADHD symptoms, and the group whose scale scores were found to be at risk was referred to the child and adolescent psychiatry outpatient clinic for Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL). The SDQ-Tur is a brief behavioral screening questionnaire developed by Robert Goodman in 1977. The Turkish validity and reliability study was conducted by Güvenir et al.[10]. The survey aims to evaluate the behavior, emotions and relationships of children and adolescents. SDQ-Tur contains 25 questions about the positive and negative behavior characteristics. It contains 5 subheadings, each consisting of 5 questions; these subheadings are behavioral problems, emotional problems, attention deficit and hyperactivity, peer problems and social behaviors. In our study, this scale was used for ADHD screening.

Patients who received an initial diagnosis were evaluated by the Child and Adolescent Psychiatry Department of Trakya University Medical Hospital. During our study, patients still under follow-up and treatment with a diagnosis of ADHD were excluded from the study, considering the possible side effects of psychostimulant therapy on bone tissue. The cases who had not received ADHD diagnosis and treatment until that day were included in our study. Written informed consent was obtained from all patients.

Statistical Analysis

Statistical analyses were carried out with SPSS v.21.0 software (SPSS Inc., IBM Corporation, Armonk, New York, USA) and power analysis was carried out with G-Power v.3.1.9.4 software (Franz Faul, Universitat Kiel, Germany). For this study, alfa error was accepted as 5% and $p<0.05$ values were accepted as statistically significant. Before the study, a power analysis was

Table 1. Demographic data

		Trauma	Non-trauma	p value
Age	**Mean**	10.70	9.47	0.218[1]
	SD[2]	3.62	4.03	-
Gender	**Male**	15 (25.0%)	18 (30.0%)	0.604[3]
	Female	15 (25.0%)	12 (20.0%)	-
BMI	**Normal**	29 (48.3%)	28 (46.7%)	1.000[3]
	Over-weight	1 (1.7%)	2 (3.3%)	

[1]: Student's t-test, [2]: Standard deviation, [3]: Chi-square test, BMI: Body mass index

performed. Due to similar studies in the literature, statistical power (1-β) was accepted as 80% and the total sample size was determined as 60 patients. The groups were compared in terms of their demographic data, using the CPRS and SDQ for ADHD subgroups, ODD, and CD. Data were classified according to the distribution pattern. Parametric data were evaluated with the Student's t-test, non-parametric data were evaluated with the Mann-Whitney U test, and categorical data were evaluated with the chi-square test.

RESULTS

The study was finished with 30 patients in each group. Group 1 consisted of 15 male and 15 female patients with the mean age of 10.70 years (±3.62) and group 2 consisted of 18 male and 12 female patients with the mean age of 9, 47 years (±4.03) (p=0.604, p=0.218). Patients were classified as normal or overweight by using body mass index (BMI) calculations. BMI was calculated by dividing weight (in kilograms) by height (in meters) squared. There are different results in the literature about the relationship between trauma and BMI, and in our study, the groups were compared in terms of this variable[11]. One patient in group 1 and 2 patients in group 2 were overweight, so no significant difference was found (p=1.000) in the trauma group, all patients were injured with direct and low-energy trauma and treated conservatively. In the trauma group, 18 patients had upper and 12 patients had lower extremity injuries. Also, the groups were compared for previous trauma history and no significant difference was found (6/30-12/30, p=0.159). In addition to the CPRS and SDQ, patients were questioned for their or families' psychiatric medical histories and no statistical significance was found (p=0.513, p=0.671). In the literature, socio-economic status (SES) and parents' educational levels were inversely proportional to trauma risk, so groups were compared in terms of SES and parents' (especially mother) educational levels. SES was classified as low, medium and high. Educational levels of parents were defined as illiterate, literate, elementary school, middle school, high school, university and postgraduate and no statistical significance was found (p=1.000, p=0.754, p=0.218) (Table 1, 2).

Patients who were diagnozed as ADHD were significantly higher in the trauma group (p=0.025) but no statistical significance was found for any subgroups of ADHD, ODD and CD by the CPRS or SDQ at the initial evaluations (Table 5, 6).

Nineteen patients (31.7%) whose scores were higher than the cut-off value with CPRS and SDQ were examined by the Child

Table 2. Medical history

		Trauma	Non-trauma	p value[1]
Former trauma history	**No**	24 (40.0%)	18 (30.0%)	0.159
	Yes	6 (10.0%)	12 (20.0%)	-
Patients' psychiatric medical history	**No**	30 (50.0%)	30 (50.0%)	1.000
	Yes (ADHD)	0 (0.0%)	0 (0.0%)	-
	Yes (other)	0 (0.0%)	0 (0.0%)	-
Familial psychiatric medical history	**No**	26 (43.3%)	28 (46.7%)	0.671
	Yes	4 (6.7%)	2 (3.3%)	-
Socio-economic status	**Low**	0 (0.0%)	0 (0.0%)	1.000
	Medium	24 (40.0%)	23 (38.3%)	-
	High	6 (10.0%)	7 (11.7%)	-
Mother's educational level	**No literate**	0 (0.0%)	0 (0.0%)	0.754
	Literate	1 (1.7%)	0 (0.0%)	-
	Elementary school	11 (18.3%)	11 (18.3%)	-
	Middle school	4 (6.7%)	6 (10.0%)	-
	High school	10 (16.7%)	11 (18.3%)	-
	University	3 (5.0%)	2 (3.3%)	-
	Postgraduate	1 (1.7%)	0 (0.0%)	-
Father's educational level	**No literate**	0 (0.0%)	0 (0.0%)	0.218
	Literate	0 (0.0%)	0 (0.0%)	-
	Elementary school	11 (18.3%)	10 (16.7%)	-
	Middle school	4 (6.7%)	3 (5.0%)	-
	High school	6 (10.0%)	11 (18.3%)	-
	University	5 (8.3%)	6 (10.0%)	-
	Postgraduate	4 (6.7%)	0	-

[1]: Chi-square test, ADHD: Attention deficit hyperactivity disorder

and Adolescent Psychiatry Department of Medical Faculty Hospital of Trakya University with clinical assessment and "K-SADS-PL". After final evaluations, 11 patients (18.3%) were diagnosed as ADHD. Patients who were diagnosed as ADHD were significantly higher in the trauma group (p=0.042), but no statistical significance was found for any subgroups of ADHD, OD and CD (Table 7). Also, based on Chou et al.[2] and Hurtig et al.[12] studies, results were examined by the cut-off value of 7 and the age of 12 years and no statistical significance was found (Table 8).

Table 3. Trauma group

Upper extremity	18
Shoulder contusion	1
Elbow contusion	3
Wrist contusion	5
Distal radius fracture	4
Phalanx contusion	3
Phalanx fracture of hand	2
Lower extremity	12
Knee contusion	2
Ankle contusion	6
Foot contusion	3
Phalanx fracture of foot	1
Total	30

Table 4. Non-trauma group

Posture disorder	6
Pes planovalgus	5
Osgood Schlatter disease	4
Scoliosis	4
Severe disease	3
Gait disturbance	3
Mass in soft tissue	3
Mass in bone	2
Total	**30**

DISCUSSION

Several studies have tried to determine the relationship between ADHD and unintentional injuries in children[1-3,5,6]. Increased risk due to ADHD was controversial but the risk was statistically higher and there is consensus in the literature[13-16]. Chen at al.[17] concluded that treatment longer than 6 months was associated with a lower risk for fracture among ADHD patients, but the overall risk is still higher than in the healthy population[18] and ADHD treatment does not result in a decrease in the frequency of hospitalization[19].

Brehaut et al.[16] reported that children with behavioral disorders had 1.5 times higher risk of injury compared to those without such disorders. A meta-analysis by Ruiz-Goikoetxea et al.[13] indicated a significantly higher risk of injuries in ADHD compared to children or adolescents without ADHD [odds ratio (OR): 1.53]. In another study of Maxson et al.[14], they investigated 6 to 12-year-old children who were admitted to the medical center for the treatment of an injury and appendicitis; the injured patient group was 3.25 times more likely to be positive for ADHD than appendicitis group. In another meta-analysis of 35 studies in children by Amiri et al.[15], it was concluded that ADHD patients were injured nearly two times more than others (OR: 1.96). In our study, we calculated the OR as 4.35 at the first evaluation [OR: 4.35, 95% confidence interval (CI): 1.320-14.504] and as 6 (OR: 6, 95% CI: 1.172-30.725) at the final evaluation, which was higher compared to the literature but we concluded that the final evaluation by child and adolescent department eliminated the false-positive results in the non-trauma group and it is important. Also, in our study, no significance was found for any subgroups of ADHD or ODD and patients who diagnosed as ADHD were significantly higher in the trauma group (p=0.042). In discordance with our study,

Table 5. Results of Conner's parent rating scale

		Trauma	Non-trauma	p value[1]
Type 1 ADHD (inattentive type)	**Healthy**	23 (38.3%)	28 (46.7%)	0.145
	Risky	7 (11.7%)	2 (3.3%)	-
Type 2 ADHD (hyperactive-impulsive type)	**Healthy**	25 (41.7%)	28 (46.7%)	0.424
	Risky	5 (8.3%)	2 (3.3%)	-
Type 3 ADHD (combined type)	**Healthy**	28 (46.7%)	29 (48.3%)	1.000
	Risky	2 (3.3%)	1 (1.7%)	-
ADHD	**Healthy**	16 (26.7%)	25 (41.7%)	0.025
	Risky	14 (23.3%)	5 (8.3%)	-
Oppositional defiant disorder	**Healthy**	27 (45.0%)	29 (48.3%)	0.612
	Risky	3 (5.0%)	1 (1.7%)	-
Conduct disorder	**Healthy**	29 (46.7%)	30 (50.0%)	1.000
	Risky	1 (1.7%)	0 (0.0%)	-

[1]: Chi-square test, ADHD: Attention deficit hyperactivity disorder

Karayağmurlu et al.[20] concluded that all subgroups with ADHD and ODD were significantly increased in the trauma group compared to the control group for otorhinologic trauma.

Some studies concluded that ADHD's injury risk varied by age. Chou et al.[2] compared 3,640 children with ADHD and 11,496 children without ADHD; no statistical significance was found for the risks of subsequent fracture in older age groups (≥12 years old), but in younger age groups (5-12 years old), ADHD group was significantly associated with increased risk of fractures compared to the non-ADHD group. In a cohort study by Hurtig et al.[12], they investigated 6,111 children who were born in 1986. The risk for hospital-treated injuries was 1.7 times higher in younger age groups (≤7 years old), which was statistically significant. Also, the ADHD group was treated more for injuries than the non-ADHD group considering older age groups, but no statistical significance was found for injuries except intoxication[21]. Contrary to these studies, we classified our results for cut-off ages of 7 and 12 years between the groups and no statistical significance was found in any subgroups or ADHD (Table 8). Low SES status is associated with high injury rates in children[22]. In our study, no statistical significance was found for SES (p=1.000, Table 2).

Maxson et al.[14], reported ADHD frequency as 29% in children who were admitted to emergency services due to injuries. Also our trauma group consisted of patients that were directed by the emergency service and our ADHD frequency was found to be 30%, which is similar with that study.

In our study, we calculated the OR as 4.35 at the first evaluation (OR: 4.35, 95% CI: 1.320-14.504) and as 6 (OR: 6, 95% CI: 1.172-30.725) at the final evaluation, which is a higher value compared to the literature. In discordance with Chou et al.[2] and Hurtig et al.[12] studies, we classified our results for cut-off

Table 6. Results of Strength and Difficulties Questionnaire

		Trauma	Non-trauma	p value
Hyperactivity/inattention	**Normal**	10 (16.7%)	7 (11.7%)	0.457[1]
	Borderline	6 (10.0%)	10 (16.7%)	-
	Abnormal	14 (23.3%)	13 (21.7%)	-
Conduct problems	**Normal**	14 (23.3%)	16 (26.7%)	0.274[1]
	Borderline	9 (15.0%)	4 (6.7%)	-
	Abnormal	7 (11.7%)	10 (16.7%)	-
Emotional symptoms	**Normal**	17 (28.3%)	17 (28.3%)	0.734[1]
	Borderline	7 (11.7%)	5 (8.3%)	-
	Abnormal	6 (10.0%)	8 (13.3%)	-
Peer relationship problems	**Normal**	0 (0.0%)	1 (1.7%)	1.000[1]
	Borderline	0 (0.0%)	0 (0.0%)	-
	Abnormal	30 (50.0%)	29 (48.3%)	-
Score	**Mean**	18.17	18.30	0.920[2]
	SD[3]	5.12	5.13	-

[1]: Chi-square test, [2]: Student's t-test, [3]: Standard deviation

Table 7. Final evaluation

		Trauma	Non-trauma	p value[1]
Type 1 ADHD (inattentive type)	**Healthy**	25 (41.7%)	29 (48.3%)	0.195
	Diagnosed	5 (8.3%)	1 (1.7%)	-
Type 2 ADHD (hyperactive-impulsive type)	**Healthy**	27 (45.0%)	29 (48.3%)	0.612
	Diagnosed	3 (5.0%)	1 (1.7%)	-
Type 3 ADHD (combined type)	**Healthy**	29 (48.3%)	30 (50.0%)	1.000
	Diagnosed	1 (1.7%)	0 (0.0%)	-
ADHD	**Healthy**	21 (35.0%)	28 (46.7%)	0.042
	Diagnosed	9 (15.0%)	2 (3.3%)	-
Oppositional defiant disorder	**Healthy**	30 (50.0%)	30 (50.0%)	1.000
	Diagnosed	0 (0.0%)	0 (0.0%)	-
Conduct disorder	**Healthy**	30 (50.0%)	30 (50.0%)	1.000
	Diagnosed	0 (0.0%)	0 (0.0%)	-

[1]: Chi-square test, ADHD: Attention deficit hyperactivity disorder

Table 8. Final evaluation with age

		Trauma	Non-trauma	p value[1]
Type 1 ADHD (inattentive type)	**≤7[2] years old**	2/7 (28.6%)	0/8 (0.0%)	0.492
	>7 years old	3/23 (13.0%)	1/22 (4.5%)	0.612
	≤12[3] years old	2/18 (11.1%)	1/20 (5.0%)	1.000
	>12 years old	3/12 (25.0%)	0/10 (0.0%)	0.237
Type 2 ADHD (hyperactive-impulsive type)	**≤7 years old**	1/7 (14.3%)	0/8 (0.0%)	1.000
	>7 years old	2/23 (8.7%)	1/22 (4.5%)	1.000
	≤12 years old	2/18 (11.1%)	2/20 (10.0%)	1.000
	>12 years old	1/12 (8.3%)	0/10 (0.0%)	1.000
Type 3 ADHD (combined type)	**≤7 years old**	0/7 (0.0%)	0/8 (0.0%)	1.000
	>7 years old	1/23 (4.3%)	0/22 (0.0%)	1.000
	≤12 years old	1/18 (5.6%)	0/20 (0.0%)	1.000
	>12 years old	0/12 (0.0%)	0/10 (0.0%)	1.000
ADHD	**≤7 years old**	3/7 (42.9%)	1/8 (12.5%)	0.612
	>7 years old	6/23 (26.1%)	1/22 (4.5%)	0.470
	≤12 years old	5/18 (27.8%)	2/20 (10.0%)	0.424
	>12 years old	4/12 (33.4%)	0/10 (0.0%)	0.112

[1]: Chi-square test, [2]: Cut-off value in Hurtig et al.[11] study, [3]: Cut-off value in Chou et al.[2] study, ADHD: Attention deficit hyperactivity disorder

ages of 7 and 12 years between the groups and no statistical significance was found in any subgroups or ADHD (Table 7). In discordance with Karayağmurlu et al.[20] study, no statistical significance was found for any subgroups of ADHD or ODD at the first and final evaluations.

Study Limitations

Pediatric extremity injuries, which have an important place in the daily routine of orthopedic outpatient clinics, affect the functionality of not only the child but the whole family, and it is especially important to evaluate recurrent extremity injuries in terms of etiology. In the planning phase of our study, our aim was to detect ADHD cases, which we considered as one of the possible causes of extremity injuries, to provide access to treatment and to prevent recurrence of extremity injuries. For this reason, the group that we considered as risky in terms of ADHD diagnosis in our study was determined as pediatric extremity injuries. The cases that were found to be at risk according to one of the two scales which we used for screening in our study were referred to the child and adolescent psychiatry outpatient clinic and these cases were evaluated with clinical interview and K-SADS application.

One of the important limitations of our study was that clinical interview and K-SADS could not be applied to each patient. The reason for this was that polyclinic working conditions were unfavorable for applying K-SADS to every patient due to the density. And the motivation of the pediatric patient group with orthopedic injuries and their parents for clinical interviews was insufficient. Another important limitation of our study was that only ADHD, CD and ODD diagnoses were evaluated due to the low number of patients who underwent K-SADS.

CONCLUSION

In the current study, we found that ADHD was diagnosed significantly higher in the trauma group, which is in concordance with the vast majority of literature. ADHD is also associated with a significantly increased risk of unintentional injuries[1-3,5,6]. Detection of the high-risk group in children examined for different types of traumas and referral of them directly to psychiatric evaluation are essential for the prevention of possible extremity injuries and for early diagnosis of ADHD.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Medical Ethics Committee of the Medical Faculty Hospital of Trakya University (protocol no: TÜTF-BAEK 2018/226).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.G.Ş., Z.A.Ş., L.B., Concept: İ.G.Ş., L.B., I.G., Design: I.G., Z.A.Ş., L.B., Data Collection or Processing: İ.G.Ş., Z.A.Ş., Analysis or Interpretation: İ.G.Ş., Literature Search: I.G., Z.A.Ş., L.B., Writing: İ.G.Ş., Z.A.Ş., L.B.

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The Relationship Between Aterosclerotic Cardiovascular Diseases and Drinking Water Hardness Level in Çanakkale Province

Çanakkale İlinde Aterosklerotik Kardiyovasküler Hastalıkların İçme Suyu Sertlik Seviyesi ile İlişkisi

Sonay OĞUZ

Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Carvicascular Surgery, Çanakkale, Turkey

ABSTRACT

Aim: Cardiovascular diseases (CVH) still maintain their leadership among causes of death. Many studies have been carried out on risk factors and the relationship of disease and their proven recommendations have entered current guidelines. However, it is seen that there are opposing interpretations in the literature regarding the relationship between water hardness and CVH and definite conclusions are still not reached. In Çanakkale province center, drinking water needs are met from two different sources with different hardness degrees. This may help to better understand the relationship between water hardness level and CVH. The study was designed for this purpose.

Materials and Methods: Patients with a diagnosis of atherosclerosis (coronary artery, carotid artery and peripheral artery disease), who applied to Çanakkale Onsekiz Mart University Training and Practice Hospital between 2015 and 2020, were retrospectively identified, and atherosclerotic group was formed. Corresponding to this group, a non-atherosclerotic (non-AS) group was formed by observing "propensity score matching" according to age, gender, arterial hypertension (HT), diabetes mellitus (DM), and presence of dyslipidemia (DL). The pH, hardness, calcium, magnesium values of the last five years were determined from the city center drinking water analyses taken from local governments and were associated with the address. Using this information, cases consuming water of different hardness were determined. Statistically, the significance of the water hardness values between the two groups was evaluated.

Results: There was no significant difference in age, gender, arterial HT, DM, DL between the groups ($p>0.05$), and very high hardness water consumption was found significantly higher in the non-AS group ($p<0.001$).

Conclusion: The results show that there may be an inverse relationship between the hardness level of drinking water and atherosclerosis. We strongly recommend that the results should be supported by field studies in appropriate locations and the public should be made aware of drinking water according to the results to obtain high scientific data.

Keywords: Cardiovascular diseases, drink water hardness, prevention

ÖZ

Amaç: Kardiyovasküler hastalıklar (KVH) ölüm sebepleri içerisindeki liderliğini halen korumaktadır. Risk faktörleri ve hastalık ilişkisi ile ilgili pek çok çalışma yapılmış ve ispatlanan öneriler güncel kılavuzlara girmiştir. Fakat su sertliği ve KVH ilişkisi ile ilgili literatürde karşıt yorumların olduğu ve halen kesin kanaatlere varılamadığı görülmektedir. Çanakkale şehir merkezinde içme suyu ihtiyacı sertlik derecesi farklı iki ayrı kaynaktan karşılanmaktadır. Bu durum su sertlik seviyesi ve KVH ilişkisinin daha iyi anlaşılmasına yardımcı olabilir. Bu amaçla çalışma planlanmıştır.

Gereç ve Yöntem: 2015-2020 yılları arasında Çanakkale Onsekiz Mart Üniversitesi Eğitim ve Uygulama Hastanesi'ne başvurmuş ateroskleroz ile ilişkili tanısı olan (koroner arter, karotis arter ve periferik arter hastalığı) Çanakkale il merkezine kayıtlı olgular retrospektif olarak tespit edilerek aterosklerotik (AS) grup oluşturuldu. Bu gruba karşılık gelecek şekilde olguların yaş, cinsiyet, arteriyel hipertansiyon (HT), diabetes mellitus (DM), dislipidemi (DL) mevcut olması durumuna göre, "propencity score matching" gözetilerek non-AS grup oluşturuldu. Yerel yönetimlerden elde edilen il merkezi içme suyu analizlerinden pH, sertlik, kalsiyum, magnezyumun son beş yıllık değerleri tespit edilip adres ile ilişkilendirildi. Bu bilgiler kullanılarak farklı sertlikte su tüketen olgular tespit edildi. İstatistiki olarak iki grup arasındaki su sertlik değeri açısından anlamlılık değerlendirildi.

Address for Correspondence: Sonay OĞUZ MD, Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Carvicascular Surgery, Çanakkale, Turkey
Phone: +90 286 263 59 50 **E-mail:** soguz@comu.edu.tr **ORCID ID:** orcid.org/0000-0002-4274-3828
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ÖZ

Bulgular: Gruplar arasında yaş, cinsiyet, HT, DM, DL'de anlamlı farklılık yoktu (p>0,05), non-AS grubunda çok yüksek sertlikte su tüketiminin anlamlı seviyede yüksek olduğu tespit edildi (p<0,001).

Sonuç: Elde edilen sonuçlar içme suyunun sertlik seviyesi ile ateroskleroz arasında ters bir ilişki olabileceğini göstermektedir. Bilimsel değeri yüksek veriler elde etmek için uygun lokasyonlarda saha çalışmaları ile sonuçların desteklenmesi ve çıkan sonuçlara göre halkın içme suyu konusunda bilinçlendirilmesi gerektiğini şiddetle tavsiye ediyoruz.

Anahtar Kelimeler: Kardiyovasküler hastalıklar, içme suyu sertliği, önlem

INTRODUCTION

In the world, cardiovascular system diseases are common in society and are the leading cause of death[1]. Many studies have tried to find the effects of environmental factors by examining their relationship with death and risk factors. The fact that life depends on water and water is essential for the body gives water special importance. The effects of drinking water on health have been shown in many studies and the importance of drinking water quality has been emphasized[2-4]. However, different results were found in existing studies on the relationship between drinking water hardness level and cardiovascular diseases (CVH). While there is a consensus on the positive effect between the magnesium level and CVH[5-8], there is no consensus on the hardness level of the water. While some studies have shown a positive effect between water hardness level and CVH[9-13], some studies have shown that there is no relationship[14-16]. This issue is important for common CVH and it is still unclear, which suggests that it needs to be studied.

Çanakkale city center drink water is provided from two sources of different hardness (Table 1). The hardness levels of these spring waters are quite different from each other (Table 2). Different levels of water hardness used among the population with the same geographical, climatic and environmental conditions may be a suitable situation to show the relationship with CVH. The study was organized for this purpose.

MATERIALS AND METHODS

Patients who applied to Çanakkale Onsekiz Mart University Training and Practice Hospital between 2015 and 2020 and who were diagnosed with atherosclerotic diseases (coronary artery, carotid artery and peripheral artery disease) were retrospectively identified and atherosclerotic (AS) group was created. Corresponding to this group, non-atherosclerotic (non-AS) group was created by taking into consideration the "propensity risk score matching" according to age, gender, arterial hypertension (HT), diabetes mellitus (DM), and dyslipidemia (DL). The average and change values of pH, hardness, calcium, and magnesium for the last five years were determined from the city center drinking water supply (WS) analyses obtained from the local municipality and they were associated with the address. Using this information, cases consuming high hardness and very high hardness water were determined. Statistical significance between atherosclerotic CVH and water hardness was evaluated.

Data Processing

Hospital entries for the years of 2015-2020 were identified and filtered using Excel (Microsoft® Office 2016, Santa Rossa, California) program. Address records outside the Çanakkale city center were eliminated and only the target population registered in the city center was obtained (Figure 1). Arterial HT, DM, and DL cases diagnosed with International Classification of Disease-10 (ICD-10) codes were associated with the identification number. Age, gender, and address information were preserved. The ICD diagnosis codes (coronary artery disease, carotid artery disease, peripheral vascular disease groups) associated with the diagnosis of atherosclerotic disease were scanned and determined as the AS group. According to the data obtained from the local municipality, the address records were associated with the areas with very hard (source 1) and hard (source 2) drinking water[17].

Propensity Score Matching

By Excel filtering method and applying "propensity score matching" process according to age, gender, HT, DM, and DL criteria, the non-AS group was created equivalent to the AS group, from the target population (the target population after the records with AS are removed) (Figure 2).

Statistical Analysis

Results were analyzed by SPSS (version 23.0, IBM, Chicago, IL). Continuous variables and categorical variables were expressed as mean with standard deviation and number with percentage, respectively. Groups were compared according to sample size using the Mann-Whitney U test. Differences were considered significant when the p-value was less than 0.05.

The study was approved by the Local Ethics Committee of Çanakkale Onsekiz Mart University (2011-KAEK-27/2020-E.2000096163 approval date/number: 11.11.2020 / 13-01).

RESULTS

A total of 1,908,049 hospital admissions were detected in 2015-2020. Records with addresses outside Çanakkale (494,561) and villages (37,150) were eliminated. Records with 433,047 addresses in the city center were obtained. Of these records, 93,298 were registered in very hard drinking water (source 1) region, 339,749 in hard drinking water (source 2) region. Entries under the same duplicate ID number have been reduced to a single record. The target population was determined by decreasing 494,561 records to 112,234 (Figure 1).

Table 1 shows the water analysis reports. The water hardness, magnesium and calcium values of water resources are different and the pH value is similar (Table 1).

Of the target population, 26,248 were registered in source 1 (very high water hardness), 85,986 in source 2 (high water hardness). 10,636 HT, 12,011 DM, 3,860 DL diagnosed records were detected. There were 6,726 records in the AS group and 6,726 in the non-AS group. In both groups (AS and non-AS), age of 61 years (range 16-95 years), HT 1,849, DM 650, DL 1,296, HT + DM 200, HT + DL 92, DM + DL 193, HT + DM + DL 68 recordings were detected. In the AS group, 3,826 male (43.1%) and 2899 female (56.9%); In the non-AS group, 3,822 (43.1%) male and 2,903 (59.9%) female records were detected.

There was no difference in age, gender, HT, DM, and DL between the groups ($p>0.05$), very high hardness water consumption was found significantly higher in the non-AS group ($p<0.001$) (Table 3).

DISCUSSION

The relationship between drinking water hardness level and CVH is still unclear[6,18]. Çanakkale province center can provide information that will help enlighten this issue due to its mentioned characteristics in terms of drinking water resources. In the study model we designed, single-center patient records were used. The weak points of the study are that the individuals in the target population can contact another health center, population mobility, the use of carboys, water purifiers instead of mains water and the data that cannot be collected about other risk factors (smoking, obesity, insufficient physical activity, genetic factors, etc.).

The scientific significance of the data obtained would weak results due to these missing data points. For this reason, we used the "propensity score matching" method in the model we created to strengthen the scientific significance. Results were obtained by equating all identified risk factors (age, gender, HT, DM, DL) in two groups, which might be associated with the disease. However, it must be admitted that the field and cohort studies related to the subject will produce more scientifically meaningful results, but the high number of data collection, Çanakkale drinking water features, may have the potential to generate information that will help in this regard. For this purpose, the data were collected and processed precisely. There was no significant difference between AS and non-AS groups in age, gender, HT, DM, and DL variables ($p>0.05$). This was an expected result because the propensity score matching was done. There was a significant difference in WS ($p<0.001$). Within the groups, the AS ratio was lower in source 1, which had a very high water hardness ratio and

Table 1. Analysis results of drinking water resources

	pH	Hardness (French hardness)	Calcium (mg/L)	Magnesium (mg/L)	Consuming population (person)
Water source 1	7,67	52,80	64,20	88,48	26,248
Water source 2	7,65	18,62	48,12	12,38	85,986

Table 2. Water hardness classification[17]

French hardness	Degree of hardness
0-7,5	Soft
7,5-15	Medium hard
15-30	Hard
30 above	Very hard

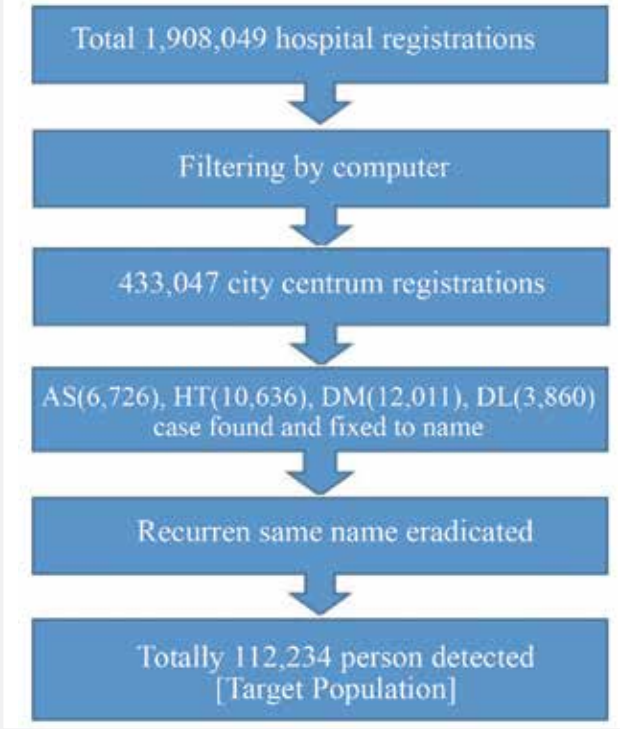

Figure 1. Data process algorithm

AS: Atherosclerotic group, HT: Hypertension, DM: Diabetes mellitus, DL: Dyslipidemia

it was statistically significant. Another notable point was the difference in magnesium value between the two sources (source 1: 88.48 mg/dL, source 2: 12.48 mg/dL). Magnesium's cardioprotective effect has been shown in studies[5-8]. In our study, we could not show whether the low atherosclerosis rate in source 1 was caused by the difference in magnesium level or by the relationship with the hardness. However, it is known that the two most important factors in forming water hardness are the calcium and magnesium level it contains[19,20]. The water hardness relationship in source 1 is a situation that may be associated with high magnesium. In addition, there was a difference in calcium levels, too (source 1: 64.20 mg/dL, source 2: 48.12 mg/dL). However, this difference was not as much as the magnesium level. These are two important values that make up the water hardness level. In many studies, it has been shown that there is an inverse correlation between water hardness level and CVH, in other words, CVH rate decreases with the consumption of high drinking water hardness[9-13]. We found similar results in our study. We even found that there was a difference between hard and very hard drinking water. Lacey and Shaper[21] stated the positive effect up to 170 mg/L water hardness level in their study. In our study, we showed that the effect continued at much higher than this level (186.2/586 mg/L).

Different hypotheses have been proposed to explain the possible inverse relationship. However, none has been enough substantiated, nor has a distinct component been found to be conclusively linked with the CVH. It may be correlated with

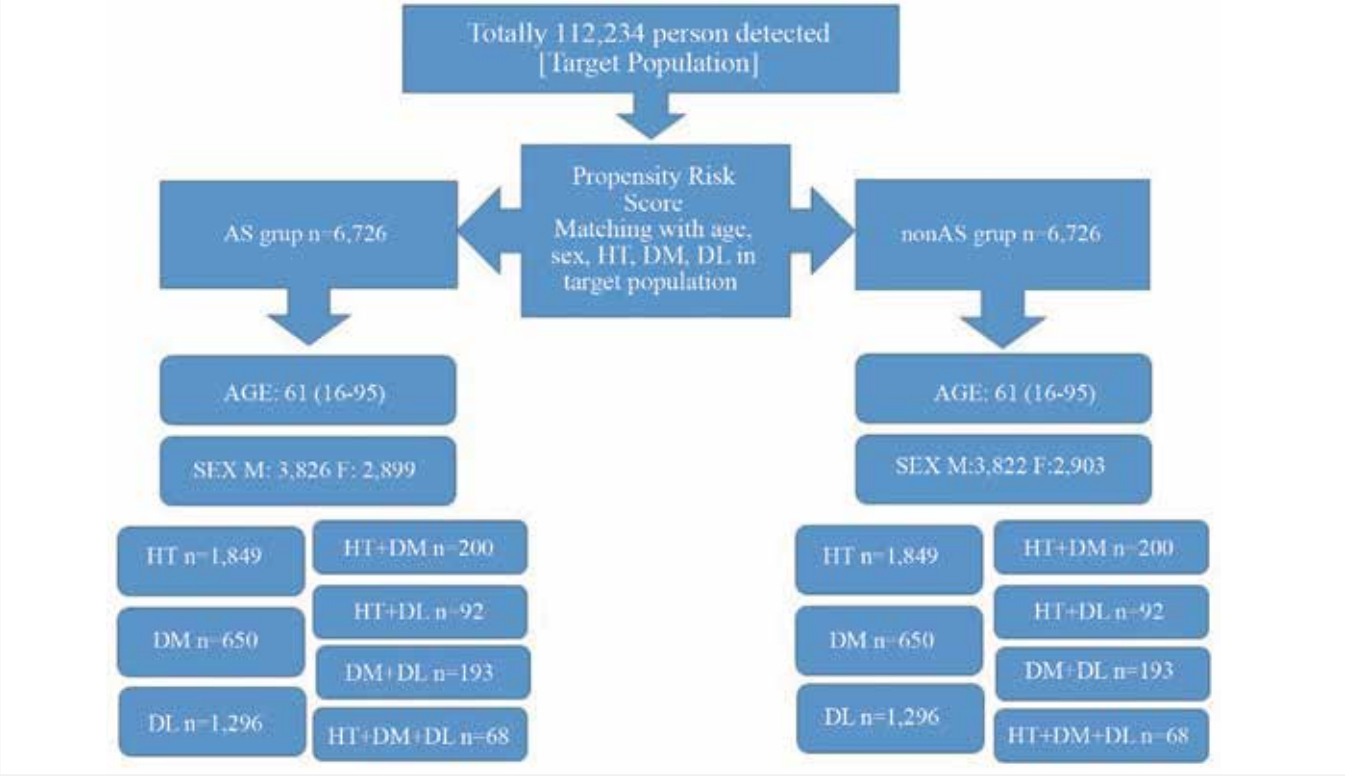

Figure 2. Propensity score matching algorithm and obtained data

AS: Atherosclerotic group, Non-AS: non-Atheroclerotic group, HT: Hypertension, DM: Diabetes mellitus, DL: Dyslipidemia, WS: Water supply, F: Female, M: Male

Table 3. Distribution of variables in groups and statistics

	Age (years)	Gender		HT	DM	DL	WS	
							Hard (2)	Very hard (1)
AS	61 (16-95)	F: 43.1%	M: 56.9%	1.849	650	1.296	5.118 (76.2%)	1.607 (23.8%)
Non-AS	61 (16-95)	F: 43.1%	M: 56.9%	1.849	650	1.296	4.585 (68.1%)	2.140 (31.9%)
P value	0.996	0.944		1.000	1.000	1.000	<0.001	

AS: Atherosclerotic group, Non-AS: non-Atheroclerotic group, HT: Hypertension, DM: Diabetes mellitus, DL: Dyslipidemia, WS: Water supply, F: Female, M: Male

P: Mann-Whitney U test in groups

high magnesium level in hard water, which has some anti-stress impacts against coronary heart disease. Magnesium is an enzyme (Na+/K+ ATPase) activator and regulates cellular energy metabolism, vascular tone, and the cell membrane ion transport. A lack of magnesium causes a reduction in the concentration of intracellular potassium and an increase in calcium levels. Magnesium deficiency may rise the contractility of blood vessels. Magnesium causes vasodilation by the stimulation of endothelial prostacyclin release and prevents vasoconstriction[6].

However, contrary to these studies, studies show that there is no relationship[14-16] and additionally, there are studies showing an increase in CVH as water hardness decreases[5,22].

This interaction is extremely important for this disease group, which is one of the most common causes of death. However, definitive interpretations are still not possible and meta-analysis suggests that further studies are required[6,18]. In addition, studies report positive effects on growth retardation, reproductive failure, gastrointestinal diseases, cancers[23-27] and diabetes[28]. When the available information on the water hardness level is examined, it is concluded that it should be seriously emphasized and considered. In addition, the contamination of drinking water, storage, transportation and heavy metal toxic containment have a separate relationship with the disease. Society may tend to consume soft hardness drinking water. Even people that are exposed to very high hardness water consumption (source 1) in Çanakkale are complaining about this and the local municipality is looking for alternative solutions to soften the water.

Study Limitations

The weak points of the study are that the individuals in the target population can contact another health center, population mobility, the use of carboys, water purifiers instead of mains water and the data that cannot be collected about other risk factors (smoking, obesity, insufficient physical activity, genetic factors, etc.).

CONCLUSION

The results of the studies on water hardness show the importance and necessity of further studies to solve the relationship between drinking water and disease in terms of public health. Our study results show that there may be an inverse relationship between the hardness level of drinking water and atherosclerosis. We believe that, to obtain high scientific data, it is necessary to support the results with field studies in appropriate locations and to raise the awareness of the public about drinking water according to the results. We strongly recommend that this issue also should be emphasized such as high blood pressure, smoking, obesity, diabetes, high cholesterol and similar risk factors.

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Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Çanakkale Onsekiz Mart University (2011-KAEK-27/2020-E.2000096163 approval date/number: 11.11.2020/13-01).

Informed Consent: Retrospective study.

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The 33-year Retrospective Analysis of Esophageal Carcinomas: Cerrahpaşa Experience

Özefagus Karsinomlarının 33 Yıllık Retrospektif Analizi: Cerrahpaşa Deneyimi

Server Sezgin ULUDAĞ[1], Ozan AKINCI[2], Sefa ERGÜN[1], Ergin ERGİNÖZ[1], Ahmet Necati ŞANLI[1], Nuray KEPİL[3], Fadıl AYAN[1], Mehmet Faik ÖZÇELİK[1], Abdullah Kağan ZENGİN[1]

[1]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of General Surgery, İstanbul, Turkey
[2]Kartal Dr. Lütfi Kırdar City Hospital, Clinic of General Surgery, İstanbul, Turkey
[3]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pathology, İstanbul, Turkey

ABSTRACT

Aim: Esophageal cancer is a fatal disease where the majority of patients are diagnosed at an advanced stage. In this study, we aimed to present the demographic and clinicopathological characteristics of patients who were operated for esophageal cancer.

Materials and Methods: A total of 847 patients who underwent surgery, chemoradiotherapy, or palliative procedures for esophageal pathology between the years of 1985 and 2018 were retrospectively analyzed. Age, gender, tumor location, histopathology, surgical technique, and chemoradiotherapy history of patients were analyzed.

Results: In the study, 488 patients were male (60.5%) and 319 were female (39.5%). The ratio of males and females was 1.52. The average age was 58.6 years, and 80.1% were older than 50 years. The most common pathological material obtained was squamous cell carcinoma (67.5%), followed by adenocarcinoma (27.7%). Total esophagectomy was performed in 435 patients; distal esophagectomy was performed in 38 patients. Transhiatal esophagectomy (n=271, 62.2%) was the most common procedure that was performed.

Conclusion: Esophagectomy is the primary treatment modality for esophageal cancers. When determining the optimal treatment, appropriate patient selection, staging, and risk assessment should be made. Patient-specific treatment should be planned with a multidisciplinary approach.

Keywords: Esophageal cancer, Cerrahpaşa, esophagus, carcinoma

ÖZ

Amaç: Özefagus kanseri, hastaların çoğunun ileri evrede teşhis edildiği ölümcül bir hastalıktır. Bu çalışmada özefagus kanseri nedeniyle ameliyat edilen hastaların demografik ve klinikopatolojik özelliklerini sunmayı amaçladık.

Gereç ve Yöntem: 1985-2018 yılları arasında özefagus patolojisi nedeniyle cerrahi, kemoradyoterapi veya palyatif prosedürler uygulanan toplam 847 hasta retrospektif olarak incelendi. Hastaların yaş, cinsiyet, tümör yerleşimi, histopatolojisi, cerrahi teknik ve kemoradyoterapi öyküleri incelendi.

Bulgular: Çalışmada 488 hasta erkek (%60,5) ve 319 hasta kadındı (%39,5). Katılımcıların yaş ortalaması 58,6 olup, %80,1'i 50 yaşın üzerindeydi. Erkeklerin ve kadınların oranı sırasıyla %60,5 ve %39,5 idi. Elde edilen en yaygın patoloji materyali skuamöz hücreli karsinom (%67,5), ardından adenokarsinomdu (%27,7). Toplam özefajektomi 435 hastaya yapıldı ve 38 hastaya distal özefajektomi yapıldı. Transhiatal özefajektomi (n=271, %62,2) en sık yapılan işlemdi.

Sonuç: Özefajektomi, özefagus kanserleri için birincil tedavi yöntemidir. Optimal tedaviyi belirlerken uygun hasta seçimi, evreleme ve risk değerlendirmesi yapılmalıdır. Hastaya özel tedavi multidisipliner bir yaklaşımla planlanmalıdır.

Anahtar Kelimeler: Özefagus kanseri, Cerrahpaşa, özefagus, karsinom

Address for Correspondence: Ergin Erginöz MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of General Surgery, İstanbul, Turkey
Phone: +90 536 879 97 71 **E-mail:** erginoz@ku.edu.tr **ORCID ID:** orcid.org/0000-0002-8349-3298
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INTRODUCTION

Esophageal cancer is accepted as one of the deadliest cancers of the digestive tract. It is ranked sixth among all cancers over the world and it constitutes about 5-7% of all cancers[1,2]. Besides its longitudinal spread, the tumor may spread from the esophageal mucosa towards the submucosa and can reach the mediastinal region as well as abdominal lymph nodes by draining through the peripheral lymph nodes via perforating lymph vessels. This drainage pathway can explain why many patients are at an advanced stage at the time when the diagnosis is made.

In countries where the disease is common, diagnosis can be made at an early stage due to the developed and different screening modalities. The esophageal cancer incidence varies widely by geographical locations. "Asian Esophageal Cancer Belt" is a region that begins from Turkey, Iraq, Iran, and Kazakhstan extending up all the way to northern China. Most of the esophageal cancers in this region are squamous cell carcinoma (SCC) and it is the region with the highest incidence of esophageal cancer in the world[3]. In Turkey, SCC is seen most commonly in the Eastern Anatolia Region[2]. While SCC is the most common histological type over the world, the incidence of adenocarcinoma has gradually increased and has become dominant over time, especially in western countries[4]. The main goal of the treatment of esophageal carcinoma is to improve patient's quality of life as well as to eliminate dysphagia, which is one of the most common symptoms known. While optimistic results are obtained in early stage esophageal cancer due to the anatomical features of the esophagus, the results are poor in the advanced metastatic stage[5]. Numerous studies have reported that the substantial results are obtained through a multidisciplinary approach in the treatment of esophageal cancer[6-9]. Although the standard treatment for early esophageal carcinomas is esophagectomy, various endoscopic treatment methods have been developed for some early esophageal tumors in the past two decades. The first successful esophageal resection was performed by the French surgeon Torek in 1913[10]. Today, proximal, distal, and total esophagectomy is performed in many clinics using open or minimally invasive techniques. Reconstruction is successfully established with the help of stomach, colon and small intestine via flaps or free flaps. In this study, we aimed to present the demographic, clinical, and pathological characteristics of patients who were operated in our clinic for esophageal cancer.

MATERIALS AND METHODS

In this retrospective study, a total of 847 patients who underwent surgery, chemoradiotherapy, or palliative procedures for esophageal pathology in the Department of General Surgery of Cerrahpaşa Medical Faculty between 1985 and 2018 were examined. Ethics committee approval was obtained for the study. Patients older than 18 years of age, patients operated under elective conditions due to malignant lesions (adenocarcinoma and SCC) of the esophagus, patients who underwent palliative stenting or enteral feeding tube due to inoperable state, or those who were treated with chemoradiotherapy were included in the study. Patients with benign lesions, leiomyoma and gastrointestinal (GIS) stromal tumor according to histopathological results were excluded from the study (n=40). Patients over the age of 18 years, who were operated on for trauma or other emergency indications, were excluded. The study was designed on 807 patients.

Patient data were obtained from discharge reports, surgical reports, and pathology reports in the hospital database. Age, gender, symptoms, location of the tumor, histopathological diagnosis, applied surgical technique, neoadjuvant and adjuvant radiotherapy and chemotherapy history of the patients were recorded. In addition, the clinical stages of the patients were evaluated according to the tumor node metastasis (TNM) staging system[5]. Patients with no metastases and no contraindications for the operation were considered eligible for surgical resection. Various surgical techniques are available for the surgery of the esophagus. Transhiatal esophagectomy was defined as total esophagectomy with the addition of abdominal and cervical incisions without thoracotomy. The Ivor Lewis procedure was defined as esophagectomy with abdominal and right thoracic incisions. Lastly, the McKeown's operation was defined as esophagectomy with abdominal, right thoracic and cervical incisions.

Statistical Analysis

Descriptive statistics were carried out. Mean and standard deviation was calculated for continuous variables, and frequencies and numbers for categorical variables. Inferential statistical analysis could not be performed because there was no group comparison.

RESULTS

The average age of 847 patients was 58.1 years and 521 (61.5%) were male and 326 (38.4%) were female. The mean age of the patients included in the study with esophageal malignancy (adenocarcinoma and SCC) (n=807) was 58.6 years and 80.1% of them were older than 50 years (Table 1). The rates of males and females in patients with esophageal malignancies were 60.5% and 39.5%, respectively (male/female=1.52). The average age of male patients was 59.2 (20-89) years, and the average age of female patients was 57.6 (18-86) years. In terms of symptoms, dysphagia was seen in 90%, weight loss was seen in 64%, odynophagia was seen in 15%, hematemesis was seen in 4%, and cough and hoarseness were seen in 2% of the patients.

As a result of the pathological examination of the endoscopic biopsy and surgical resection materials, it was found that 95.2% (n=807) of the cases had malignant esophageal neoplasms. In pathology materials, SCC was observed the most frequently (67.5%) and the second most common was adenocarcinoma (27.7%). The rest of the pathologies included chronic esophagitis,

GIS stromal tumors, and leiomyoma in decreasing order or observation (Table 1). In terms of tumor grade, 9.3% of the tumors were well differentiated (Grade 1), 50% were moderately differentiated (Grade 2), 18.5% were poorly differentiated (Grade 3), and 4.2% were very poorly differentiated (Grade 4). The rate of cases whose histopathological grade could not be determined (Grade X) was 17.8%. When the cases of esophagitis were examined, it was seen that these patients were operated due to corrosive substance drinking or stricture secondary to chronic esophagitis. Tumors were most commonly localized in the distal esophagus (44.9%), followed by middle and upper esophagus in decreasing order of occurrence (Table 1). Surgical resection was performed in 473 of the patients. Total esophagectomy was performed in 435 patients, and distal esophagectomy was performed in 38 patients. Transhiatal esophagectomy (n=271, 62.2%) was accepted to be the most common total esophagectomy procedure performed (Table 1). In 187 patients who were not operated due to irresectable state, neoadjuvant chemotherapy was applied. Enteral feeding tube for palliative therapy was applied to 63 patients with metastatic esophageal cancer, and esophageal stent procedure was applied to 31 patients. In the study, 93 patients who continued their treatment in other centers or refused treatment were excluded from follow-up. GIS continuity was established by anastomosis of the stomach with the proximal esophagus inside the thorax in cases who underwent distal esophagectomy. Among the patients who underwent total esophagectomy, 374 patients were reconstructed with stomach interposition (86%), 48 patients were reconstructed with colon interposition (11%), and 13 patients were reconstructed with jejunum interposition (3%).

Table 1. Demographic, pathological and surgical results of the study

Age	Female n (%)	Male n (%)	Total n (%)
<29	4	8	12 (1.48)
30-39	24	30	54 (6.69)
40-49	42	52	94 (11.64)
50-59	67	125	192 (23.79)
60-69	109	171	280 (34.69)
>70	73	102	175 (21.68)
Total	**319 (39.5)**	**488 (60.5)**	**807**
Histological diagnosis		**n (%)**	
Squamous cell carcinoma		572 (67.5)	
Adenocarcinoma		235 (27.7)	
Esophagitis*		26 (3.0)	
Leiomyoma		8 (0.9)	
GIST**		6 (0.7)	
Anatomical localization		**n (%)**	
Upper 1/3 esophagus		172 (21.3)	
Middle 1/3 esophagus		273 (33.8)	
Lower 1/3 esophagus		362 (44.9)	
Total		807 (100)	
Surgical technique		**n (%)**	
Transhiatal esophagectomy		271 (62.2)	
Ivor Lewis procedure		82 (18.8)	
McKeown procedure		57 (13.1)	
Minimally invasive (toracoscopic + laparoscopic)		25 (5.7)	
Total		435 (100)	

*Chronic esophagitis and esophagitis secondary to corrosive damage.
**Gastrointestinal stromal tumor.
GIST: Gastrointestinal stromal tumors

DISCUSSION

The incidence, morbidity, and mortality rates of esophageal cancer have varied greatly over the past 30 years, but it is still one of the cancer types with the highest mortality worldwide. In both sexes, the incidence of esophageal cancer increases proportionally with age and it peaks at the 7th decade[11]. The incidence in men is observed to be 2-4 times higher than that in women[12]. This male to female ratio rate has been reported as 4.9 in adenocarcinomas and 1.2 in SCC[13]. In our study, 58.4% of the patients with esophageal cancer were between the ages of 50 and 70 years, and the male/female ratio was 1.52. It was seen that the demographic features in this study were compatible with the literature.

In esophageal cancer, dysphagia is the most common presenting symptom, followed by weight loss[7]. Smoking, alcohol intake, poor diet, poor socioeconomic conditions, infections (such as HIV, *Helicobacter pylori*), genetic factors, gastroesophageal reflux and Barrett's esophagus are the main risk factors[14]. For this reason, especially in elder patients who present with dysphagia and have a history of risk factors considered to be as a red flag, esophageal imaging should be promptly completed first followed by endoscopy in order to exclude esophageal malignancy. In our series, the most common presenting symptom was dysphagia.

Esophageal cancers are mainly observed in the lower one-third segment of the esophagus, followed by the middle one-third and upper one-third segments, in decreasing order of occurrence[15]. While nearly 75% of all adenocarcinomas are localized to the distal esophagus, SCC are equally distributed in the distal two-thirds segment of the esophagus[16]. In our study, in accordance with the literature, esophageal malignancies were mostly located in the lower 1/3 segment.

Until 30 years ago, the ratio of SCC to adenocarcinoma of esophagus cancer was higher in favor of SCC. Since 2000's, this ratio seemed to increase in favor of adenocarcinoma (5:1) possibly due to the various adaptations of the risk factors[13,17]. Although the underlying cause may change, the reason for this change in the histopathological pattern is unknown since many different risk factors are involved in the development of esophageal cancer[7,13]. In our study, 67.5% of the patients had SCC, while 27.7% of the patients had adenocarcinoma. We believe that the reason why the rate of adenocarcinoma is not

as dominant as reported in the literature is that our country is in the Asian Esophageal Cancer Belt and SCC is the dominant type like other societies in this generation.

The TNM classification system is widely used for the staging of esophageal cancer. Staging is a key factor in determining the method of treatment. Although the most important radiological imaging in staging is ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography and endoscopic ultrasonography, laparoscopy and/or thoracoscopy also has an important role in selected cases[18].

The ideal treatment method for esophageal cancer has not been determined. Multimodal therapies using chemotherapy or chemoradiotherapy combined with surgical treatment give promising results. Treatment is adjusted according to the stage of the disease and clinical evaluation of the patient. Curative and palliative surgery, endoscopic intervention, medical oncology, and radiotherapy treatments are tailored for each patient. Endoscopic mucosal resection (EMR) is a reliable and curative treatment for early esophageal cancers (Tis and T1a, T1bsm1)[19]. However, we did not have EMR experience in our clinic. Esophagectomy is the preferred treatment for T1b, submucosal layer-1 (sl1), sl2, and sl3 tumors with lymphovascular invasion or other risk factors[9]. Neoadjuvant chemoradiotherapy and esophagectomy (with lymphadenectomy) should be performed in locally advanced resectable tumors. Chemotherapy, chemoradiotherapy and palliative treatments are reserved for non-resectable tumors. Salvage esophagectomy is the surgical method of choice for residual tumor or recurrence after chemoradiotherapy[9].

Currently, the most common open operations in resectable cases are transhiatal esophagectomy, Ivor Lewis surgery, and McKeown surgery[7,20]. Wide resection should be performed in these operations since esophageal tumors can spread submucosally throughout the esophageal layers and SCC causes longitudinal lymph flow skipping areas[21]. Hagen et al.[22] reported that survival was significantly better in the patient group who underwent en-block esophagectomy compared to the transhiatal esophagectomy group. In contrast, in a randomized clinical study by Hulscher et al.[23] in which transhiatal lymphadenectomy in 106 patients and transthoracic plus en-block lymphadenectomy in 114 patients was performed, it was observed that there was no difference between these two techniques in terms of postoperative mortality, but the complication rate of transthoracic resection and length of hospital stay were seen to be higher. In transhiatal esophagectomy, blind esophagectomy is performed without thoracotomy; although the failure of intrathoracic lymphadenectomy is the weakest aspect of the method, the complication rate, especially pulmonary complications, is observed less than surgeries that involve thoracotomy. This is also the type of operation that patients are able to tolerate better. In the last 33 years, we found that transhiatal esophagectomy technique was the most preferred technique (62.2%) in our clinic. One of the most important criteria in the selection of surgical technique is the surgeon's experience. For this reason, the surgeons in our clinic did not prefer the mediastinal anastomosis, so total esophagectomy was the most performed. In our clinic, mostly stomach was used for reconstruction. However, as is known, it can be performed in jejunum and colon interposition. Colon and jejunum reconstructions require more anastomosis than stomach reconstructions, technically more difficult and septic complications may occur. Therefore, it was not preferred in our clinic except for recurrence cases.

Advantages of minimally invasive esophagectomy, which has been increasingly applied in the last two decades, include smaller incisions, preservation of post-operative pulmonary function, fewer blood loss and complications, and shorter intensive care and hospital stay[24-26]. There are publications on the long-term oncological results of minimally invasive surgeries and whether the surgical margins of the esophagus and stomach are sufficient. However, in recent randomized controlled prospective studies, minimally invasive surgery was found to be noninferior in terms of oncologic results compared to open esophagectomy[27,28]. Minimally invasive surgery is used safely for oncological pathologies as well as benign pathologies (diverticulectomy)[29]. Thoracoscopic and laparoscopic total esophagectomy has been successfully performed in 25 cases in our clinic.

T4b tumors are the advanced stage cancers that invade non-resectable structures such as the aorta, left atrium, and spine. In these cases where curative treatment is not possible, palliative modalities should be performed towards symptoms in order to delay death. Chemoradiotherapy is a preferred approach for patients who are eligible for combined therapy because it provides better palliation than radiotherapy alone and increases the probability of long-term progression-free survival[30]. Patients who can take semi-solid food are treated with chemoradiotherapy, and radiotherapy is effective after six weeks[31]. Palliation can be established with an endoscopic stent in patients who can only take fluid or cannot swallow saliva. Endoscopic dilatation is another technique of treatment modality performed in these patients. Percutaneous endoscopic gastrostomy, tube gastrostomy/jejunostomy can be applied for nutritional support in patients who are not suitable for stenting or dilatation[32].

Study Limitations

Since our study is a retrospective clinical study, data regarding disease stage, intraoperative and postoperative complications, mortality rates and survival times of many patients could not be obtained. In addition, the fact that it is single-centered institutional study and the fact that the treatment modalities have been updated in 33 years are the other limitations of our study.

CONCLUSION

Esophagectomy is still the main treatment method for esophageal cancers, but the majority of patients are

unresectable due to systemic spread at the time of diagnosis. We believe that through better follow-up and surveillance programs, aggressive multidisciplinary approach, and development of minimally invasive methods, morbidity of esophagectomy will decrease, survival will be prolonged, and patients' quality of life will increase.

Ethics

Ethics Committee Approval: The study were approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (date: 09.07.2020, protocol number: 86672).

Informed Consent: Consent form was filled out by all participants.

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Authorship Contributions

Surgical and Medical Practices: S.S.U., F.A., M.F.Ö., A.K.Z., Concept: S.S.U., O.A., S.E., F.A., M.F.Ö., A.K.Z., Design: S.S.U., O.A., S.E., F.A., M.F.Ö., A.K.Z., Data Collection or Processing: S.S.U., O.A., S.E., E.E., A.N.Ş., N.K., Analysis or Interpretation: S.S.U., O.A., S.E., E.E., A.N.Ş., N.K., Literature Search: S.S.U., O.A., S.E., E.E., A.N.Ş., N.K., Writing: S.S.U., O.A., S.E., E.E., A.N.Ş.

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Morphometric Analysis of Celiac Mesenteric Trunk in Computed Tomography Images and a Review of the Literature

Bilgisayarlı Tomografi Görüntülerinde Çölyak Mezenterik Trunkusun Morfometrik Analizi ve Literatürün Gözden Geçirilmesi

Hadi SASANI

Tekirdağ Namık Kemal University Faculty of Medicine, Department of Radiology, Tekirdağ, Turkey

ABSTRACT

Aim: Evaluation of the frequency of variation and morphometric findings of the rare Celiac mesenteric trunk (CMT) in Tekirdağ province using computed tomography (CT) images.

Materials and Methods: A study population containing 1,919 patients (1,313 males, 606 females; mean age 60.47±14.88 years) with any indication of CT angiographic examination was reviewed retrospectively. The length, diameter, vertical and horizontal angles and orientations (upward, downward, right-sided, left-sided), the level of origin from abdominal aorta and their types were analyzed.

Results: Twenty-three (1.19%) CMT patients were detected. In vertical angle evaluation 20 (87%) cases had downward and three (13%) had upward orientations. In horizontal angle assessment 11 (47.8%) cases had right-sided and 12 (52.2%) had left-sided orientations. 60% of type 1 CMT cases had right-sided orientation, while 75% of type 2 cases had left-sided orientation and in both of types, the majority part had downward orientation. Fifteen (65.22%) cases were type 1 and 8 (34.78%) cases were type 2. There was a negative weak correlation between the length and diameter of CMT (p=0.048, r=-0.417). The most common level of origin of CMT was in L1-L2 level (30.4%). The most common level in type 1 was L1-L2 (40%, n=6), while L1 and L1-inferior-end-plate with the same distribution were in type 2 (37.5%).

Conclusion: In CMT, especially in terms of prior to surgical planning and arterial interventional procedures morphometric assessment is highly important. In this study, CMTs were found to be mostly type 1, as well as downward (17 degrees±14.28) and left-sided (73 degrees±6.88) orientation.

Keywords: Celiac artery, mesentery, computed tomography

ÖZ

Amaç: Bilgisayarlı tomografi (BT) görüntüleri kullanılarak Tekirdağ ilindeki nadir görülen Çölyak mezenterik trunus (CMT) varyasyon sıklığının ve morfometrik bulgularının değerlendirilmesidir.

Gereç ve Yöntem: Herhangi bir indikasyon ile BT anjiyografik incelemesi yapılan 1.919 hastayı (1.313 erkek, 606 kadın; ortalama yaş 60,47±14,88) içeren bir çalışma popülasyonu, retrospektif olarak incelendi. Uzunluk, çap, dikey ve yatay açılar ve oryantasyon (yukarı, aşağı, sağ taraflı, sol taraflı), abdominal aortadan köken aldığı düzey ve CMT tipleri analiz edildi.

Bulgular: Toplamda 23 (%1,19) CMT hastası saptandı. Dikey açı değerlendirmesinde 20 (%87) olguda aşağı, üç (%13) olguda yukarı doğru oryantasyon mevcuttu. Yatay açı değerlendirmesinde 11 olguda (%47,8) sağ taraflı, 12 olguda (%52,2) sol taraflı oryantasyon vardı. Tip 1 CMT olgularının %60'ı sağ taraflı oryantasyonlu iken, tip 2 olguların %75'inin sol taraflı oryantasyonu vardı ve her iki tipte de çoğunluğun, aşağıya doğru oryantasyonu vardı. On beş (%65,22) olgu tip 1 ve 8 (%34,78) olgu tip 2 olarak saptandı. CMT'nin uzunluğu ve çapı arasında negatif zayıf bir korelasyon vardı (p=0,048, r=-0,417). CMT'nin aortadan en yaygın orijin seviyesi L1-L2 düzeyi idi (%30,4). Tip 1'de en yaygın seviye L1-L2 (%40, n=6) iken, tip 2'de (%37,5) aynı dağılım ile L1 ve L1-alt end-plate düzeyi idi.

Sonuç: CMT'de özellikle cerrahi planlama ve arteriyel girişimsel prosedürler açısından morfometrik değerlendirme son derece önemlidir. Bu çalışmada, CMT'lerin çoğunlukla tip 1, aşağı (17 derece±14,28) ve sol taraflı (73 derece±6,88) oryantasyon olduğu bulunmuştur.

Anahtar Kelimeler: Çölyak arter, mezenter, bilgisayarlı tomografi

Address for Correspondence: Hadi SASANI MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Radiology, Tekirdağ, Turkey
Phone: +90 282 250 74 55 **E-mail:** hsasani@nku.edu.tr **ORCID ID:** orcid.org/0000-0001-6236-4123
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INTRODUCTION

Celiac trunk (CTR) is the major ventral vessel arising from the abdominal aorta (AA) at the level of T12, gives branches including the left gastric artery (LGA), common hepatic artery (CHA) and splenic artery. CTR with the superior mesentery artery (SMA) supplies the majority part of gastrointestinal tract and abdominal viscera[1-3]. SMA is the second major ventral branch of AA arising at the level of L1 and running down in front of the third part of the duodenum, and it supplies the small intestine.

Many variation forms of these arteries have been reported in several studies[4-7]. The Celiac mesenteric trunk (CMT), which comprises CTR and SMA, is the rarest arterial variation with the reported prevalence of 0.46-3.06%[7-12]. Determination and demonstration of these variations is highly important to detect the underlying pathology of CMT such as thrombosis-occlusion[13,14] or stenosis[13,15,16] and to prevent any undesirable complications and fatal outcomes prior to surgical and interventional vascular procedures[17-19]. Cross-sectional modalities such as computed tomography (CT) play an essential role in the diagnosis. CT is easy to apply, rapid, non-invasive imaging method with an excellent spatial and temporal resolution.

The aim of this study is to define the morphometric results of the rare CMT variation using CT images in the light of the literature.

MATERIALS AND METHODS

Study Population

Between February 27, 2017 and March 20, 2020, data of 4,024 patients with any indication and having CT angiographic examinations were scanned from hospital Picture Archive and Communication System by an eight-year experienced radiologist. From this population, 1,919 patients (1,313 males, 606 females; minimum age=18-year-old, maximum=103-year-old, mean age=60.47±14.88 years) with CT angiographic examinations including abdominal vascular structures (CTR, SMA and/or renal arteries) and those with best quality of diagnostic imaging were enrolled in the study and were reviewed retrospectively. CT examinations with poor image quality, non-abdominal CT examinations or those including pathologies affecting vascular structures (any intervention/surgery, stenosis, aneurysm, tumour) were excluded from the study.

A summary of the electronic search in the databases and algorithm of inclusion are shown in Figure 1.

Ethical Statement

This study was approved by the university/local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Tekirdağ Namık Kemal University Local Ethical Committee of the institution approved the study protocol (approval number: 2020.39.02.13)

Data Acquisition

CT acquisitions were performed on 128 row multi-detector CT device (Aquilion™ Prime, Canon Medical Systems).

Scanning Protocol

CT scanning parameters were as follows for each protocol: 100-250 mAs modulated by personal body mass index dose; 100-140 kV tube voltage, 0.5 mm x 80 collimation, 0.35 second gantry rotation time, 0.813 pitch factor, slice thickness 1 mm and slice interval 0.8 mm. For intravenous bolus injection of non-ionic contrast material (350 mg/100 mL, iohexol, Omnipaque®; GE Healthcare, Cork, Ireland), a mechanical injector was used at a flow rate of 4.5-5.0 mL/sec.

CT Image Assessment

An eight-year experienced radiologist retrospectively analysed the CT images and assessed all of the morphometric measurements (diameter, length, angle and orientation classification of CMTs).

CMT Morphologic Analysis

The length, diameter, and vertical and horizontal angles as well as vertical orientation (upward, downward) and horizontal orientation (right or left-sided) were analysed morphologically. The length of CMT was measured from the trunk's outlet till branching level. Vertical and horizontal angles were measured as the angle between the artery outside border and the horizontal plane line (angle of emergence). CMTs were categorized depending on their locations, orientation and the level of origin from the AA. The diameters of CMTs were measured both on sagittal and coronal planes craniocaudally (Figure 2).

In addition, type classification of CMT cases was evaluated according to the classification by Tang et al.[11]. CMT was classified into five types:

Type 1: Hepato-gastro-spleno-mesenteric trunk,

Type 2: Hepato-spleno-mesenteric trunk with the LGA arising from the AA,

Type 3: Gastro-spleno-mesenteric trunk with the CHA arising from the AA,

Type 4: Hepato-gastro-mesenteric trunk with the splenic artery arising from the AA,

Type 5: Any other variation that meets the above definition of the CMT (LGA originating from other arteries except the AA, CTR and single common trunk; the CHA arising from the SMA).

Statistical Analysis

Statistical package program (SPSS version 17, Chicago, USA) was used in analysing data. The variables were investigated using visual (histograms, probability plots) and analytical methods to determine whether they were normally or not normally distributed. Investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Pearson test. Descriptive statistics were used in data analysis. A 5% type 1 error level was used to infer statistical significance.

RESULTS

CMT Cases

Among the patient population having CT angiographic examinations (n=1919), 23 (1.19%) cases were detected to be CMT. Of 23 cases, 20 (87%) were male and three (13%) were female, with the mean age of 57.4±16.62 years (range: 18-83 years).

Morphometric Analysis

The mean length of the CMT was 25.35±9.13 (range: 7.6-38 mm), the mean diameter of CMT was 12.06±2.12 mm (range: 8.5-15.6 mm), the mean vertical and horizontal angles were 18.48±14.16 degrees (range: 0.8-51.3 degrees) and 73.65±10.74 degrees (range: 54-103.4 degrees), respectively.

A negative weak correlation was found between the length and diameter of CMT (p=0.048, r=-0.417) (Figure 3).

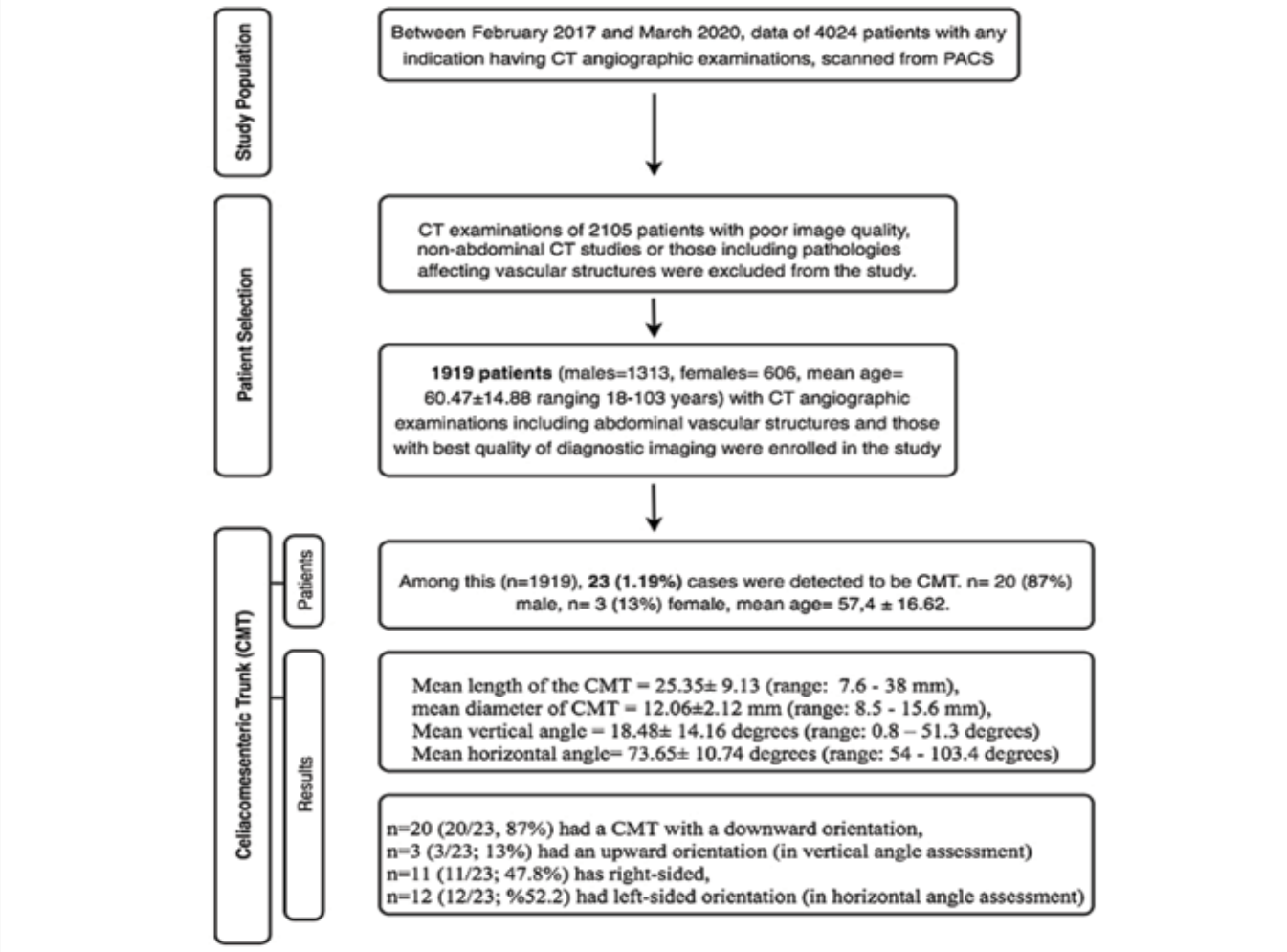

Figure 1. The flow chart diagram of the study

CT: Computed tomography, PACS: Picture Archiving and Communication Systems

In vertical angle assessment of 23 patients, 20 patients (20/23; 87%) had a CMT with a downward orientation and three patients (3/23; 13%) with an upward orientation. Eleven (11/23; 47.8%) of the patients had a CMT with right-sided and 12 (12/23; 52.2%) with a left-sided orientation in horizontal angle assessment.

The mean vertical angle with downward and upward orientations were found as 17±14.28 degrees and 28.56±9.61 degrees, respectively. The mean horizontal angle with right-sided and left-sided orientations were found as 74.44±14.16 degrees and 73±6.88 degrees, respectively.

In CMT population, 15 (65.22%) patients were detected to be type 1 and 8 (34.78%) patients were type 2, respectively (Figure 4). Although there was male preponderance in both of types, type 1 was the most common type in the male population (n=14, 93.3%), while type 2 was the most common in the females (n=2, 25%). Sixty percent (n=9) of type 1 CMT patients tended to have right-sided orientation, while 75% of type 2 CMT patients (n=6) had a tendency of left-sided orientation. In both of types, the majority parts of CMT population (type 1: n=13, 87.6%; type 2: n=7, 87.5%) showed to have downward orientation (Table 1).

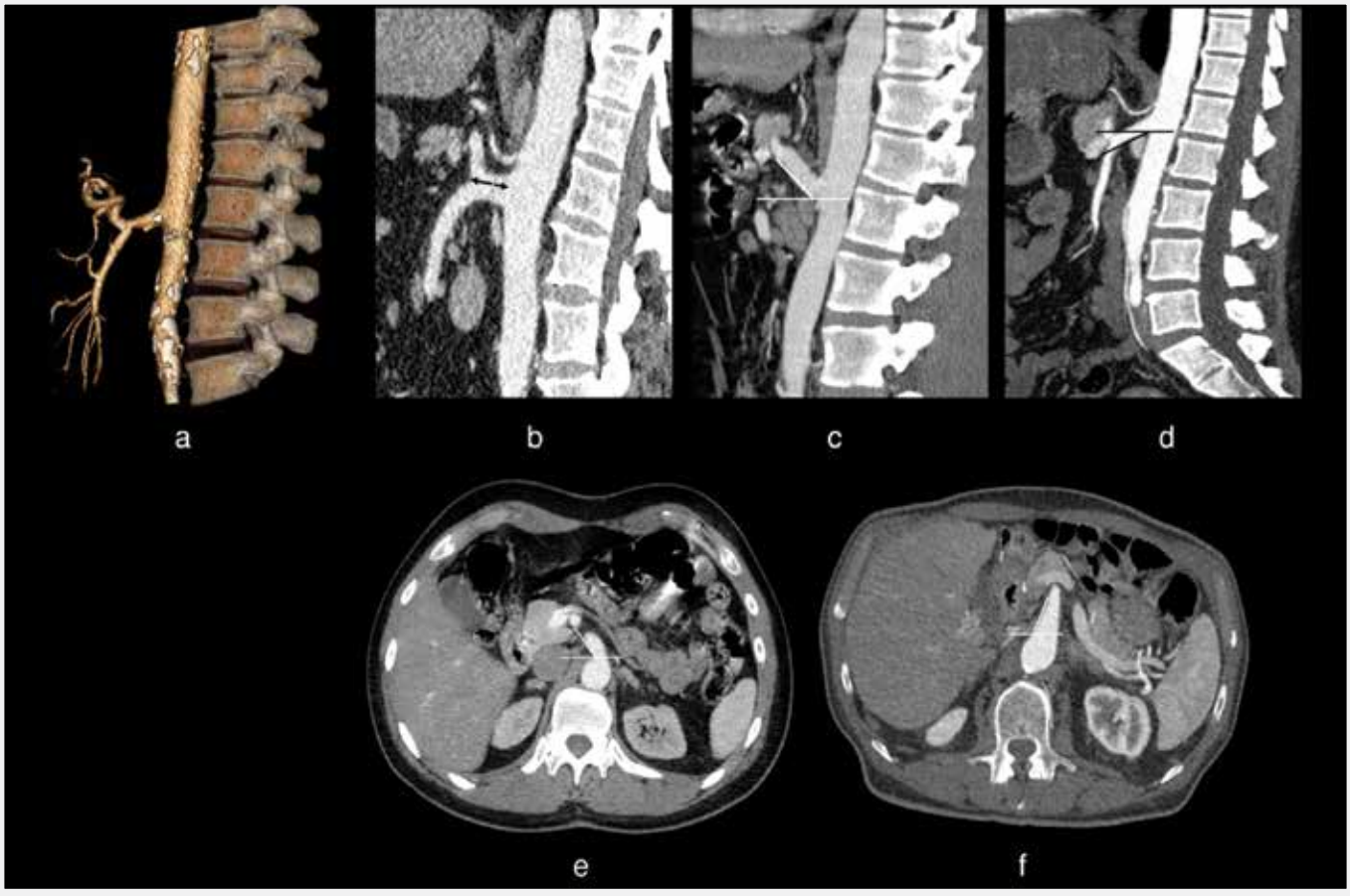

Figure 2. Morphometric evaluation of Celiac mesenteric trunk (CMT) population. (a) 3D reformat image of a CMT case, (b) measurement of the length (black double headed arrow) and diameter (white double headed arrow) of the CMT; vertical angles or angle or emergence: (c) upward orientation and (d) downward orientation; horizontal angles (e) right-sided orientation and (f) left-sided orientation

Table 1. The number of Celiac mesenteric trunk cases according to the types and orientations

Type	Vertical orientation		Total	Transvers orientation		Total
	Downward n (%)	Upward n (%)	n (%)	Right-sided n (%)	Left-sided n (%)	n (%)
Type 1	13 (86.7%)	2 (13.3%)	15 (100.0%)	9 (60.0%)	6 (40.0%)	15 (100.0%)
Type 2	7 (87.5%)	1 (12.5%)	8 (100.0%)	2 (25.0%)	6 (75.0%)	8 (100.0%)
Total	20	3	23	11	12	23

The distribution of CMT origin levels was most common in L1-L2 (30.4%, n=7), followed by L1 (26.1%, n=6) and with the same number of patients in T12-L1 and L1- inferior-end-plate level (21.7%, n=5), respectively. The level of origin in type 1 was detected to be most common in L1-L2 level (40%, n=6) and the level of origin in type 2 was mostly at both levels in the L1 and L1-inferior-end-plate (37.5%, n=3). Type 1 was the most dominant type (65.2%, n=6) among all of the levels (T12-L1, L1, L1-inferior- end-plate and L1-L2), while type 2 was dominant only in L1-inferior-end-plate level (60%, n=3). L1-L2 level was the most common level of origin in male population (35%, n=7), while L1 was the most common level in females (66.7%, n=2) (Table 2).

DISCUSSION

In the literature, some studies reported the variations of CTR and CMT with different range of incidence[7-12] and quantitative measurements (length, diameter, type and level of origin, angle)[8,11,19-22]. In the current study, unlike the literature, both vertical and horizontal orientations, angles of CMTs and their relationship with their types have been analysed. In the present study, the incidence of CMT was found to be 1.2% in Tekirdağ province and more attention should be paid to CMT vascular evaluation. It is more common for CMT variation to be longest type, type 1, L1 output-level and downward orientation, and these parameters should be considered in vascular surgery or interventional procedures to be performed in the population in this region.

During embryonic period, the 10th to 13th vitelline arteries communicate between the aorta and a primitive ventral

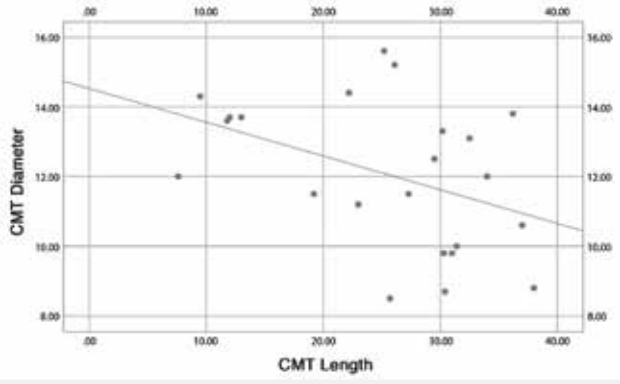

Figure 3. A negative weak correlation between the length and diameter of Celiac mesenteric (p=0.048, r=-0.417)

CMT: Celiac mesenteric trunk

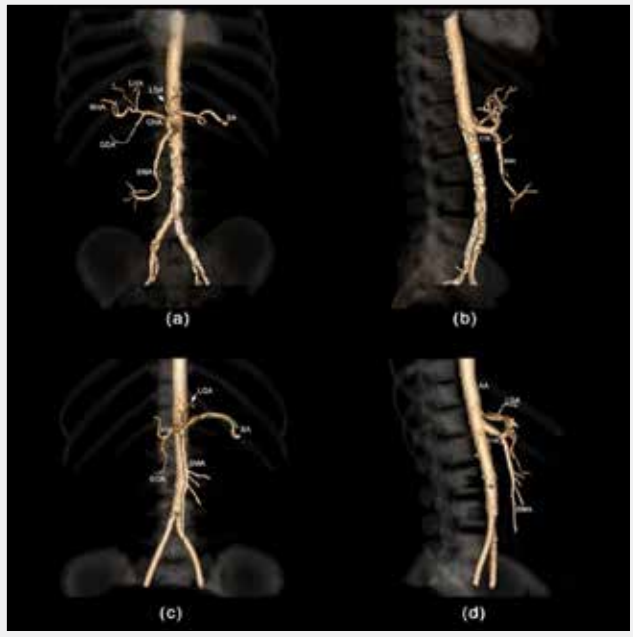

Figure 4. Celiac mesenteric trunk (CMT) types: (a) coronal (b) sagittal 3D reformat computed tomography (CT) images of CMT type 1 (hepato-gastro-spleno-mesenteric trunk); (c) coronal (d) sagittal 3D reformat CT images of CMT type 1 (hepato-spleno-mesenteric trunk with left gastric artery arising from the abdominal aorta)

Table 2. Distribution of Celiac mesenteric trunk cases by origin level and types

			Level of origin				Total
			T12-L1	L1	L1 inferior-end-plate	L1-L2	
Type	Type 1	(n)	**4**	**3**	**2**	**6**	**15**
		Type (%)	26.7	20.0	13.3	40.0	100.0
		Level of origin (%)	80.0	50.0	40.0	85.7	65.2
	Type 2	(n)	**1**	**3**	**3**	**1**	**8**
		Type (%)	12.5%	37.5%	37.5%	12.5%	100.0%
		Level of origin (%)	20.0%	50.0%	60.0%	14.3%	34.8%
Total		(n)	**5**	**6**	**5**	**7**	**23**
		Type (%)	21.7%	26.1%	21.7%	30.4%	100.0%
		Level of origin (%)	100.0%	100.0%	100.0%	100.0%	100.0%

anastomotic artery. The regression of the ventral anastomosis and vitelline arteries (11th and 12th) and the persistence of the 10th and 13th roots provide giving origin to the CTR and the SMA. When the 10th to 12th vitelline arteries regress and a large portion of the ventral anastomosis persists (13th), CMT occurs (Figure 5)[23].

There are some classifications about CTR variations available in the literature. Lipshutz[24] suggested a classification of CTR into four types in 1917, and Adachi et al.[25] classified more detailed anatomical variation of CTR and SMA in six types in 1928. Followed by Morita[26], Michels[27] and Uflacker[28] presented their classifications. In the recent work by Tang et al.[11], they have focused on the classification of CMT variation. In the current study, CMT type 1 according to Tang classification is compatible with Adachi type 4, and Tang type 2 is compatible with Adachi type 3.

Although gender and race had an effect on the presence or absence of variations in CTR[5], most studies[5,29,30] revealed that it had only relationship with ethnicity and origin of the study population, not with gender. According to the literature, Japanese, Caucasian, Korean, Indian and black-coloured populations have more variations of CTR, respectively[5]. On the other hand, in a meta-analysis including 36 studies (total subjects n=17,391) from fourteen countries and four continents, there was a preponderance of males (male/female ratio of 2.36:1). The pooled prevalence estimates of variant CTR with 95% confidence interval depending on the geographical region were mostly found in South America (0.3340) followed by Europe, West Asia, Africa and West Asia, respectively[12]. To date, the highest incidence of CMT has been reported as 3.06% in 171 CMT patients[11]. The incidence of CMT in the current study was detected to be 1.2%.

The length of CTR varies between 8 and 40 mm[8]. In the study by Tang et al.[11], they divided 171 CMT patients into long-type (17-39 mm) and short-type (6-14 mm) CMT groups. The long type (61.99%) was more common than the short type. In the current study, CMT length was ranging from 7.6 mm to 38 mm; similarly, the longest type (n=18; mean value=29.4 mm±5.2, range: 19.2 mm-38 mm) was more common than the shortest-type (n=5; mean value=10.78 mm±2.19, range: 7.6 mm-11.8 mm).

In the study by Tang et al.[11], the most common type was found to be type 1 that was accounting for 56.14%, followed by type 2 33.33%, type 3 2.34%, and type 4 1.75%. Similarly, in the

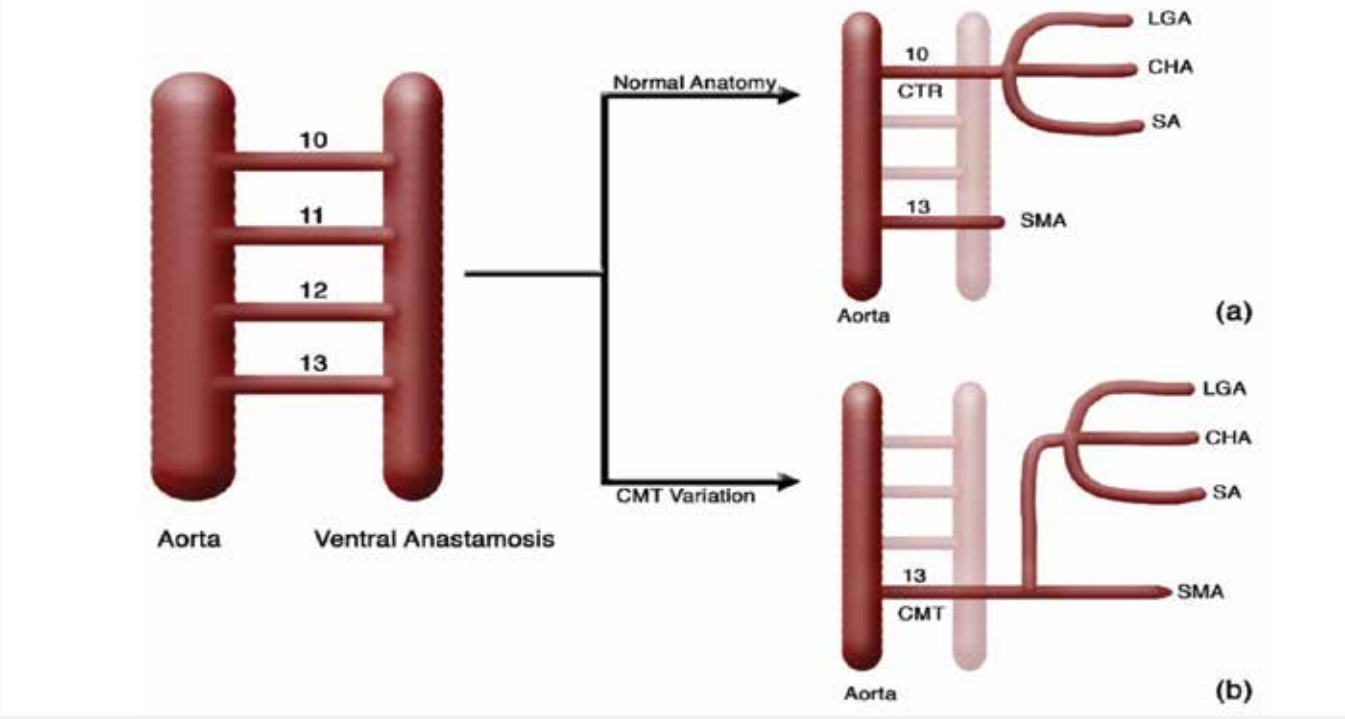

Figure 5. Embryological development of normal mesenteric vascular structures and the Celiac mesenteric trunk (CMT). (a) The 10th-13th vitelline arteries communicate between the aorta and a primitive ventral anastomotic artery (b) When the 10th to 12th vitelline arteries regress and a large portion of the ventral anastomosis persists (13th), CMT occurs

*CHA: Common hepatic artery, LGA: Left gastric artery, SA: Splenic artery, CTR: Celiac trunk, SMA: Superior mesenteric artery, *: Liver segment 4A feeding artery*

current study, the most common type was type 1 (65.22%) followed by type 2 (34.78%).

The diameter of CTR has been reported to range from 6.61±1.67 mm to 8±0.9 mm in some studies in the literature[19,20,22]. In another study, the mean diameter of CTR was measured as 6.22 mm (ranging from 5.4 mm to 7.3 mm) and the mean diameter of CMT was 8.42 mm (ranging from 5.2 mm to 11.6 mm)[10]. In the study on 155 adult cadavers, it was found that the length of CTR increased quickly until the age of 20 years (in new-borns ranging from 3 mm to 8 mm; in adults ranging from 15 mm to 54 mm), while the diameter of CTR increased by the age (new-borns: 1.5-2.0 mm, adults: 3.1-4.3 mm). Also, she mentioned the measured diameter and the length of CTR in pyknics (obese or rounded body structure) were found to be larger (length: 12-29 mm), while in leptosomes (thin body structure), the diameter was smaller (3.1 mm), but the length was greater (39-54 mm)[21]. In the current study, the mean diameter of CMT was measured as 12.06±2.12 mm and a statistically weak negative correlation was found between the CMT length and diameter (p=0.048, r=-0.417), which means that CMT diameter increases as length decreases (Figure 3).

Although the CTR had various levels of origin ranging from the T11 to L1 vertebra, the most common level was found to be T12–L1 (45.83%) followed by T12 (29.17), L1 (22.92) and T11-T12 (2.08%), respectively[1]. Selvaraj and Sundaramurthi[2] reported the similar findings of CTR origin levels that were T12-L1 (70.7%), L1 (18.6%) and T12 vertebra (10.7%), respectively. In the study by 10 CMT patients, the most common level of origin was found to be L1 (30%); T12-L1, L1 end-plate level, L1-L2 (20%) and T12 (10%), respectively[10]. The originating level of CTR in pyknics tended to be higher, while in leptosomes, it was lower [21]. In the current study, as shown in the Table 2, the most common level of CMT origin in type 1 was found to be L1-L2 (40%, n=6), followed by T12-L1 level (26.7%, n=4); and in type 2, it was in both L1 and L1-inferior-end-plate levels with the same counts (37.5%, n=3).

The angle between CTR and AA was studied in some literatures[10,31]. The angle of emergence of CTR was reported to be less than 90 degrees, ranging from 7 to 83 degrees. Before the first branch, there was an upward shift in 95% (n=306) and downward shift in 4.36% (n=14) of 321 patients. In one patient, CTR remained straight[31]. In another study in CMT patients, in the sagittal plane, the mean angle between the CMT and AA was measured as 26.65 degrees ranging from 13.5 to 38 degrees[10]. The angle of CTR in pyknics was greater measuring between 106 and 115 degrees; in contrast, it was smaller (<73 degree) in leptosomes[21]. In the current study, both vertical and horizontal angles were studied and found to be 18.48±14.16 degrees and 73.65±10.74 degrees, respectively. The majority part of the patients was constituted with those with downward orientation (87%, n=20) in vertical angle and had left-sided orientation in horizontal angle (52.2%, n=12) assessment. Both of the reports[10,31] have studied only vertical angle between CMT and AA in which the values are in the similar ranges but none has studied the horizontal angle.

The direction of CTR is influenced by the origin of the hepatic artery and the topography of the pancreatic neck. If CTR is not the origin of the hepatic artery (gastrosplenic trunk), it is directed to the left side, attending as the splenic artery[32]. Although underdevelopment of rightward component is observed in new-borns, it is the hepatic artery that pulls CTR to the right-side[33,34].

It is very important to know other underlying diseases or pathologies associated with CMT. Aneurysm[15], stenosis[16], thrombosis[13,14], mesenteric ischemia[13,16], arterial compression (egg. median arcuate ligament syndrome)[15] and nutcracker syndrome[35] can be associated with CMT which may have important results and may affect the survival specially in the occlusive diseases[13]. Here, CT plays an important role in the detection of variation. Also, as a new technique, cinematic rendering with random sampling computational algorithms and different light maps provides a realistic depiction of anatomical details from CT data[36].

Study Limitations

The limitation of the study was that it was conducted with few patients (23 CMTs of 1919 patient population) having CT angiographic examinations. Although the incidence of variation is rare, the patient population participating in this study has the largest patient population included in the studies across the country. However, due to only three female patients, there was not a homogeneous sample group in this study. Due to the retrospective nature of the study, the patients could not be classified in their morphology as leptosomes or pyknics.

CONCLUSION

Having knowledge about arterial variations such as CMT is very important for both surgical approach and planning of interventional procedures and management of CMT-related pathologies. Particularly in vascular interventions, morphometric features of the arterial structures are most of value. As a result, in this study, CMT was found to be mostly type 1, as well as downward (17 degrees±14.28) and left-sided (73 degrees±6.88) orientation.

Ethics

Ethics Committee Approval: Tekirdağ Namık Kemal University Local Ethical Committee of the institution approved the study protocol (approval number: 2020.39.02.13).

Informed Consent: Retrospective study.

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Use of Bipolar Electrosurgical Device for Sealing of Ureter During Laparoscopic Live Donor Nephrectomy: Single-center Experience

Laparoskopik Donör Nefrektomide Damarların ve Üreterin Mühürlenmesinde Kullanılan Teknikler ve Önemleri: Tek Merkez Deneyimi

Ulaş SÖZENER

Medicana International Ankara Hospital, Kidney Transplantation Centre; Atılım University Faculty of Medicine, Department of General Surgery, Ankara, Turkey

ABSTRACT

Aim: In this study, we evaluated our method of using bipolar sealing and cutting of terminal ureter in donor nephrectomy and discussed its safety and effectiveness.

Materials and Methods: A total of 200 patients who underwent laparoscopic donor nephrectomy between August 2018 and August 2020 were included in the study. All the surgeries were performed by the same surgeon with the same technique. Patient variables including age, gender, body mass index, estimated blood loss, surgical times and postoperative drainage creatinine values were all recorded.

Results: On the first postoperative day, creatinine measurement was performed from drainage collection which was repeated on the second postoperative day. After the second recording of creatinine level, the drain was taken out. In all of the patients, the values were all within ranges of the blood creatinine levels, which was consistent with no urinary leak. We did not need to perform any further invasive test to check for a leak like a cystography.

Conclusion: Our results demonstrate that the use of energy devices for sealing vessels can be used safely and effectively for sealing distal ureter.

Keywords: Donor nephrectomy, laparoscopy, kidney transplantation

ÖZ

Amaç: Bu çalışmada, donör nefrektomide bipolar mühürleme ve terminal üreterin kesilmesi yöntemimizi değerlendirdik ve güvenliğini ve etkinliğini tartıştık.

Gereç ve Yöntem: Ağustos 2018 ile Ağustos 2020 tarihleri arasında laparoskopik donör nefrektomi yapılan toplam 200 hasta çalışmaya dahil edildi. Tüm ameliyatlar aynı cerrah tarafından aynı teknikle yapıldı. Yaş, cinsiyet, vücut kitle indeksi, tahmini kan kaybı, cerrahi süreler ve postoperatif drenaj kreatinin değerleri gibi hasta değişkenlerinin tümü kaydedildi.

Bulgular: Postoperatif birinci günde, postoperatif ikinci günde tekrarlanan drenaj koleksiyonundan kreatinin ölçümü yapıldı. İkinci kreatinin düzeyi kaydedildikten sonra dren çekildi. Tüm hastalarda, değerler kan kreatinin seviyeleri aralığında idi ve bu durum idrar kaçağı olmamasıyla tutarlıydı. Sızıntı olup olmadığını kontrol etmek için sistografi gibi invaziv testler yapmamıza gerek olmadı.

Sonuç: Sonuçlarımız damarları kapatmak için kullanılan enerji cihazlarının, distal üreterin kapatılmasında güvenli ve etkili bir şekilde kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Donör nefrektomi, laparoskopi, böbrek nakli

Address for Correspondence: Ulaş SÖZENER MD, Medicana International Ankara Hospital, Kidney Transplantation Centre, Ankara, Turkey
Phone: +90 532 664 17 58 **E-mail:** ulassozener@gmail.com **ORCID ID:** orcid.org/0000-0001-6719-0062
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INTRODUCTION

Kidney transplantation is the best treatment for patients with end-stage renal disease, and it provides significantly better survival rates for patients than dialysis. Living donor kidney transplantation is a valuable alternative to cadaveric transplantation in countries with low organ donation rates. Despite having numerous advantages to cadaveric grafts like shorter ischemia time, improved surgical extraction quality, and preemptive transplant access, operating a living, healthy individual brings its own concerns.

Establishing uttermost safety and comfort to donors is paramount for living donor nephrectomy. With advancements like minimal invasive surgery, laparoscopy, retroperitonoscopy and robotic surgery, postoperative donor comfort has significantly improved over the past years[1]. Usage of sophisticated electrosurgical devices allows the surgeon to perform more precise dissection with less bleeding and less trauma to neighbor tissues. The safety of electro sealing devices allows us to achieve less complicated and faster surgical techniques without worrying about complications.

In this study, we evaluated our method of using bipolar sealing and cutting of terminal ureter in donor nephrectomy and discussed its safety and effectiveness.

MATERIALS AND METHODS

This study was conducted under the Declaration of Helsinki Ethical Principles and Good Clinical Practices. This study was reviewed and approved by the Ethical Committee of Medicana Interantional Ankara Hospital at 06.01.2021 (approval number: BSH-2020/18). Patient consents were taken. Two-hundred patients who were operated laparoscopic donor nephrectomy (LDN) between August 2018 and August 2020 were enrolled to the study. All the surgeries were performed by same attending transplant surgeon with the same technique. Patient variables including age, gender, body mass index (BMI), estimated blood loss (EBL), surgery time (minutes), postoperative blood creatinine values and drainage fluid creatinine values were all measured and recorded.

A computerized tomography angiogram was performed to all donor candidates for the identification of renal vasculature as well as the anatomy of ureters before the operation.

LDN Technique[2]

Patient was operated in lateral decubitus position. The technique described by Sozener[2] was the routine operation procedure. Following periumbilical trocar insertion and insufflation, the abdominal cavity was explored videoscopically. Three to four additional trocars were inserted, as described previously by Ratner et al.[3]. The right or left hemi colon was dissected from the lateral abdominal wall and mobilized medially. Fascia was transected, and the perirenal fatty tissue and other connective tissue was separated. The renal vessels and ureter were dissected. A Pfannenstiel incision ranging 6 to 8 cm was made. The ureter was dissected to the point of its crossing under the iliac vessel, sealed and divided with LigaSure™ Blunt Tip Open and Laparoscopic Sealer/Divider with Nano-coating device (Medtronic, Minneapolis, Minn, United States). An automatic cutting laparoscopic stapler was used to divide the renal vessels. Subsequently, the kidney was extracted by hand and cooled immediately.

Statistical Analysis

Data were analyzed by using SPSS 20 statistical software (SPSS Inc., Chicago, IL, USA). Categorical variables were reported as percentages, while continuous variables were reported as means and standard deviations. For continuous variables, group comparisons were analyzed using the by Kruskal-Wallis test, Student's t-test or analysis of variance followed by Bonferroni posttests in the case that overall p value was significant. Categorical variables were compared with the chi-square test. Patient and graft survival rates were calculated by the Kaplan-Meier method, and the log rank test was used to compare the differences in survival.

RESULTS

Patient Demographic and Surgical Data

Among 200 live donors, 92 (46%) were male, and 108 (54%) were female. The mean patient age was 48.27 years. The mean BMI was 28.6. The left kidney in 79 (77.5%) cases and the right kidney in 23 (22.5%) cases were retrieved. The mean EBL was 80 milliliters (20-150). The mean surgical time of LDN was (30-86) minutes.

A single renal artery was encountered in 165 (82.5%) donors has a single renal artery, while 33 (16.5%) had double renal arteries. Three renal arteries were present only in 2 (1%) cases. Majority of the donors had a single renal vein (180 donors, 90%) and 20 (10%) donors had double renal veins. Division of renal artery and vein was performed by the single stapler technique described previous by Genc et al.[4], Tokaç et al.[5] and Sozener[6] in 156 donors (78%). Stapling of multiple vessels separately was performed in 44 donors (22%). Minor accessory veins were either sealed by energy device or clipped.

Conversion to the open donor nephrectomy was not required in any operation. No postoperative surgical complication was observed.

Minor morbidities like delayed bowel movement and atelectasis were seen in some patients during postoperative stay but no interventions were necessary beyond simple modifications in

treatment. Mean hospital stay time was 2.5±1.5 days. Main points were summarized in Table 1.

On the first postoperative day, creatinine measurement was performed from drainage collection, which was repeated on the second postoperative day. After the second creatinine level was recorded, the drain was taken out. Since we routinely monitor blood creatinine levels of donors postoperatively, we compared our results with drainage fluid creatinine levels. In all of the patients, the values were all within ranges of the blood creatinine levels, which was consistent with no urinary leak. We did not need to perform any further invasive test, like a cystography, to check for a leak.

DISCUSSION

Minimally invasive surgery techniques changed the approach to living donor operations drastically. Once considered as a big operation with debilitating effects on the early, mid-term to the patient, new techniques moved donor nephrectomy to the group of surgeries like cholecystectomy, and hernia repair.

While being minimally invasive and more comforting to the patient, safety of the operation and the preservation of the graft can never be compromised. For this purpose, most efficient devices must always be utilized. Sealing on main vessels, for example, should always be performed with appropriate vascular stapling devices. For sealing renal arteries, the use of titanium or hem-o-lok polymer clips (Teleflex Medical, PA, United States) are currently contraindicated for living donor nephrectomies.

Table 1. Demographic and surgical data

	n	%
Age (years)	48.27±12.0	
Male/female	92/108	46/54
BMI (kg/m^2)	28.6±2	
Kidney side (left/right)	79/23	
EBL (mL)	80±10	
Surgical time (minutes)	45±15	
Arteries		
Single	165	82.5
Two	33	16.5
Three	2	1
Veins		
Single	180	90
Double	20	10
Conversion to open surgery	-	-
Perioperative/postoperative complications	-	-
Stapling of vessels		
Single stapler technique	156	78
Multiple staplers	44	22
Ligation and division of ureters	200	100
Ligasure	-	-
Other methods		

EBL: Estimated blood loss, BMI: Body mass index

When we designed the study, our first step was to review the literature for alternative methods of ureter sealing during minimally invasive nephrectomies. The extensive search revealed that although numerous papers were published on the techniques and results on the subject, ligation of ureter was not detailed in any of those studies[7-9]. This is also consistent with the common knowledge that any physiologically normal vesicoureteral junction prevents backflow of urine.

Despite this common knowledge, almost all of the surgeons either ligate the ureteral stump or use hemoclips. This extra maneuver either adds to the time or increases the cost of the surgery. It may seem like an unimportant step but when you substitute this step with a simple sealing maneuver with a device, you already use during the procedure to both reduce the operative time and the cost, however minimum. Our results demonstrate that the use of energy devices for sealing vessels can be used safely and effectively for sealing distal ureter. Added the fact that the suggested maneuver is perfectly fast and easy, it can totally replace the standard ligating/clipping habit.

The guideline of European Association of Urology on transplantation defines ureteral stenosis as a common complication in recipients, with an incidence of 0.6-10.5%[10]. Early stenosis (within three months of surgery) is usually caused by surgical technique or compromised ureteral blood supply during surgery. Dinckan et al.[11] and Helfand et al.[12] suggested that, late stenosis (after >six months) is provoked by infection, fibrosis, progressive vascular disease and/or rejection. Although these factors are not related to the donors, the distal 3 cm part of the graft ureter is always resected to eliminate risk of thermal damage.

Study Limitations

This study has limitations in terms of comparing the suggested methods with other methods. Although not considered as a control group, conventional methods for sealing vascular structures and ureter have been firmly established with known and accepted success and failure rates.

CONCLUSION

To sum up; laparoscopic nephrectomy for transplantation, benign or oncological purposes can be safely and effectively performed. Electro sealing devices are safely and effectively used for vessel sealing but sealing of ureter has not been discussed in the literature. Results of the large group of patients in this study demonstrate the efficiency and ease of use of electro sealing devices for this purpose.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Ethical Committee of Medicana Interantional Ankara Hospital at 06.01.2021 (approval number: BSH-2020/18).

Informed Consent: Consent form was filled out by all participants.

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Risk of Malnutrition and Its Effects on the Quality of Life of Hospitalized Cancer Patients

Hospitalize Kanser Hastalarında Malnütrisyon Riski ve Yaşam Kalitesine Etkisi

Emir ÇELİK[1], Muhammed Şamil ASLAN[2], Nilay ŞENGÜL SAMANCI[1], Mehmet KARADAĞ[3], Veysel SUZAN[4], Yasemin ÇAKAN ÇELİK[5], Nebi Serkan DEMİRCİ[1], Fuat Hulusi DEMİRELLİ[1]

[1]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Medical Oncology, İstanbul, Turkey*
[2]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Internal Medicine, İstanbul, Turkey*
[3]*Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine, Department of Biostatistics, Hatay, Turkey*
[4]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Geriatrics, İstanbul, Turkey*
[5]*Gaziosmanpaşa Training and Research Hospital, Clinic of Child and Adolescent Mental Health and Diseases, İstanbul, Turkey*

ABSTRACT

Aim: Malnutrition is one of the most common clinical problems in cancer patients. Its frequency increases in hospitalized cancer patients. In this study, it was aimed to investigate the frequency of malnutrition and its effect on quality of life (QOL) in hospitalized cancer patients.

Materials and Methods: In this cross-sectional study, Nutrition Risk Screening-2002 (NRS-2002) and European Organization for the Research and Treatment of Cancer (EORTC)-QLQ C30 scales were completed for patients with cancer diagnosed in the medical oncology service. The relationship between clinical and laboratory parameters, malnutrition risk and QOL was analyzed by statistical methods.

Results: One-hundred thirteen patients were included in the study. According to the results of NRS-2002, 42.5% (n=48) patients were at risk of malnutrition. There was no difference between the groups in terms of gender and age. When the EORTC-QLQ C30 scale scores were compared, the risk of malnutrition had no effect on the overall health score (p=0.679). Physical function and role function scores were significantly lower in those at risk of malnutrition (worse QOL). There was no statistically significant difference between the groups in terms of other functional scales. When univariate logistic regression (LR) was applied to the factors affecting better general health score, only hemoglobin level was found to be a significant factor. Therefore, multivariate LR was not done.

Conclusion: Malnutrition risk assessment should be performed routinely in every hospitalized cancer patient. Early nutritional support should be given to patients at risk. It was observed that patients with malnutrition risk had worse QOL compared to the EORTC-QLQ C30 scale.

Keywords: Malnutrition, quality of life, NRS-2002, EORTC-QLQ C30

ÖZ

Amaç: Malnutrisyon kanser hastalarında en sık klinik sorunlardan biridir. Hospitalize kanser hastalarında sıklığı daha da artar. Bu çalışmada hospitalize edilmiş kanser hastalarında malnutrisyon sıklığı ve yaşam kalitesine (YK) etkisinin araştırılması amaçlandı.

Gereç ve Yöntem: Kesitsel olarak dizayn edilen bu çalışmada medikal onkoloji servisine yatan kanser tanılı hastalar için Nutrisyon Risk Skorlaması-2002 (NRS-2002) ve "Avrupa Kanser Araştırma ve Tedavi Teşkilatı" (EORTC)-QLQ C30 ölçekleri dolduruldu. Klinik ve laboratuvar paramatreleri ile malnutrisyon riski ve YK arasındaki ilişki istatistik yöntemleri ile analiz edildi.

Bulgular: Çalışmaya 113 hasta dahil edildi. NRS-2002 sonuçlarına göre %42,5 (n=48) hastada malnutrisyon riski tespit edildi. Cinsiyet ve yaş açısından gruplar arasında fark yoktu. EORTC-QLQ C30 ölçek puanları karşılaştırıldığında malnutrisyon riskinin genel sağlık skoru üzerine etkisi yoktu (p=0,679). Fiziksel fonksiyon ve rol fonksiyon skorları malnutrisyon riski olanlarda anlamlı olarak daha düşüktü (daha kötü YK). Diğer fonksiyonel skalalar açısından gruplar arasında anlamlı istatistiksel fark yoktu. Daha iyi genel sağlık skoruna etki eden faktörlere tek değişkenli lojistik regresyon (LR) uygulandığında sadece hemoglobin düzeyi anlamlı faktör olarak bulundu. Bu yüzden çok değişkenli LR yapılmadı.

Sonuç: Malnutrisyon risk değerlendirmesi hastaneye yatan her kanser hastasına mutlaka yapılmalıdır. Malnutrisyon riski olan hastalarda EORTC-QLQ C30 ölçeğine göre daha kötü YK olduğu görüldü. Risk saptanan hastalara erken dönemde nutrisyon desteği verilmelidir.

Anahtar Kelimeler: Malnutrisyon, yaşam kalitesi, NRS-2002, EORTC-QLQ C30

Address for Correspondence: Emir ÇELİK MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Medical Oncology, İstanbul, Turkey
Phone: +90 505 557 70 42 **E-mail:** emircelikk@gmail.com **ORCID ID:** orcid.org/0000-0001-8440-3082
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INTRODUCTION

Malnutrition is a condition that causes changes in body components due to a decrease in food intake and leads to decreased physical and mental functions and poor clinical outcomes[1]. Basically, malnutrition is due to insufficient energy and/or protein intake or processing or increased catabolism. Malnutrition is common in cancer patients due to the tumor itself or the complications of treatment, and it has been reported to occur at a higher rate than expected in all stages of the disease[2,3]. The incidence of malnutrition, independent of cancer type, increases to approximately 40%[3]. Malnutrition and weight loss are an important poor prognostic factor in cancer patients[4]. Cachexia typically occurs with weight loss and decreased body mass index (BMI), and it can be prevented by early screening and intervention for malnutrition risk[5]. Malnutrition is also a very common problem for hospitalized cancer patients. In the literature, malnutrition has been reported to be an independent risk factor in terms of long hospitalization time, nosocomial infection, shorter survival, poorer quality of life (QOL) and chemotherapy toxicity in hospitalized cancer patients[4,6,7]. In addition, treatment costs of patients with malnutrition also increase[8].

Anamnesis, physical examination, screening scales, analysis of body components and blood biochemical markers (such as total protein, albumin, prealbumin, lymphocyte count, transferrin) are used in the evaluation of malnutrition. Definitive diagnostic criteria for the diagnosis of malnutrition are not clear and various nutritional evaluation methods have been described in the literature[6,9]. In this study, our aim is to investigate the effects of malnutrition on the QOL and on clinical problems encountered during hospitalization in cancer patients.

MATERIALS AND METHODS

Patients diagnosed with cancer and admitted to the medical oncology service were included in this study in which a cross-sectional study design was used. Before starting the study, İstanbul University-Cerrahpaşa Local Ethics Committee approval was obtained (date: 08.07.2020 number: 86049).

Patients who volunteered to participate in the study and signed the consent form were evaluated within the first 72 hours of their hospitalization with Nutrition Risk Score-2002 (NRS-2002). Those who were not pathologically diagnosed with cancer and those who did not have sufficient mental functions to answer the questions due to their general condition were excluded from the study. From the medical files of the patients included in the study and through a screening form, data about the disease and socio-demographic information were collected. Physical examination information at the time of hospitalization was recorded. BMI was calculated. Mid-arm muscle circumference (MAMC)[10,11] and calf circumference were measured[12].

The hemoglobin, C-reactive protein (CRP), albumin and thrombocyte values of all patients at the time of admission were retrospectively collected after completing the inclusion of patients to the study. Hospitalization epicrises were examined and the presence of infection requiring treatment and length of hospitalization were recorded. The survivability of each patient on the 90th day after the first day of hospitalization was examined and the 3rd month mortality rate was calculated. Nutrition Risk Index (NRI) and NRS-2002 were used to screen malnutrition risk. NRI was calculated by the formula: NRI=(1.519 × serum albumin, g/dL) + [41.7 × final weight (kg) / ideal body weight (kg)]. If the NRI score was >100, it was defined as no risk, 97.5-100 as mild risk, 83.5-97.5 as moderate risk, and <83.5 as severe risk[13]. The NRS-2002 scale, which was completed within the first 72 hours of hospitalization, was developed by Kondrup et al.[14,15] and it is used to identify patients who may benefit from nutritional support by screening the risk of malnutrition with reduced nutrition. The European Parenteral Enteral Nutrition Association recommended NRS-2002 for screening malnutrition risk in hospitalized patients[6]. NRS-2002 scale consists of three parts as "disease severity", "nutritional status" and "age". The points from each section are added up. A total score of 3 and above means an increased risk of malnutrition[15].

European Organization for the Research and Treatment of Cancer (EORTC)-QLQ C30 (Turkish version) QOL forms developed by the European Organization for the Research and Treatment of Cancer-EORTC were filled in by all patients. EORTC QLQ-C30 Version 3.0 is a QOL scale and consists of 30 questions. There are 2 questions in the "general health" questionnaire. "Functional scales" consists of physical function, role function, emotional function, cognitive function and social function. "Symptom scales" consists of weakness, nausea-vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial difficulties. Scoring was calculated according to the EORTC QLQ-C30 scoring manual. Each parameter has a score between 0 and 100.

A high score for general health and functional scales indicates good health, while a high score on the symptom scale indicates an excess of symptoms, that is, a worse QOL.

Statistical Analysis

Statistical analyses of the data obtained as a result of the evaluation were performed using a statistical package program (SPSS 21 for Windows, SPSS, Inc, Chicago, Illinois, USA) on the computer. Whether the data distribution was normal or not was checked with the Kolmogorov-Smirnov test. Results were expressed as median and interquartile range in all cases. In

subgroups formed based on socio-demographic characteristics, tumor characteristics, laboratory parameters, BMI, MAMC and calf circumference parameters, the difference between the 2 groups in terms of malnutrition risk was evaluated by the non-parametric Mann-Whitney U test, and the difference between more than 2 different groups was evaluated by the non-parametric Kruskal-Wallis test. The difference between qualitative groups was analyzed using the chi-square test. Fischer's correction was performed when necessary. It was planned to examine the differences between the patient groups with and without malnutrition risk in terms of all sub-parameters of the EORTC QLQ-C30 by using the Mann-Whitney U test. Later, it was planned to divide the patients into two groups according to the median value for the "general health status" score of the EORTC QLQ-C30 questionnaire. Patients above the median value constituted better overall QOL, patients below the median value constituted poorer overall QOL group. In order to find the predictors of the better QOL group, univariate logistic regression (LR) analysis was planned first, followed by multivariate LR analysis for factors found to be significant. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 113 patients were included in the study. According to the results of NRS-2002, 42.5% (n=48) of the patients were found to have a malnutrition risk. The comparison results of patients with and without malnutrition risk are shown in Table 1. Gender and age were similar in both groups. The median age was 60 years in those at risk of malnutrition and 59 years in those without risk. Primary tumor was in the gastrointestinal system (GIS) in 21.2% of the patients and there was no statistically significant difference between the groups in terms of frequency. The rate of metastatic (tumor node metastasis

Table 1. Comparison of patients with and without malnutrition risk according to Nutrition Risk Screening-2002

	With malnutrition risk (n=48)	Without malnutrition risk (n=65)	p
Variables	**n (%) or median [Q1-Q3]**		
Gender			
Male	28 (58.3)	37 (56.9)	0.881
Female	20 (41.7)	28 (43.1)	
Age	60 [49-70]	59 [48-63]	0.172
Smoking			
Smoker/quitted	34 (70.8)	41 (63.1)	0.388
Never smoked	14 (29.2)	24 (36.9)	
Location of tumor			
GIS	13 (27.1)	11 (16.9)	0.192
Non-GIS	35 (72.9)	54 (83.1)	
TNM stage			
3	1 (2.1)	9 (13.8)	**0.030**
4	47 (97.9)	56 (86.2)	
Presence of infection (during hospitalization)	34 (70.8)	42 (64.6)	0.486
Nutritional support before hospitalization	20 (41.7)	3 (4.6)	**<0.001**
Low MAMC	12 (25)	10 (15.4)	0.202
Low calf circumference	9 (18.8)	7 (10.8)	0.229
3rd month mortality after hospitalization	34 (70.8)	24 (36.9)	**<0.001**
Hemoglobin (g/dL)	9.7 [8.6-11]	9.5 [8.9-11]	0.691
Platelet ($x10^3$)	281.5 [222.5-352.5]	271 [181-417]	0.81
CRP (mg/L)	67 [39-136]	49 [22-114]	0.193
Albumin (gr/dL)	2.78 [2.45-3.4]	2.8 [2.4-3.4]	0.543
Body mass index	22 [20.63-24.83]	24.69 [22.49-27.55]	**0.001**
Nutritional Risk Index	80 [71.5-87]	83 [78-92]	0.018
Length of hospital stay (day)	21 [11-39]	17 [12-29]	0.508

For quantitative variables M [Q1-Q3] (M: Median Q1: percentage 25, Q3: percentage 75).

P-values for quantitative variables were obtained with the Mann-Whitney U test, p values for qualitative variables were obtained with the chi-square test. Statistically significant "p" values were stated in bold.

GIS: Gastrointestinal system, MAMC: Mid-arm muscle circumference, TNM: Tumor node metastasis, CRP: C-reactive protein

stage 4) patients was higher in those at risk of malnutrition (p=0.030). Eastern Cooperative Oncology Group-Performance Scores (ECOG-PS) of patients with malnutrition risk are shown in Figure 1. ECOG-PS values of all patients were between 2 and 4. Malnutrition risk was 33.8% in those with ECOG-PS 2, 60.7% in those with 3, and 45% in those with 4. The difference between the groups was not statistically significant (p=0.054). The rate of patients who received chemotherapy and/or radiotherapy within 30 days before hospitalization was 62.5% (n=30) in the group with malnutrition risk and 66.1% (n=43) in the group without malnutrition risk (p=0.121).

As expected, BMI at hospitalization was significantly lower in the group with malnutrition risk (p=0.001). However, there was no difference between the groups in terms of calf circumference and MAMC. There was no significant difference between the groups in terms of albumin, CRP, hemoglobin and platelet count obtained from laboratory tests. The median length of stay in the hospital was 21 days in those at risk of malnutrition, while it was 17 days in those without risk. Although there was a numerically longer hospitalization period in those with malnutrition risk, the difference was not statistically significant (p=0.508). The rate of infection requiring treatment was slightly higher in those at risk of malnutrition (70.8%), but the difference between the groups was not statistically significant (p=0.486). When the groups were examined in terms of 3rd month mortality rate, the mortality rate was 70.8% in those with malnutrition risk and 36.9% in those without malnutrition risk (p<0.001). While the rate of nutritional support before hospitalization was 41.7% in patients with malnutrition risk at admission, it was 4.6% in those without risk (p<0.001).

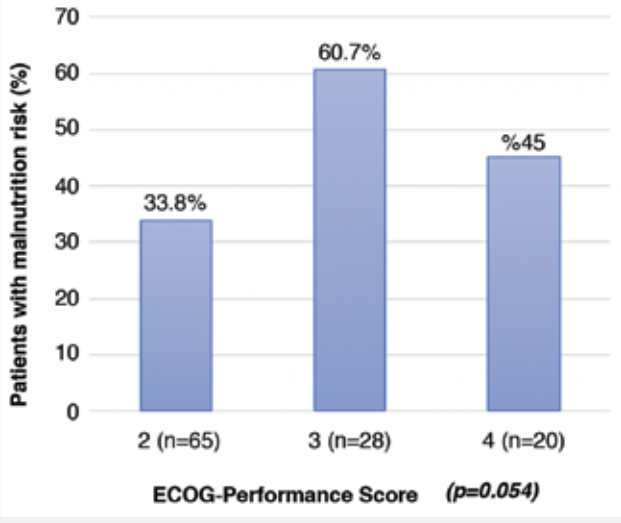

Figure 1. Distribution of patients with malnutrition risk according to Eastern Cooperative Oncology Group-Performance Score and Nutrition Risk Screening-2002

ECOG: Eastern Cooperative Oncology Group

Figure 2 shows the distributions for NRI in patients with and without malnutrition risk. The rate of patients with NRI<83.5, which indicates the risk of severe malnutrition (according to NRS-2002), was detected to be 69% in those with malnutrition risk and 52% in those without risk. The rate of patients with NRI>100, which indicates that there is no malnutrition (according to NRS-2002), was 6% in those with malnutrition risk, while it was 12% in those without risk. The patients were asked whether there was a decrease in food consumption in the last week (vv). In patients with malnutrition risk, food consumption was found to be less than half of normal in 50%, half of normal in 21% and normal in 29%. In patients without malnutrition risk, food consumption was found to be less than half of normal in 22%, half of normal in 23% and normal in 55%.

The comparison results of patients with and without malnutrition risk in terms of general health, functional scales and symptom scales are shown in Table 2. Malnutrition risk had no significant effect on overall health score (p=0.679). Physical function and role function scores were significantly lower in those at risk of malnutrition (poorer QOL). There was no statistically significant difference between the groups in terms of other functional scales. For symptom scales, scores for symptoms other than constipation and diarrhea were higher (poorer QOL) in patients at risk of malnutrition. The high scores detected for pain, nausea/vomiting, insomnia, and loss of appetite were also statistically significant. In Table 3, the characteristics of patients whose EORTC QLQ-C30 general health score was above the median value (better QOL) were investigated by univariate and multivariate LR analysis. According to the One-Way analysis results, only hemoglobin level was found as a significant factor.

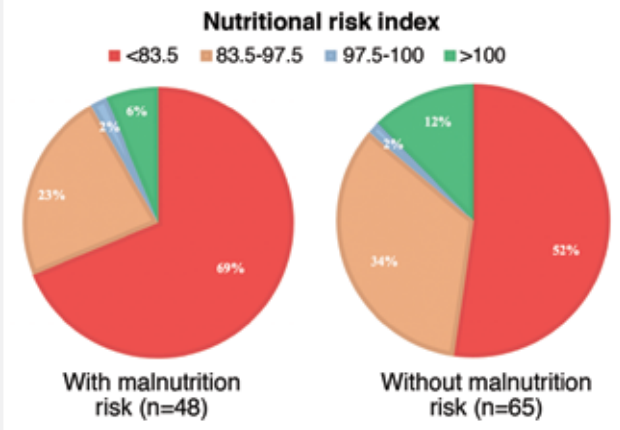

Figure 2. Nutritional risk indexes of patients with and without malnutrition risk according to Nutrition Risk Screening-2002

A significant correlation was found between higher hemoglobin level and better general health score (p=0.028). It was observed that the risk of malnutrition, age, gender, ECOG PS and other variables given in Table 3 had no effect on the better overall health score. Multivariate LR analysis was not performed because only one factor had a significant effect.

Table 2. Comparison of EORTC QLQ-C30 quality of life scale scores of patients with and without malnutrition risk according to Nutrition Risk Screening-2002

	With malnutrition risk	Without malnutrition risk	p
	Median [Q1-Q3]		
Overall health	16.67 [0-33.33]	16.67 [0-33.3]	0.679
Functional scales			
Physical function	42 [33.3-53.3]	51.6 [40-73.3]	**0.019**
Emotional function	49 [33.3-66.7]	55.4 [41.7-75]	0.120
Role function	16.67 [0-33.3]	33.3 [0-50]	**0.017**
Mental function	53.7 [66.7-59.3]	59.3 [50-83.3]	0.218
Social function	33.72 [0-50]	44.5 [33.3-50]	0.057
Symptom scales			
Pain	83.33 [66.7-100]	66.7 [33.3-83.3]	**0.009**
Nausea or vomiting	56 [25-100]	33.3 [0-50]	**0.004**
Weakness	88.89 [77.8-100]	77.8 [55.6-100]	0.068
Dyspnea	58 [33.3-100]	48 [33.3-66.7]	0.155
Insomnia	68 [66.7-100]	54.5 [33.3-100]	**0.019**
Loss of appetite	100 [66.7-100]	66.7 [33.3-100]	**0.002**
Constipation	33.3 [0-83.4]	33.3 [0-66.7]	0.711
Diarrhea	22 [0-33.3]	24.8 [0-33.3]	0.890
Financial difficulty	55 [33.3-66.7]	33.3 [33.3-66.7]	0.155

P value was obtained with the Mann-Whitney U test. Q1: percentage 25, Q3: percentage 75.

Statistically significant "p" values were stated in bold.

EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer

Table 3. Univariate and multivariate logistic regression analysis for better overall health score variables on the EORTC-QLQ C30 scale

	Univariate LR		Multivariate LR	
Variables	**Odds ratio (95% CI)**	**p**	**Odds ratio (95% CI)**	**p**
With malnutritional risk	1.288 (0.584-2.84)	0.531		
Age	0.984 (0.954-1.016)	0.322		
Male gender	1.729 (0789-3.788)	0.171		
Smoking	1.167 (0.516-2.637)	0.711		
GIS tumor	0.847 (0.332-2.161)	0.729		
TNM stage 4	0.190 (0.023-1.559)	0.122		
ECOG-PS 3 (Ref: 2)	0.938 (0.362-2.431)	0.896		
ECOG-PS 4 (Ref: 2)	0.444 (0.160-1.236)	0.120		
Hemoglobin (g/dL)	1.318 (1.030-1.687)	**0.028**		
Platelet (x10^3)	1.000 (0.997-1.002)	0.873		
CRP (mg/L)	0.996 (0.991-1.001)	0.102		
Body mass index	0.978 (0.890-1.075)	0.648		
Low MAMC	1.517 (0.541-4.254)	0.428		
Low calf circumference	0.859 (0.287-2.571)	0.786		

Statistically significant "p" values were stated in bold.

CI: Confidence interval, LR, Logistic regression, GIS: Gastrointestinal system, MAMC: Mid-arm muscle circumference, TNM: Tumor node metastasis, CRP: C-reactive protein, EORTC-QLQ C30: European Organization for the Research and Treatment of Cancer, ECOG-PS: Eastern Cooperative Oncology Group-Performance Scores

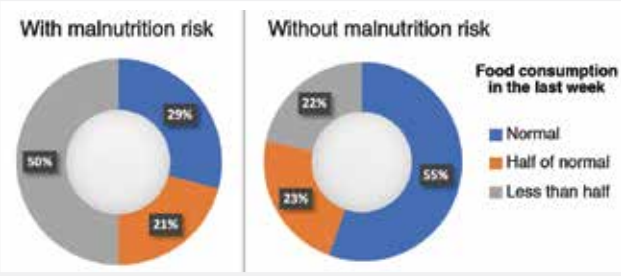

Figure 3. Food consumption of patients with and without malnutrition risk in the last 1 week according to Nutrition Risk Screening-2002

DISCUSSION

It is obvious how important it is to evaluate every hospitalized patient for malnutrition. In this cross-sectional study, nearly half of the 113 cancer patients hospitalized were found to be at risk of malnutrition, and it was observed that it negatively affected the QOL.

In the literature, while gender does not affect the frequency of malnutrition in cancer patients in general, it has been reported that the frequency of malnutrition increases in older patients[3,16]. In our study, no significant difference was found in terms of age and gender. It is known that malnutrition risk is higher in GIS cancers and tumors at the metastatic stage[6,16]. In our study, the rate of metastatic patients was significantly higher in those with malnutrition risk, in line with the literature. Although the frequency of GIS cancer was numerically higher, the difference was not significant. In Table 1, the comparison of patients with and without malnutrition risk was made to give information about the general patient population. Our primary aim in this study was not to investigate factors that increase the risk of malnutrition. For this reason, detailed and advanced statistical analyses (LR analysis etc.) were not performed for the factors affecting malnutrition risk. Rather, the effects of malnutrition risk on QOL and on clinical problems encountered during hospitalization were the topics to be examined.

In this study, scores of physical function, role function, pain, nausea/vomiting, insomnia and loss of appetite on the EORTC QLQ-C30 scale were found to be significantly associated with poorer QOL in those at risk of malnutrition (Table 2). In the literature, it has been reported that malnutrition impairs the QOL, in line with the results of our study[16,17]. The issue of QOL in cancer patients is an issue that needs to be handled in a multi-directional way. In addition to malnutrition, there are factors affecting QOL such as tumor type, tumor stage, patient's ECOG-PS and other defined risk factors[4,16,17]. For this reason, LR analysis was performed to determine the characteristics of patients with higher general health scores, that is, better overall QOL, on the EORTC QLQ-C30 scale. According to the univariate analysis, it was observed that factors other than hemoglobin did not affect the overall health score (Table 3). The relatively small patient population may be the reason for the low number of significant factors. For validity of these results, it should be repeated with more participants using the same QOL scale and a similar patient population.

Although NRI is used to determine nutritional risk in cancer and non-cancer patients, its success in cancer patients is low[13]. Consistent with the results reported in the literature, NRI scores were generally found to be low in those with or without malnutrition risk. The albumin and weight loss used in the calculation of this index are more or less encountered in most cancer patients. Therefore, NRI does not appear to be useful in evaluating nutritional status in hospitalized cancer patients. In previous studies, it was reported that the length of hospital stay was longer in those with malnutrition[16]. In our study, the median hospital stay was four days longer in the group with malnutrition risk. However, the difference was not statistically significant. The relatively low number of patients may have caused this. It has been reported that providing nutritional support in the early period after hospitalization may shorten the length of stay[18]. One of the most common clinical problems in hospitalized cancer patients is the development of infection. We found the frequency of infection at the rate of 70.8% in those with malnutrition risk, which was slightly higher than in those without risk (p=0.486). The 3rd month mortality rate was significantly higher in those at risk of malnutrition (p<0.001). While interpreting these results, it should be kept in mind that the risk of malnutrition may develop during hospitalization, although not at the initial diagnosis. Therefore, the possibility of malnutrition risk that can develop later should be kept in mind while interpreting the duration of hospital stay, the frequency of infection and the mortality rates in the 3rd month.

Although it could not be done in this study, the effect of malnutrition on the problems that occur during hospitalization can be understood more clearly by repeating the NRS-2002 scale periodically during hospitalization.

Figure 3 highlights the important points in assessing malnutrition risk. Food consumption in the last one week was reported as normal in 29% of those at risk of malnutrition. In other words, nutritional evaluation made by questioning only oral intake means that an important patient group with malnutrition risk is overlooked. Again, in 45% of the patients without malnutrition risk, decreased oral intake was found. Re-application of the NRS-2002 scale at regular intervals, especially in these patients, may reveal the risk of malnutrition in the early period[18]. Consequently, decreased oral intake is common in hospitalized cancer patients and it should be kept in mind that malnutrition risk may develop without a decrease in oral intake.

Study Limitations

There are some limitations in our study. Although all cancer patients admitted to the medical oncology service were planned to be included in the study, some patients did not want to participate because of their poor general condition or being excessively symptomatic. Another limitation is that the effects of nutritional support given to patients on admission were not evaluated. In addition, the fact that each tumor type was not evaluated separately is another limitation. Considering the limitations we have reported may increase the strength of future studies to be carried out.

CONCLUSION

In conclusion, detailed nutritional assessment at the time of admission is an important issue in hospitalized cancer patients. Its frequency is quite high. It negatively affects the patients physically and emotionally and impairs the QOL. Patients having malnutrition at the time of admission have longer hospitalization periods and they have higher frequency of infection. Survival is shorter in patients with malnutrition. It should be kept in mind that malnutrition may develop without a decrease in oral food intake.

Ethics

Ethics Committee Approval: The study were approved by the İstanbul University-Cerrahpaşa University of Local Ethics Committee (date: 08.07.2020, protocol number: 86049).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Concept: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Design: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Data Collection or Processing: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Analysis or Interpretation: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Literature Search: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Writing: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D.

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The Relation of Empathy Levels with Internalizing and Externalizing Problems among Children and Adolescents Who Refer to Child Psychiatry Outpatients

Çocuk ve Ergen Psikiyatri Polikliniğine Başvuran Olgularda Empati Düzeylerinin İçe Yönelim ve Dışa Yönelim Sorunları ile İlişkisi

Ömer BAŞAY[1], Seda Nur EZBER[2], Utku Emre İNCİ[2], Merve ÖZTÜRK[2], Muhammet Orhan SOYUGÜZEL[2], Bürge KABUKÇU BAŞAY[1]

[1]Pamukkale University Faculty of Medicine, Department of Child and Adolescent Mental Health and Diseases, Denizli, Turkey
[2]Pamukkale University Faculty of Medicine, Medical Student, Denizli, Turkey

ABSTRACT

Aim: The aim of our study was to investigate the relationship between empathy levels and internalizing-externalizing problems in children and adolescents admitted to child psychiatry outpatient clinics for various reasons, and how this relationship changed according to gender. In addition, it was aimed to investigate the relationship between empathy and the child's functionality according to parental reporting.

Materials and Methods: In the period of May-June 2018, 39 girls and 61 boys (n=100) aged 8-14 years (mean=11.1±2.23) who applied to Pamukkale University Medical Faculty Child and Adolescent Psychiatry Department outpatient clinics and volunteered to participate in the study were included in the study. The participants' parents filled the socio-demographic data form and the Strengths and Difficulties Questionnaire (SDQ), and the children and adolescents filled an Index of Empathy for Children and Adolescents.

Results: The girls' empathy level was statistically significantly higher than boys (p=0.039). There was no significant relationship between empathy skills and age and family income level (p>0.05). There was a negative correlation between empathy levels and emotional problems, conduct problems, peer problems, internalizing and externalizing problems and the SDQ total difficulty score; and a positive relationship between empathy levels and prosocial behaviors (p<0.05; correlation coefficients (r) were between -0.201 and -0.393; 0.370 for prosocial behaviors). When only girls were evaluated, all relationships that were found to be statistically significant disappeared (p>0.05), but stronger relationships were recorded when only boys were evaluated (p<0.05; correlation coefficients (r) were between -0.361 and -0.451; 0.403 for prosocial behaviors). Children and adolescents with better school success, homework habits, and peer relationships also had better empathy skills (p<0.05).

Conclusion: Our study results showed an inverse association between children's internalizing and externalizing problems and their empathy ability. In the clinical sample, especially boys' empathy skills seem to be related to emotional and behavioral problems. Attempts to improve empathic attitudes can help reduce emotional and behavioral difficulties that children and adolescents will experience and improve their functionality.

Keywords: Empathy, emotional problems, conduct problems

ÖZ

Amaç: Çalışmamızın amacı çocuk psikiyatrisi polikliniklerine çeşitli nedenlerle başvuran çocuk ve ergenlerde empati düzeylerinin, içe yönelim-dışa yönelim sorunları ile ilişkisini ve bu ilişkinin cinsiyete göre ne şekilde değiştiğini araştırmaktır. Ayrıca, empati ile ebeveyn bildirimine göre çocuğun işlevselliğinin ilişkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Mayıs-Haziran 2018 döneminde Pamukkale Üniversitesi Tıp Fakültesi, Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Anabilim Dalı polikliniklerine herhangi bir nedenle başvuran ve çalışmaya katılmaya gönüllü olan 8-14 yaş arası (ortalama=11,1±2,23) 39'u kız, 61'i erkek (n=100) olgu çalışmaya dahil edilmiştir. Çalışmada yer alan katılımcıların ebeveynleri sosyo-demografik veri formu ve Güçler ve Güçlükler Anketi'ni (GGA), çocuk ve ergenler de Çocuk ve Ergenler için Empati Ölçeği'ni doldurmuşlardır.

Address for Correspondence: Ömer BAŞAY MD, Pamukkale University Faculty of Medicine, Department of Child and Adolescent Mental Health and Diseases, Denizli, Turkey
Phone: +90 505 950 22 10 **E-mail:** omerbasay@gmail.com **ORCID ID:** orcid.org/0000-0001-7816-3983
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ÖZ

Bulgular: Kız çocuklarının empati düzeyi erkek çocuklarınkinden istatistiksel olarak anlamlı şekilde daha yüksektir (p=0,039). Empati becerisi ile yaş ve ailenin gelir düzeyi arasında anlamlı bir ilişki yoktur (p>0,05). Emosyonel sorunlar, davranım sorunları, akran sorunları, içe yönelim ve dışa yönelim sorunları ve GGA toplam güçlük puanı ile empati düzeyi arasında negatif yönlü; prososyal davranışlar ile empati düzeyi arasında pozitif yönlü bir ilişki mevcuttur [p<0,05; korelasyon katsayıları (r): -0,201 ve -0,393 arasında; prososyal davranışlar için 0,370]. Yalnızca kız çocukları değerlendirmeye alındığında istatistiksel olarak anlamlı elde edilen tüm ilişkiler kaybolmuş (p>0,05), yalnızca erkek çocukları değerlendirmeye alındığında ise daha güçlü ilişkiler kaydedilmiştir [p<0,05; korelasyon katsayıları (r): -0,361 ve -0,451 arasında; prososyal davranışlar için 0,403]. Okul başarısı, ödev yapma alışkanlıkları ve akran ilişkileri daha iyi olan çocuk ve gençlerin empati becerileri daha iyi düzeyde bulunmuştur (p<0,05).

Sonuç: Çalışma sonuçlarımız, çocukların içe yönelim ve dışa yönelim sorunları ile empati becerisi arasında ters yönde bir ilişki varlığı ortaya koymuştur. Klinik örneklemde, özellikle erkek çocuklarının empati becerisi, emosyonel ve davranışsal sorunlarıyla ilişkili gözükmektedir. Empatik tutumları iyileştirmeye yönelik yapılacak girişimler, çocuk ve gençlerin yaşayacağı emosyonel ve davranışsal güçlüklerin azalmasına, işlevselliklerinin artmasına yardım edebilir.

Anahtar Kelimeler: Empati, emosyonel sorunlar, davranım sorunları

INTRODUCTION

Empathy is an important social cognitive ability that ensures the adaptation of living things and individuals to social life[1]. There are many definitions that explain the concept of empathy and emphasize various aspects of empathy[2]. In addition to studies that report empathy as a multidimensional structure, there are also studies to classify them in two dimensions as cognitive (understanding the emotions of others) and emotional (feeling the emotion of others, and giving appropriate emotional response) empathy[2-4]. In the model that defines empathy, at least three basic elements are mentioned: (1) recognizing emotions in himself and others through facial expressions, speech or behavior, (2) sharing emotional states with others, the ability to experience similar emotions with others, with the awareness that the emotion experienced in the meantime is a simulation and not one's own (emotional sensitivity); and (3) taking of another's perspective without disrupting the distinction between self and other (emotional perspective taking)[5]. Empathy has been defined as the core component of social and emotional functioning throughout development[6]. According to meta-analytical findings, it is known that adolescents who have higher quality relationships with their environment, especially with their peers, are more interested in understanding the feelings of others[7]. There are literature studies showing that better empathy skills have a mediating role not only in social life but also in academic success[8,9]. Therefore, empathy seems to be an effective concept on the social and academic functionality of the child.

The relationship between empathy and mental disorders is an ongoing research topic. It has been repeatedly demonstrated that low empathy skills are associated with conduct disorder and related callous unemotional traits, oppositional defiant disorder (ODD), and aggressive behavior[10-13]. Findings from studies examining the relationship between anxiety and affective disorders and empathy are less consistent than externalising disorders. Many studies in adults and adolescents have reported an increase in internalizing disorders with increased empathy pattern[14-17]. However, there are also studies that found that children and adolescents with anxiety disorder have less empathy skills[18-20]. There are few studies in the literature that examine the relationship between internalizing and externalizing problems and empathy together. In a study conducted by Gambin and Sharp[14] (2016) on a clinical adolescent sample, empathy was evaluated with its cognitive and emotional sub-dimensions; as a result of the study, some differences were revealed according to gender. Accordingly, both cognitive and emotional empathy in girls were found to be inversely related to behavioral problems, but no such relationship was found in boys. Internalizing problems showed a positive relationship with emotional empathy in both girls and boys. Differently, in a study with community samples, total empathy and cognitive empathy were found to be negatively associated with internalizing and externalizing problems and positively with prosocial behaviors. Emotional empathy, on the other hand, differs by gender, negatively correlated with all emotional and behavioral problems in girls, and positively correlated with only prosocial behaviors in males[21]. Although it is known that female gender's empathy skill is better than male gender[22], how gender plays a role in the relationship between empathy and internalizing and externalizing problems is a research question that requires new studies.

The relationship between child and adolescent mental health problems/disorders and empathy have been investigated in very few studies carried out in Turkey; in terms of results, there are areas that overlap and diverge with the literature. These studies were conducted with children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD) and anxiety disorders, which are the most common mental disorders in children and adolescents and also the most common reasons for admission to child psychiatry outpatient clinics[18,23-27]. In one study examining the ADHD group, empathy level was found to be lower in the ADHD group compared to the control group in the other one, no difference was found between

the two groups[26,27]. The common point of the two studies is that ODD symptoms accompanying ADHD are associated with low empathy. In another study conducted with children and adolescents with anxiety disorders, it was found that the empathy levels of the anxiety disorder group were lower than the control group, and the aggression levels were higher in this group[18]. We could not reach a study conducted in our country that evaluated the relationship between internalizing and externalizing problems and empathy.

Considering that the concept of empathy can be shaped by cultural influences[28,29], it was thought that, by evaluating the relationship between internalizing and externalizing problems and empathy skills in a clinical sample of children and adolescents, we may contribute to the literature that consists mostly of studies from Western countries. Based on this, in our study, we aimed to investigate the relationship between externalizing and internalizing problems and empathy in clinical sample cases who applied to child and adolescent psychiatry outpatient clinics with various problems; and we also aimed to determine how this relationship changed according to gender. A second aim of our study was to examine the relationship between empathy and the child's functionality level according to the parent statement.

MATERIALS AND METHODS

Children and adolescents aged 8-14 years and their parents who applied voluntarily to Pamukkale University Faculty of Medicine, Child and Adolescent Psychiatry Outpatient Clinics for any reason in the period of May-June 2018 were included in our study, which was designed as a cross-sectional study. Being literate, not having mental disorders that prevents filling the forms (mental retardation, autism, acute psychotic attack, acute manic attack) and completing the study forms completely and reliably are the inclusion criteria. One-hundred children and young people who met the inclusion criteria formed the study sample. The data collection tools used in the study were filled in the waiting room by the child or adolescent and their parents at the time they waited for a psychiatric interview. First, the parents and the child or adolescent were informed about the study, and the volunteers were asked to fill in the forms in the waiting room. It took about 15 minutes to complete the study scales. Prior to the study, the Ethics Committee approval was obtained from the Pamukkale University Non-Invasive Research Ethics Committee with the number 60116787-020/34252, dated 18.05.2018. Participants and their parents signed a study consent form before the study.

Study Scales

In the study, the parents filled in the socio-demographic data form in which socio-demographic characteristics and information about the functionality of the child or young person were questioned. In addition, the child or adolescent was asked to fill the Empathy Scale for Children and Adolescents, and the Strengths and Difficulties Questionnaire (SDQ) from the parents. Data collection tools are detailed below.

1. Socio-demographic Data Form: This form was created by the study authors for the current study. "In the form, questions were asked that question the functionality of the child's school success, homework habits, peer and sibling relationships according to the parent's own perception; as well as the age and gender of the child, educational status of the parents (primary education, high school, university) and the family income. (Ex: "If you consider the last semester grades on the school report, how is your child's school success?", "How is your child's peer relationships in your opinion?", "How is your child's ability to do homework in your opinion?", "In your opinion, how is your child's relationship with his siblings?"). Parents evaluated the questions in a 5-point Likert style, ranging from "very problematic" (1 point) to "very good" (5 points). In the socio-demographic data form, it was aimed to directly evaluate the situation of the child in the relevant areas in line with the perception of the parent and independent of the behavioral and emotional difficulties experienced by the child.

2. Empathy Scale for Children and Adolescents: Empathy Scale for Children and Adolescents (ESCA) was created by Bryant[30] (1982) to measure the empathy skills of children and adolescents. The original form of the scale contains 22 items. The Turkish validity and reliability study of the scale was conducted by Gürtunca[31] (2013) and the scale was reported as a valid and reliable measurement tool that can be used to evaluate empathy skills in children aged 8-14 years. One item was removed in the Turkish adaptation and validity reliability study, thus the scale included 21 items. Scale questions are evaluated as "no" (0 point) or "yes" (1 point) by the child or young person. The lowest score that can be obtained from the scale is 0, and the highest score is 21. Increasing scores indicate higher empathy skills.

3. Strengths and Difficulties Questionnaire-parent Form: The SDQ is an assessment tool consisting of 25 items developed by Goodman[32] (1997) to evaluate the emotional and behavioral difficulties experienced by children and young people. Each item is scored between 0-2 points in a 3-point likert as "not correct", "partially correct" and "absolutely correct". The scale evaluates the difficulties and strengths experienced by the child on 5 dimensions (emotional problems, behavioral problems, hyperactivity, peer problems and prosocial behaviors). An increasing score indicates improved functionality in prosocial behavior and increased problems in other sub-dimensions. The sum of the sub-dimensions other than prosocial behavior gives the total difficulty score. The total score of internalizing

problems is obtained from the sum of the emotional problems and peer problems sub-dimensions, and the total score of the externalizing problems is obtained from the behavioral problems and hyperactivity sub-dimensions. The Turkish validity and reliability study of the scale was conducted by Güvenir et al.[33] (2008), and the scale has been reported as a valid and reliable measurement tool to measure the emotional and behavioral problems of children and adolescents aged 4-17.

Statistical Analysis

SPSS 15.0 package program was used to evaluate the data. Descriptive data are presented with mean, standard deviation (SD), number, and percentage. Whether the data is normally distributed or not was tested with the Kolmogorov-Smirnov test. Student's t-test was used for the comparison of continuous variables between normally distributed groups, and Mann-Whitney U test was used to compare continuous variables that did not show normal distribution. Correlations between numerical data that are not normally distributed were evaluated using the Spearman correlation test. Statistical significance is defined for cases of $p<0.05$.

RESULTS

One-hundred children and adolescents, including 39 (39%) girls and 61 (61%) boys, participated in the study. The average age of the participants was 11.1 (SD=2.23). The socio-demographic characteristics of the children and adolescents included in the study are presented in Table 1.

Table 1. Socio-demographic characteristics of the participants

	Mean ± SD / n (%)
Age	11.1±2.23
Gender	
Girls	39 (39%)
Boys	61 (61%)
Educational status of the mother	
Primary school	51 (51%)
Secondary school	34 (34%)
University	15 (15%)
Educational status of the father	
Primary school	36 (36%)
Secondary school	38 (38%)
University	26 (26%)
Monthly income	
Less than 3,000 TL	45 (45%)
3.000-5.000 TL	29 (29%)
More than 5.000 TL	26 (26%)

SD: Standard deviation

The mean total score of the ESCA, which was filled out by children and adolescents within the scope of the study, was 12.67 (SD=3.37). In the statistical analysis conducted to investigate whether the empathy level differs according to gender, age and income level, it was seen that girls have higher empathy skills at a statistically significant level compared to boys (t=2.094, p=0.039). In order to examine whether the empathy scores differ between the child age group and the adolescent age group, the analysis was conducted by dividing the participants into two groups as under 12 and equal to and over 12 years old, and no significant difference was found between the groups according to age (t=-0.247, p=0.805). In addition, the relationship between age and empathy level was analyzed with Spearman correlation analysis and no statistically significant relationship was found (r=0.007, p=0.942). Empathy level did not show a statistically significant difference according to the income level of the participants (t=0.380, p=0.705) (Table 2).

In our study, the distribution of the SDQ subscale and total score averages in the whole group, in girls and in boys, filled by the parents is presented in Table 3. In the paired group comparisons, there was no statistically significant difference between girls and boys in any subscale scores, internalizing, externalizing, and total scale scores (p>0.05) (Table 3).

Correlation analysis was conducted to investigate the presence and direction of the relationship between the total score of the ESCA and the SDQ subscale scores, internalizing, externalizing, and total scale score. In the whole group, it was found that there was a mild-moderate inverse relationship between the empathy level of the child and adolescent and emotional problems, behavioral problems, peer problems, internalizing problems, externalizing problems and total difficulty score (r=-0.201 p=0.045, respectively, r=-0.393 p=0.000, r=-0.213 p=0.033, r=-0.239 p=0.017, r=-0.287 p=0.004, r=-0.277 p=0.005), there was no significant

Table 2. Empathy level by gender, age and income

	ESCA-Total empathy score		
	Mean ± SD	T	p
Gender			
Girl	13.53±3.35	2.094	0.039
Boy	12.11±3.29		
Age			
Child age group (8-11 years)	12.59±3.49	-0.247	0.805
Adolescent age group (12-14 years)	12.76±3.26		
Monthly Income			
Less than the minimum wage	12.83±3.75	0.380	0.705
Minimum wage and over	12.57±3.15		

Student's t-test.
ESCA: Empathy Scale for Children and Adolescents, SD: Standard deviation

relationship with hyperactivity (p=0.033 r=-0.173). Empathy level is positively correlated with prosocial behavior (r=0.370 p=0.000). When the same analysis was conducted with only girls, there was no statistically significant relationship; when it was applied only with boys, it was observed that the same-direction relationship preserved for the same items and even the correlation coefficients were increased (Table 4).

In functional evaluations, the mean scores (±SD) obtained in the whole group are as follows: School achievement 3.8±1.0, homework habits 3.6±1.1, peer relations 3.8±0.9, and sibling relationships 3.7±1.1. When the relationship between total empathy level and functionality parameters was evaluated, it was observed that there was a moderate positive correlation between school achievement, homework habits and peer relationships in the whole group (r=0.394 p=0.000, r=0.332 p=0.001, r=0.407 p=0.000, respectively). When the analysis was made only with the girls group, school achievement and homework habits were positively correlated with the total empathy level, when the analysis was made only with the boys school achievement, peer relationships and sibling relationships were found to be positively correlated with the total empathy level (Table 5).

DISCUSSION

Our study, examining the relationship between the parent-rated internalizing and externalizing problems and self-rated empathy levels of the cases who applied to child and adolescent psychiatry outpatients for various reasons, found that the empathy skill of girls was better than that of boys and empathy levels were negatively correlated with internalizing and externalizing scores, total difficulty score and all problem areas except hyperactivity subscale and positively correlated with prosocial behavior. In other words, as the empathy skills of children and adolescents increase, behavioral problems in particular, emotional problems and peer problems decrease and prosocial behaviors increase. Interestingly, when only girls were evaluated, all relationships that were found to be statistically significant disappeared, while stronger relationships were recorded when only boys were taken into consideration. Empathy levels also seem to be related to the areas of functionality specified by the family. In this clinical sample, there was no effect of age and socioeconomic level (SEL) on empathy.

Table 3. Score distribution of the Strengths and Difficulties of the Participants

	SDQ Whole sample (n=100) Mean ± SD	SDQ Girls (n=39) Mean ± SD	SDQ Boys (n=61) Mean ± SD
Emotional problems	4.2±4.3	5.2±6.1	3.5±2.5
Behavioral problems	2.6±1.9	2.4±1.9	2.8±1.9
Hyperactivity	5.0±2.4	4.6±2.5	5.2±2.3
Peer problems	3.7±1.9	3.6±2.1	3.8±1.8
Prosocial behavior	7.0±2.2	7.1±2.2	6.9±2.2
Introversion issues	7.9±5.3	8.8±7.1	7.4±3.8
Extroversion issues	7.7±3.8	7.1±4.0	8.0±3.6
Total difficulty	15.6±7.7	15.9±9.4	15.5±6.5

*There was no statistically significant difference in the paired group comparisons of all subscale and total scale scores in girls and boys. P>0.05; Student's t-test was used for group comparison of normally distributed data, and Mann-Whitney U test was used for group comparison of non-normally distributed data.

SDQ: Strengths and Difficulties Questionnaire, SD: Standard deviation

Table 4. The relationship between empathy level and internalizing and externalizing problems

Total empathy	Emotional problems	Behavioral problems	Hyperactivity	Peer problems	Prosocial behavior	Introversion issues	Extroversion issues	Total difficulty
Whole sample (n=100)	p=0.045 r=-0.201*	p=0.000 r=-0.393**	p=0.086 r=-0.173	p=0.033 r=-0.213*	p=0.000 r=0.370**	p=0.017 r=-0.239**	p=0.004 r=-0.287**	p=0.005 r=-0.277**
Girls (n=39)	p=0.997 r=0.001	p=0.101 r=-0.267	p=0.538 r=-0.102	p=0.653 r=0.074	p=0.062 r=0.302	p=0.963 r=0.008	p=0.474 r=-0.118	p=0.821 r=-0.0.38
Boys (n=61)	p=0.004 r=-0.361**	p=0.000 r=-0.451**	p=0.181 r=-0.174	p=0.001 r=-0.402**	p=0.001 r=0.403**	p=0.001 r=-0.418**	p=0.004 r=-0.366**	p=0.000 r=-0.448**

Spearman correlation analysis.

*The correlation is statistically significant at the p=0.05 level.

**The correlation is statistically significant at the p=0.01 level

Table 5. The relationship of empathy level with the child's functionality according to parental statement

Total empathy	School achievement	Homework habits	Peer relations	Sibling relations
Whole sample (n=100)	p=0.000 r=0.394**	p=0.001 r=0.332**	p=0.000 r=0.407**	p=0.290 r=0.111
Girls (n=39)	p=0.034 r=0.340*	p=0.010 r=0.407*	p=0.236 r=0.194	p=0.171 r=0.224
Boys (n=61)	p=0.001 r=0.411**	p=0.060 r=0.242	p=0.000 r=0.525**	p=0.048 r=0.272*

Spearman correlation analysis.

*The correlation is statistically significant at the p=0.05 level.

**The correlation is statistically significant at the p=0.01 level.

In our study, empathy level was found significantly higher in girls compared to boys, as expected. This finding is consistent with the literature, which is supported by other studies in which girls have higher empathy levels compared to boys[34,35]. It has been reported that these gender differences seen in empathy are based on phylogenetic and ontogenetic origins, females develop empathic adaptations to be sensitive to the signals of their babies, these differences persist throughout life, and the female brain gives different neuronal empathic responses to that of the male brain[22].

In the analyzes we conducted to investigate the change in empathy by age, it was found that empathy levels did not change according to age. There are different results in the literature regarding the effect of age on empathy. In one study, it was reported that there was no difference in empathy scores between the 1st and 4th grades, but empathy scores at the 7th grade level were higher than these two classes[30]. Another study showed that the empathy level decreases as the age increases in the boys, while the empathy levels in the girls increase with the age[36]. In the first of two studies with large population samples including 9-18 and 4-16 age groups, it was found that both emotional and cognitive empathy levels increased with age, in the other, age was found to be effective only on the increase in cognitive empathy level[21,37]. Another study found that there was no increase in empathy levels between the ages of 10-14, similar to our study[38]. Findings regarding the effect of age on empathy do not seem consistent. The lack of change in empathy levels according to age in our study may be due to the narrow age range in our study, or to the fact that the children and adolescents included in the study were selected from the clinical sample. In addition, the fact that the emotional and cognitive components of empathy were not evaluated separately may be another factor. However, studies conducted in our country have also found have also found no relationship between age and empathic tendency levels in adults and adolescents[39,40].

In our study, no significant difference was found in empathy scores between the two groups, which were compared in terms of SEL as below the minimum wage and the minimum wage and above. Similar to our study, in a study conducted with secondary school students in our country, no difference was found between empathy and SEL[41]. In another study, in support of these findings, no difference was found between SEL and empathy levels[42]. In studies abroad, in addition to studies reporting that there is no relationship between empathy and SEL, there are also studies showing that there is a relationship between SEL and empathy level[43-45]. However, it is important to evaluate what factors the relationship between empathy and SEL depends on. One possible approach is that excessive emotional arousal caused by economic tension and related family conflicts may prevent empathy[46]. We may consider that that we could not find a relationship between SEL and empathy because that our study was conducted with a relatively small study group in a clinical sample. This relation may be better revealed by studies that investigate the effects of economic difficulties and the familial responses to them in more detail.

One of the main aims of our study was to evaluate the relationship between internalizing and externalizing problems and the empathy level of children and adolescents in a clinical sample. For this purpose, the SDQ subscale, internalizing, externalizing, and total scale scores were evaluated, and then the relationship between SDQ scores and total empathy score was investigated in the whole sample, in girls and in boys. It is seen that the mean scores obtained from the SDQ are close to or slightly lower than the scores reported by Güvenir et al.[33] (2008) in the clinical sample. In our study, the mean scores (±SD) of emotional problems, behavioral problems, hyperactivity, peer problems and total difficulty evaluated by the parents were respectively 4.2±4.3; 2.6±1.9; 5.0±2.4; 3.7±1.9 and 15.6±7.7, while the mean score values found by Güvenir et al.[33] for the same evaluations were 4.1±2.5; 3.3±2.0; 6.2±2.6; 3.6±1.8 and 17.4±6.0. We found that the SDQ scores did not show a statistically significant difference between female and male participants. According to the information obtained from the literature[47], as expected, emotional problems score is higher for girls and behavioral problems score is higher for boys; however, the difference is not at the level of statistical

significance. The fact that girls' and boys' scores were close to each other, in other words, their having difficulties with similar severity, enabled us to evaluate the relationship of empathy level with internalizing and externalizing problems in different genders, regardless of the potential confounding effect of the problem level difference.

Studies that repeatedly reveal the relationship between low empathy levels and behavioral problems in the literature are consistent with the findings of our study[14,21,48,49]. It has been reported that individuals with externalizing disorders have cognitive distortions that protect themselves and blame others, and aggressive, antisocial behaviors may stem from low empathy skills[50-52]. Empathy development has been shown to be associated with cognitive and social-environmental processes[53]. Empathy deficiencies in children with behavioral problems have been suggested to be linked to impaired neurocognitive capacities related to emotional attention and response to certain stimuli and neurochemical systems in related brain pathways[53]. In light of this information, as we reported in our study, the fact that children and adolescents with better empathy have lower behavioral problems and more prosocial behaviors is an expected finding.

Studies investigating the relationship between empathy skills and ADHD symptoms are limited and did not reveal consistent results such as behavioral problems. As there are studies showing that ADHD diagnosis or symptoms are associated with low empathy[21,54], similar to our study[55], there are studies that fails to show this association or that this relationship exists only in the presence of opposition or behavioral problems[27,56]. In another study, contrary to expectations, a positive relationship was reported between the ADHD problems and empathy skills[14].

In some of the studies examining the relationships between internalizing problems and empathy, it has been found that, unlike externalizing disorders, high levels of empathy are associated with depression and anxiety disorders[14,57]. These studies suggest that high levels of empathy may be associated with being more prone to get emotionally affected by other peoples problems, the anxiety of giving harm to others and experiencing worry and anxiety. However, there are also studies in the literature that find a reverse relationship. Dadds et al.[21] (2008), in a study conducted with a population sample of 2,612 participants between the ages of 4-16, found that children and adolescents with high levels of empathy show lower emotional problems according to the SDQ scores completed by the parents. Similarly, a study from our country compared children aged 8-12 with anxiety disorders with controls, and reported that the anxiety disorder group had lower levels of empathy compared to the control group[18]. The differences between studies may differ according to the study population or clinical sample, age group, and the effects of different dimensions of empathy.

When we evaluated the relationship of SDQ subscales, internalizing and externalizing scores with empathy, separately by gender, we found that the relationships determined in the analyzes performed by including the whole sample went on strengthening in the sample consisting only of boys; however, all relationships disappeared in girls. Although this result should be considered with caution due to the relatively low sample size of girls (n=39), this segregation detected in the clinical sample was considered to be significant in terms of shedding light on future studies. In addition, there is no difference between girls and boys in terms of problem severity, as explained above regarding the scores obtained from the SDQ. In the literature, there are very few studies evaluating the interaction of empathy levels in girls and boys with psychopathology by gender. The only clinical sample study available was the study conducted by Gambin and Sharp[14] (2016) with 507 inpatient adolescents aged 12-17 years. This study evaluated empathy by its emotional and cognitive dimensions and some differences were found between girls and boys. For example, emotional and cognitive empathy was found to be negatively associated with behavioral problems only in girls, while internalizing problems and ADHD symptoms were positively associated with emotional empathy in both boys and girls. While evaluating the positive relationship between internalizing symptoms and empathy in parallel with previous studies, the authors stated that it was surprising to find a same way relationship in ADHD symptoms, and they explained this result with the high emotional reactivity common to both disorders. In particular, they noted that the fact that behavioral problems were associated with empathy, only in girls was different from literature knowledge; and they explained that this finding might be associated with high severity and narrow variability of boys' symptoms in their samples. They emphasized that new research is needed on this issue[14]. Our study findings differ from this study completely. The results of our present study suggest that low empathy skills in the clinical sample show a moderate relationship with mental and behavioral difficulties in boys, whereas there is no such relationship in girls. It is stated that empathy development has evolutionary and developmental origins, hereditary and environmental interactions have different effects on brain and behavior in girls and boys; and these are shaped by social and cultural influences[22]. One study has shown that the effect of culture on empathy differs according to gender[58]. In our society, lack of empathy may be one of the reasons that predispose to the development of psychopathology in boys.

In our study, a positive relationship was found between empathy level and school achievement, homework habits and peer relationships, while no relationship was found with

sibling relationships. Similarly, in a study conducted in our country, it was determined that students with high academic achievement had high levels of empathy[59]. Studies abroad have also shown that empathy level plays an important role in academic achievement[8,9]. These findings are considered to explain the good homework habits of those with high empathy. In addition, since our study was conducted in a clinical sample, as discussed above the relationship between emotional and behavioral problems and empathy also should be taken into consideration. Because it is known that behavioral problems and internalizing problems negatively affect academic achievement[59-62]. In the meta-analysis of studies evaluating the level of empathy and friendship relations, a mild-moderate positive relationship was found between the empathy level and friendship relations, supporting the relationship we found in our study[7].

Relationships with siblings are known to be associated with development of empathy[63]. However, in our study, no significant relationship was found between parent-evaluated sibling relationships and empathy. The reason for this difference may be the fact that our study was conducted with a clinical sample of children and adolescents with various mental health problems that might affect the sibling relationships. When the functionality parameters assessed by the parents were evaluated separately for girls and boys, we found that the association between empathy and peer relationships disappeared in girls and the association between empathy and homework habits was lost in boys; on the other hand, association of empathy with sibling relationships reached a statistically significant level in boys, even if it was weak. As discussed above, empathy develops differently in male and female gender and appears to have different effects.

Study Limitations

TThe following limitations should be taken into account when interpreting the results of our study, which is the first in our country, by examining children and adolescents' empathy levels in regard to internalizing and externalizing symptoms in child and adolescent psychiatry outpatients: Our study is a cross-sectional study. Considering the follow-up studies that provide a neurodevelopmental explanation for empathy and examine the interaction of various familial factors with empathy, prospective follow-up studies are needed to effectively evaluate the relationship between empathy and psychiatric symptoms/disorders[64-66]. One of the limitations of our study is that empathy level was determined from children and adolescents in the form of self-report. It is thought that it is important to evaluate the empathy level from different and plural sources such as family and teacher.

The level of functionality was also evaluated with the questions asked in the socio-demographic data form and based solely on the parental report, and an assessment tool was not used for this, and no information was obtained from another source such as a teacher. Finally, since the main purpose of the study was to evaluate the relationship between internalizing and externalizing problems and empathy levels, no grouping and comparison was made in the study design according to the clinical diagnoses of the cases. However, evaluations to be made according to clinical diagnoses and including disease severity will provide useful information in understanding the relationship between empathy and psychopathology.

CONCLUSION

In our study, a negative correlation was found between empathy levels and internalizing problems and externalizing problems in children and adolescents aged 8-14 years in a clinical sample. When this relationship was evaluated according to gender, it disappeared in girls and got stronger in boys. Consistent with the literature, behavior problems are more strongly associated with low empathy. In addition, as empathy skills increase, academic achievement and positive friendship relationships, which are important for the psychological development of children and adolescents, increase. However, in order to better understand the relationship between empathy levels and internalizing and externalizing problems, there is need for cross-sectional studies and follow-up studies that are planned to address the effects of age, gender and cultural differences in clinical and community samples. Considering the results of our study, it can be argued that improving empathy skills may have a healing effect in the treatment of mental difficulties of children and adolescents, and will contribute positively to the academic achievement and functionality of children and adolescents in their social relations. In addition, attempts to observe and develop children's empathy skills starting from the preschool period have the potential to make significant contributions to preventive mental health.

Ethics

Ethics Committee Approval: The Ethics Committee approval was obtained from the Pamukkale University Non-Invasive Research Ethics Committee with the number 60116787-020/34252, dated 18.05.2018.

Informed Consent: Participants and their parents signed a study consent form before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Medical Practices: Ö.B., S.N.E., U.E.İ., M.Ö., M.O.S., B.K.B., Concept: Ö.B., S.N.E., U.E.İ., M.Ö., M.O.S., B.K.B., Design: Ö.B., S.N.E., U.E.İ., M.Ö., M.O.S., B.K.B., Data Collection or Processing: Ö.B., S.N.E., U.E.İ., M.Ö., M.O.S., B.K.B., Analysis or Interpretation: Ö.B., S.N.E., U.E.İ., M.Ö., M.O.S., B.K.B., Literature Search: Ö.B., S.N.E., U.E.İ., M.Ö., M.O.S., B.K.B., Writing: Ö.B., S.N.E., U.E.İ., M.Ö., M.O.S., B.K.B.

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