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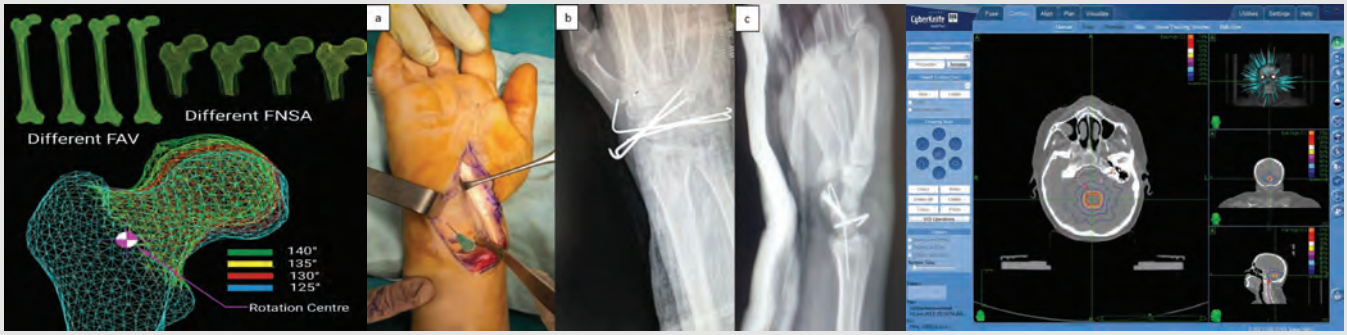

Highlights

galenos yayınevi

Official Journal of University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital

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Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

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Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

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Figure Legend: Reference citations should appear in the legends, not in the abstract. Since there is no manuscript text, the legends for illustrations should be prepared in considerable detail but should be no more than 500 words total. The case should be presented and discussed in the Figure legend section.

References: Maximum eight references (see Original article section).

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables.

Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text).

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Review Article	5000	250	80	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Stephane A. Management of Congenital Cholesteatoma with Otoendoscopic Surgery: Case Report. Turkiye Klinikleri J Med Sci 2010;30:803-7.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press;2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme;2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland;1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dçent Res. 1974. Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5):1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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CONTENTS

REVIEW

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Education in Pathology: What is the Place of Pathology Education in the "Online" Education Model?

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Abstract

In Turkish, education is derived from the verb root "bending", which means to bend, apply, teach, train, develop, exercise, dominate, defeat, crush, break, and direct. Considering the continuous and forward-moving role of pathology in modern medical practice, the importance of the concept of education in pathology becomes clear. In this review article, we aimed to create awareness of the dynamic and absolute continuous aspect of education in pathology.

Keywords: Pathology practice, online education, distance education

INTRODUCTION

According to the philosopher Kant, "Man can only be human through education, or he is nothing more than what education brings about". When we examine the educational relationships between people, we find that the same goal is always pursued (including today's "online" presentations and seminars) from primitive writings of thousands of years ago, such as murals, nails, and hieroglyphs, a phenomenon known as "educational instinct" . Considering the continuous and forward-moving role of pathology in modern medical practice, the importance of the concept of education in pathology becomes clear.

In Turkish, education is derived from the verb root "bending", which means to bend, apply, teach, train, develop, exercise, dominate, defeat, crush, break, and direct (1,2). Approaches regarding the different learning characteristics of adults first coincided in the late 1940s. Regarding the theoretical basis of the studies on adult learning, Malcolm Knowles puts forward a detailed adult learning theory in his book, *Adult Student*, published in 1973. Knowles introduced the concept of "andragogy", drawing attention to the fact that adults need certain situations to learn. By combining the words "andra", which means adult human, and "agosos", which means guiding, he created a discipline that examines adult education method (3). In this context, since our target audience in pathology education is residents and technicians, we must act with this discipline.

One of the most important principles in education is to make the participant understand why it is important to learn the subject (4). Especially, it is seen that trainings where cause and effect relationship is shown through examples and that those described with direct examples are more successful.

Campella (5) emphasizes in his work, *The Land of the Sun*, that having a craft and a profession glorifies one's self. We should emphasize how the technician and assistant will be more effective and how the given information would facilitate their work.

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Everyone's experiences are valuable for learning and, therefore, there is a versatile communication shared by all. It should be associated with the experiences of the participants and considered that the mature person's accumulation of experience constitutes an important resource in learning (6). In trainings attended by people from all seniorities and where experiences are shared, we see that the subject is more easily understood and memorable.

As stated in polytechnic education, learning by doing rather than memorization and theory is essential in education (7). Adults should be active in the learning process and learn by doing and experiencing. This is especially important for the acquisition of skills and their permanence. Although the information about macroscopy is explained verbally in pathology, it is seen that the resident is more effective when she/he starts to look at his own sample under the microscope. Adults tend to be hasty in applying their learned knowledge and have a problem-centered approach toward learning. They should be assisted to overcome their established behaviors, beliefs, and concerns about learning (8). Especially in routinely used techniques, more senior technicians and experts are seen to be more conservative in abandoning their habits. As stated by Descartes, "All that we understand very clearly and distinctly is true". In order to see the basic elements of the problem and the relationships between them, the issue should be structured and prepared in detail.

In fact, at this point, we are faced with a completely different education model, apart from all these written and experienced educational concepts. Atatürk said that "Science is the most real guide for civilization, life, and success in the world; to search for a guide other than science is absurdity, ignorance, and heresy" (9). An "online" education model has emerged due to the changing social conditions (such as the Coronavirus Disease-2019 pandemic) and the need to continuously renew or update the information, depending on evolving technology.

Founded in 1938, the International Council for Open and Distance Education defined the distance education model as the delivery of education to distant students with the help of tools, such as satellite, video, sound, graphics, computer, and multimedia technology.

One of the advantages of distant education is its cost-effectiveness. It is a great convenience that everyone can access education without paying fees for travel, accommodation, and participation. In addition, the fact that a person can be connected to education from anywhere (home, work, and road) eliminates time and geographic difficulties. Our attention has been drawn to the fact that the number of participants in pathology courses and presentations has increased significantly in "online" presentations. It is also a great convenience to reach the recorded course/presentation at any time and place. Being away from the psychological pressure also provides an advantage for the learning process. In this context, it is another remarkable concept that "online" courses offer and ask more questions than the internet environment and that all kinds of comments can be made.

In addition to these, "online" education has disadvantages, such as connection problems and preventable disruptions, including interruption of incoming sound and video due to poor internet access. Wherever there is human activity, there is communication and communication is the basis of social life. The origin of the concept of communication is the word "communis" in Latin. The concept of communication has nearly five thousand uses. Some of its uses are as follows: Exchange of thought, understanding-explaining, interaction, reducing uncertainty, transfer process, process of change, process of establishing connections, process of sharing, tool-method-techniques, stimulation of memory, responding, stimulating, influencing, and transition process (10). Failure to meet the needs of using expressive elements, such as human facial expressions and body movements, in "online" trainings, not being able to make affirmation-reinforcement movements, and lack of social activities (coffee, tea drinking-meal conversations, and meeting new people) negatively affects education.

Although the Standardization Committee of Federation of Turkish Pathology Societies regularly organizes courses, a more structured course program has been implemented in the last four terms. In these courses, participants' profile was determined by a test. This test was done before and after the course and the contribution to the course was questioned. In the second period, it aimed to educate the trainers, but had the participation of a limited number of volunteers. According to a study, students keep in mind 10% of what they read, 26% of what they hear, 30% of what they see, 50% of what they see and hear, 70% of what they say, and 90% of what they say about what they do (11). Each participant was asked a question and it was ensured that they present their answer to other participants attending the course. After this presentation, the subject was discussed and all questions were answered. A total of 51 residents, 434 technicians, and 167 experts, totaling up to 652 people, was reached in 17 courses held in three terms. Recently, due to the pandemic, the course was held online. "We are rebuilding our pathology laboratory: '5N1K' in quality standards. You ask, let us explain!" titled course was held on two separate dates and 185 and 123 people attended these courses, respectively. Video

recordings of these courses have been made available on the web page.

Results of the third course (12) and the feedback of the latest "online" test show that a single form of education is not enough in pathology education. Regardless of the education model, it emerges that students should come to education by working, effectively using audio and visual elements in education, and devoting sufficient time to questions and answers during and after the education.

CONCLUSION

As a result, education in pathology is a continuous process that is responsible for innovations. With the awareness of the dynamic and absolute continuous aspect of education, we should always aim further in education, in whatever form and condition it may be, especially in the field of pathology, which has many details.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Ö.Y., Z.B.E., H.N.Ü., K.Y., Design: Ö.Y., Z.B.E., H.N.Ü., K.Y., Data Collection or Processing: Ö.Y., Z.B.E., Analysis or Interpretation: Ö.Y., H.N.Ü., K.Y., Literature Search: Ö.Y., Z.B.E., Writing: Ö.Y., Z.B.E.

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ORIGINAL ARTICLE

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Quantitative Measurement of Retinal Vessel Density in Non-proliferative and Proliferative Macular Telangiectasia Type 2 with Optical Coherence Tomography Angiography

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Abstract

Objective: The purpose of the study was to quantify the optical coherence tomography angiography (OCTA) features of non-proliferative and proliferative macular telangiectasia type 2 (MacTel2). The retinal vessel density (RVD) of the superficial and deep layers of the retina were studied.

Methods: This cross-sectional and observational study was carried out at İstanbul Beyoğlu Eye Training and Research Hospital. Patients clinically diagnosed with MacTel2 underwent fundus photography, fluorescein angiography, spectral domain OCT, and OCTA imaging. Superficial and deep RVD in the foveal and parafoveal regions were calculated using device automated software.

Results: Thirteen eyes of 8 patients (4 male, 4 female) with a mean age of 64.6±3.8 years were included. The mean RVD of the superficial fovea and parafovea were 30.3%±9.3% and 49.5%±6.4% in non-proliferative MacTel2, compared with 39.4%±3.3% and 43.8%±2.9% in the proliferative MacTel2, respectively. No statistically significant difference was found between non-proliferative and proliferative MacTel2 (p=0.31, p=0.41; respectively). The mean deep foveal and parafoveal RVD was 30.4%±7.8% and 50.7%±3.8% in non-proliferative MacTel2 versus 47.5%±0.2% and 55.3%±8.4% in proliferative MacTel2, respectively. There was a significant difference in deep foveal RVD between proliferative and non-proliferative MacTel2 patients, whereas no difference was found in deep parafoveal RVD (p=0.02 and p=0.23, respectively).

Conclusion: The mean deep foveal RVD was significantly higher in proliferative MacTel2 than in non-proliferative MacTel2. Measurement of RVD in the deep retinal layers by OCTA may have diagnostic value in patients with proliferative MacTel2.

Keywords: Macular telangiectasia type 2, optical coherence tomography angiography, non-proliferative, proliferative

INTRODUCTION

Type 2 macular telangiectasia (MacTel2) is a progressive, bilateral retinal vascular disease that arises within the temporal, juxtafoveal region of the macula. Initially, the microvascular features of non-proliferative MacTel2 include telangiectatic abnormalities within the deep retinal capillary plexus (DRCP), temporal to the fovea, and these changes continue to invade the superficial retinal capillary plexus with subsequent extension circumferentially to involve the perifoveal microvasculature (1,2). In the later proliferative stages of MacTel2, neovascularization may arise and extend under the retina, often leading to pigment deposition and disciform scar formation (3). Fluorescein angiography (FA) continues to be the gold standard method for confirming the diagnosis of proliferative MacTel2 (1,2). Gass and Oyakawa (4) have reported that vascular alterations mainly include the DRCP and that the late leakage of fluorescence on FA seems to arise from the outer retina in non-proliferative MacTel2. Diffuse hyperfluorescence conceals the morphological changes

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in the vascular network, and FA is insufficient to give detailed information about the deep retinal layers and pathological changes therein (5). On the other hand, FA is an invasive imaging method, and it may not be possible to repeat the test at each visit.

Optical coherence tomography angiography (OCTA) is a novel, non-invasive imaging method that provides high-resolution imaging of retinal morphology, primarily individual vascular layers, as an important advantage (6,7). Additionally, OCTA allows better visualization of subretinal neovascularization (SNV), compared with FA, due to the absence of fluorescence leakage (8).

In this study, we aimed to determine whether retinal vascular density (RVD) was different between non-proliferative and proliferative MacTel2. With this new, non-invasive technique, we aim to identify proliferative changes in MacTel2 without the need for FA.

METHODS

Patients diagnosed with MacTel2 at İstanbul Beyoğlu Eye Training and Research Hospital were included in this retrospective, cross-sectional, and observational study. Institutional review board approval was achieved from İstanbul Beyoğlu Eye Training and Research Hospital Review Board (approval date: 31.08.2018, approval no: 18/I-1). The study was carried out in accordance with the principles of the Declaration of Helsinki. As a criterion for inclusion in the study, patients had to be diagnosed with non-proliferative or proliferative MacTel2 in at least one eye. Patients with retinal vein occlusion, diabetic retinopathy, choroidal neovascularization secondary to age-related macular degeneration, previous vitreoretinal surgery history, or history of photodynamic therapy were excluded from the study. All patients underwent a complete ophthalmologic evaluation, including slit lamp biomicroscopy, intraocular pressure measurement with applanation tonometry, and dilated fundus examination after best corrected visual acuity measurement using Snellen charts. Besides a comprehensive ocular examination, all patients underwent color fundus imaging, FA imaging with HRA 2 (Germany, Heidelberg, Heidelberg Engineering), and spectral domain OCT imaging (Germany, Heidelberg, Heidelberg Engineering). In addition, patients were imaged with the Optovue AngioVue system (Optovue, CA, Inc., Freemont) for OCTA imaging. This device has a scanning speed of 70,000 A-scans per second using a light source with a bandwidth of 50 nm and centered at 840 nm. The retinal region of a volume scan included a 3 mm x3 mm field of view obtained with at least 49 B-scans per volume. Patients whose images had inadequate signal strength were excluded from the study. A split-spectrum amplitude-decor correlation angiography algorithm was used to calculate a flow map for each scan. In this study, two-layer imaging of the OCT angiogram was analyzed, including superficial and DRCs. In this study, we included two layers from the en face OCT angiogram in our analysis: The superficial retinal capillaries and the DRCs. The OCT system's software performs automatic segmentation of these vessel layers. The capillaries between the inner limiting membrane and the posterior border of the inner plexiform layer (IPL) form the superficial plexus, while the deep plexus form the capillary layer between the posterior border of the IPL and the posterior border of the outer plexiform layer. Quantitative data consisting of RVD for each microvascular layer were generated by the device software. RVD was measured at two concentric circular regions: The fovea-centered 1.0 mm radius area and the parafoveal region from the 1.0-3.0 mm radius area.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics, Version 20.0 (IBM Corp.; Armonk, NY, USA). Mean, standard deviation, median, frequency, and ratio values were used in descriptive statistics of the data. For the analysis of independent quantitative data, The Mann-Whitney U test was used. For all tests, a $p<0.05$ was defined as statistically significant.

RESULTS

Thirteen eyes of 8 patients (4 males, 4 females) with MacTel2 were included in the study. The mean age of the patients was 64.6±3.8 years (61-73). Three eyes had subfoveal SNV secondary to MacTel2.

The mean superficial (foveal and parafoveal) and deep (foveal and parafoveal) RVD measurements in patients with proliferative and non-proliferative MacTel2 are shown in Table 1. There was a significant difference only in deep foveal RVD between proliferative and non-proliferative MacTel2 patients (Figure 1).

DISCUSSION

MacTel2 is a bilateral condition with typical changes in the macular capillary network with neurosensitive atrophy. Distinguishing features of the disease include hyporeflective intraretinal cavitation, abnormal vascular anastomosis, retinal pigment epithelial hyperplasia, foveal thinning, and progressive photoreceptor loss due to pathophysiological and biochemical changes primarily involving Müller cells (9). Eyes with MacTel2 are divided into non-proliferative and proliferative. The non-

proliferative stage is characterized by foveal atrophy and telangiectasia, while the proliferative stage is characterized by SNV (1,2). OCT features of non-proliferative MacTel2 are IS/OS disruption, hyporeflective areas in the inner retinal layers and pigment plaques (10). FA is the best imaging method for diagnosing MacTel2 by showing dilated perifoveal capillaries with leakage in the parafoveal temporal area as well as being able to show right-angled vessels and intraretinal and/or subretinal anastomoses (11). When present, SNV is characterized by visualization of early and late fluorescence leakage; however, the existence of SNV may be difficult to detect due to fluorescence leakage in the corresponding region from the abnormal retinal vasculature (12,13). With the development of OCTA, non-invasive imaging of the retina and choroidal microvasculature has been possible without the use of exogenous intravenous dye injection. OCTA is capable of detecting abnormal microvasculature in the perifoveal region and correlating with leakage seen in FA images on OCTA images. in addition, it has the typical advantages of OCT imaging in cases such as the ability to diagnose MacTel2 and monitor its progress, and thus helps to confirm the diagnosis. OCTA is a non-invasive method and offers the advantages over FA of being faster, less espensive, safer, and easily repeatable; producing a better image quality; and generating fewer effects from fluorescent leaks that hide the microvasculature (5-7). Previous studies have demonstrated multiple telangiectatic, microaneurysm-like dilated vessels in the middle retinal layers on OCTA imaging. SNV, which is a neovascular complex, communicates with both the choroidal and retinal circulation, and OCTA imaging is capable of providing better visualization of SNV than FA due to the absence of fluorescence leakage. OCTA imaging is often useful for monitoring non-proliferative MacTel2 patients for timely detection of subretinal neovascular changes, as imaging can be repeated frequently (12-14). In this study, we found that deep foveal RVD was significantly higher in proliferative MacTel2 than in non-proliferative MacTel2. This may have been due to the hyporeflective intraretinal cavitation in non-proliferative MacTel2 and subfoveal vascular membrane in prolifertive MacTel2. While the features of SNV with OCTA have been described thoroughly in previous studies, the procurement of quantitative data on the deep retinal layers may help to differentiate proliferative MacTel2 from non-proliferative disease.

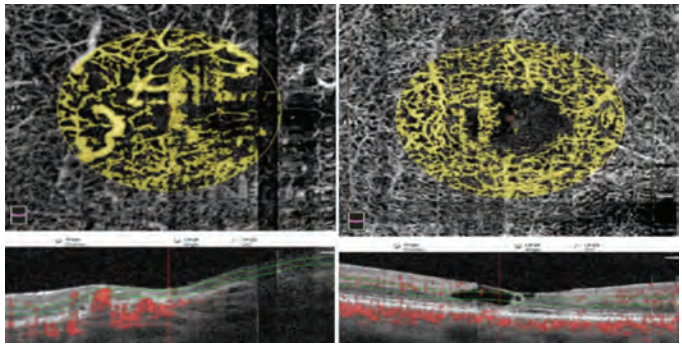

Figure 1. Deep retinal vascular density images provided with optical cohorence tomography angiography. Deep foveal retinal vascular density was significantly higher in proliferative MacTel2 (left) than in non-proliferative MacTel2 (right)
MacTel2: Macular telangiectasia type 2

Table 1. Retinal vascular density measurements in non-proliferative and proliferative MacTel2 patients

	Non-proliferative MacTel2	Proliferative MacTel2	p
Foveal superficial RVD	30.3%±9.3%	39.4%±3.3%	0.31
Parafoveal superficial RVD	49.5%±6.4%	43.8%±2.9%	0.41
Foveal deep RVD	30.4%±7.8%	47.5%±0.2%	**0.02**
Parafoveal deep RVD	50.7%±3.8%	55.3%±8.4%	0.23

RVD: Retinal vascular density, MacTel2: Macular telangiectasia type 2

Study Limitations

The limitations of the current study are its retrospective design and the limited number of included patients. Further prospective studies with larger sample sizes are needed to confirm the realistic value of RVD in the diagnosis of SNV in MacTel2.

CONCLUSION

We obtained superficial and deep foveal and parafoveal RVD in patients with either non-proliferative or proliferative MacTel2. The results of this study showed that quantification of RVD in different retinal layers using OCTA imaging is a promising method for use in the diagnosis of SNV secondary to MacTel2.

Ethics

Ethics Committee Approval: İstanbul Beyoğlu Eye Training and Research Hospital Review Board (approval date: 31.08.2018, approval no: 18/I-1).

Informed Consent: Retrospective consent of the patient was not obtained, since measurements were not performed prospectively on the patient and previous documents were scanned.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.D., Z.A., G.E., Design: A.D., Z.A., G.E., Data Collection or Processing: A.D., C.Y., G.G., D.Y., Analysis or Interpretation: A.D., C.Y., G.G., Literature Search: A.D., G.E., Writing: A.D.

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ORIGINAL ARTICLE

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Evaluation of Load Transmission to the Knee Joint in a Three-dimensional Femur Model Using a Finite Element Analysis Method

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Abstract

Objective: This study aimed to evaluate and determine the effects of femoral anteversion (FAV) and femoral neck shaft angles (FNSA) changes on the medial and lateral compartments of the distal femur using finite element analysis (FEA).

Methods: The study was designed in two stages. First, the FEA was used to evaluate the imaginary environment (IE). Then, solid models were formed and tested in an experimental environment to validate the three-dimensional (3D) models. Three adult male cadaver femurs were scanned for the IE study. The computed tomography cross-sectional scans were reconstructed to provide a 3D surface model of cancellous and cortical bones. This model was accepted as a basic model, and this model was modified with software to create 42 models by using seven different FAV and six FNSA. These modified models were then analyzed to define mesh structure. The stress values were obtained after the FEA.

Results: In the lateral compartment of the distal femur (LCDF), the highest force recorded was 625.47 N, and the lowest force recorded was 239.41 N. In the medial compartment of the distal femur (MCDF), the highest force recorded was 910.59 N and the lowest force recorded was 524.53 N. The standard femoral model (SFM), which had an FNSA of 135° and FAV of 10°, was chosen due to the close resemblance of its anatomic features to human femur. According to SFM, a maximum decrease of 44% and an increase of 47% in LCDF and a maximum decrease of 28% and an increase of 26% in MCDF were observed.

Conclusion: In the study, we found that changed FAV and FNSA significantly affected LCDF compared with MCDF.

Keywords: Femoral anteversion, femur neck shaft angle, knee osteoarthritis, finite element analysis, biomechanics

INTRODUCTION

Knee alignment plays an important role in the formation and development of osteoarthritis (OA) (1,2). The axis extending from the center of the femoral head to the intercondylar notch of the distal femur is called the mechanical axis of the femur. The axis extending from the center of the proximal tibia to the center of the ankle is called the mechanical axis of the tibia. The medial angle formed between the mechanical axis of the femur and the mechanical axis of the tibia is called the hip knee angle (HKA). The normal range of HKA is 0°-2° varus. Alternatively, the anatomical axis of the femur has an approximate 5°-7° of inclination difference compared with the mechanical axis. The lateral angle between the anatomic axes of the femur and tibia is called the femorotibial angle (FTA). The average FTA is approximately 178° in men and 176° in women (3). With daily activities, the knee is usually more loaded into the medial compartment. This loading difference may explain why medial OA is more common (4,5).

The Framingham Osteoarthritis Study showed that the lateral and medial OA differed according to gender, and lateral OA was more common in women (6). The higher incidence of lateral OA in women can simply be explained by the high

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prevalence of valgus alignment in women (7,8). Alternatively, Brouwer et al. (9) found that although varus alignment had a strong effect on OA, valgus alignment had a limited effect on the development of OA. Sharma et al. (2) found an association between varus alignment and the increasing risk of radiological OA, but they could not find this connection in valgus alignment. Furthermore, Lee et al. (10) showed that one-third of the knees with stage 4 lateral OA have a varus alignment on hip-knee-ankle radiograph.

Lateral OA was previously explained by changes in the hip's morphology due to the limited effect of knee valgus alignment on lateral OA. In contrast with men, the hip adductor muscles in women are stronger than abductor muscles (11,12). The reduction in the strength of abductor muscles decreases hip control and causes abnormal knee kinematics. The reduction in the femoral offset and presence of coxa valga decrease the abductor lever arm, which may cause an abductor moment reduction (13). In other words, reduction in the strength of hip abductor muscle may result in an increased valgus load in the knee (14,15).

Weidow (16) studied the morphological changes of cartilage wear and found that more anterior wear occurs in medial knee OA and more posterior wear occurs in lateral knee OA. Weidow et al. (17) measured pelvic width, femoral offset, femoral neck length, and femoral neck shaft angles (FNSA) in patients with lateral knee OA. They emphasized that the anatomical variables in the pelvis and hip joints may change the distribution of the load on the knee joint and may have an effect on medial and lateral OA. In a gait analysis study, Weidow et al. (18) also found an association between the presence of lateral knee OA and the biomechanics of the hip joint. There is little information available in the literature on the relationship between the femoral anteversion (FAV) and FNSA and knee OA. Therefore, the purpose of this study is to evaluate and determine the effects of the changed FAV and FNSA regarding load transmission to the knee joint in 42 femur models using finite element analysis (FEA) method.

METHODS

This is a two-step study because it was not possible to study 42 different femoral models in vivo. First, FEA was used to evaluate the imaginary environment (IE). Solid models were then created and tested in an experimental environment (EE) to validate the three-dimensional (3D) models.

Three adult male cadaver femurs were scanned using Siemens Somatom Series, Sensation 16 Multi Detector (Forchheim, Germany) for IE study. Cancellous and cortical bone area between 2 mm and 4 mm and 5 mm-to-9 mm intervals were obtained using cross-sectional (CT) scans, respectively. On the CT scan, the voxel dimension was 0.74 on X and Y coordinates and 0.7 on Z coordinates. CT scans were reconstructed using 3D-Doctor (3.5.050106, Able Software, USA) software to provide a 3D surface model of cancellous and cortical bone (Figure 1). This model was accepted as a basic model and this basic model was modified with Autodesk AutoCAD 2005 (Autodesk, Inc., USA) software to create 42 models using seven different FAV (-5°, 0°, 5°, 10°, 15°, 20°, and 25°) and six different FNSA (120°, 125°, 130°, 135°, 140°, and 145°) (Figure 1). These modified models were then analyzed with ANSYS Workbench 14.5 (ANSYS, Inc., USA) software to define the mesh structure (3D configuration like spider's web). The mesh structure is made up of elements and node units (Figure 2). The number of elements and nodes show a positive correlation with the complexity of the mesh structure. In our study, the mean numbers of nodes and elements were 74,000 and 44,000, respectively.

As a result, 21,846 nodes were intersected. A node cloud was formed with the intersected points using AutoCAD software to compare the stress value of different areas. A transactional scan was performed at 100 mm distal of the intertrochanteric region, and 15 regions were formed with a 15 mm distance between them. Stress distributions were evaluated in each region and in the lateral and medial femoral condyle. FEA was run and reaction forces on the fixation point and von Mises stresses on each node were recorded.

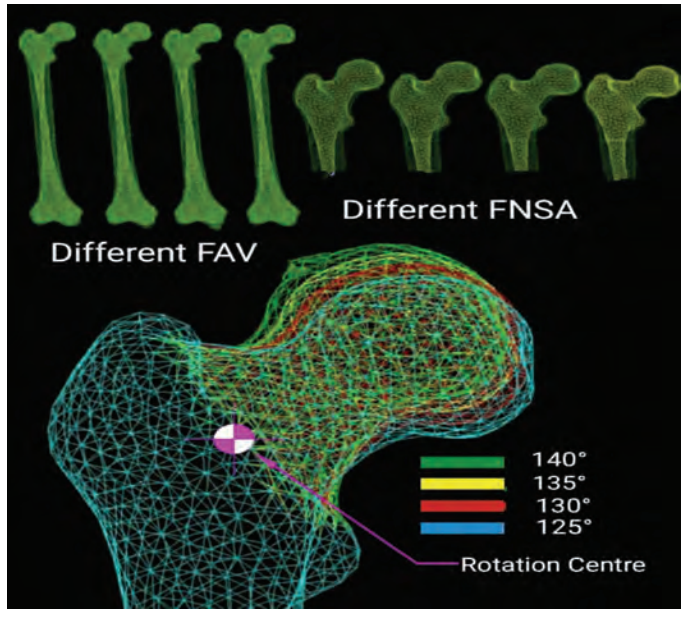

Figure 1. View of seven different FAV and six different FNSA created by software
FAV: Femoral anteversion, FNSA: Femoral neck shaft angles

The stress value in the cortical bone elastic modulus is 14,217 N/mm^2 and Poisson's ratio is 0.32, whereas the stress value in the cancellous bone elastic modulus is 1,000 N/mm^2 and Poisson's ratio is 0.3. In this study, the bone tissue is treated as a homogeneous, isotropic, and linear material, even though it shows heterogeneous, non-linear and anisotropic features due to different structures of cortical and cancellous bone. This study aims to investigate the variables that affect the biomechanical properties and perform a comparative biomechanical analysis. Therefore, the average properties used are sufficiently accurate. A force of 1,150 N was applied vertically to the solid model during walking (Figure 3A). The solid models were fixed from the medial and lateral femoral condyle points (Figure 3B) (18).

As a result, 21,846 nodes were intersected. A node cloud was formed with the intersected points using AutoCAD software to compare the stress value of different areas. A transactional scan was performed at 100 mm distal of the intertrochanteric region, and 15 regions were formed with a 15 mm distance between them. Stress distributions were evaluated in each region and in the lateral and medial femoral condyle.

In a biomechanical real environmental study, the experimental bone model was created using cylinder industrial polyamide. Its mechanical properties have a close resemblance to the cortical bone tissue (19). A polyamide bone model was created by combining three components using two joints. The first and second joints were used to change the varus valgus and anteversion angles, respectively. Bars were used on joints to minimize the errors on varus valgus and anteversion angles (Figure 4). The sagittal view of 0°, 10°, and 15° angles and frontal view of 120°, 125°, 130°, 135°, 140°, and 145° angles were selected to be used in biomechanical real environmental study, and the results were compared with the results of the imaginary studies. The polyamide model was fixed onto an aluminum platform using a cylindrical -shaped joint, which represented the lateral cortex allowing a rotation on the X axis. This platform was fixed onto a measurement frame using cylindrical beds to enable movement on the Z axis. A load cell was placed under the polyamide model in the same region, which represented the medial fixation points in the imaginary study. To prevent elasticity in the joints, a force of 500 N was selected as the load cell maximum measurement capacity. The force was applied vertically, and the steel balls were used to secure vertical force and enable moment forces (Figure 5). The results of the force applied to the joints were then transferred to the computer using a data logger.

Eskişehir Osmangazi University Faculty of Medicine Ethics Committee approved (date: 08.2.2007, project number: PR-07-02-08-17).

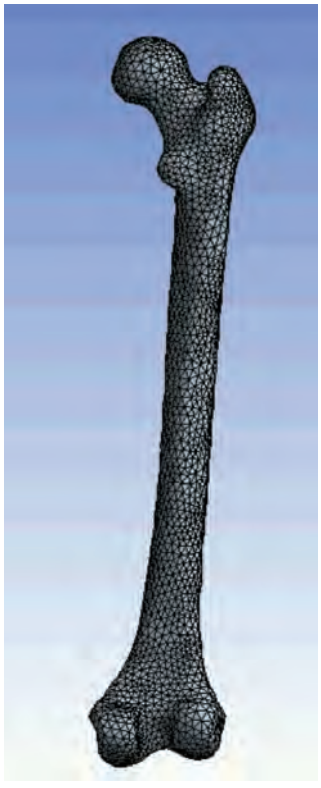

Figure 2. Mesh structure of model view

Statistical Analysis

The statistical analysis was performed using the SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The variables were investigated using Kolmogorov-Simirnov/Shapiro-Wilk's test to determine whether they are normally distributed. Mann-Whitney U test was used to compare the reaction forces

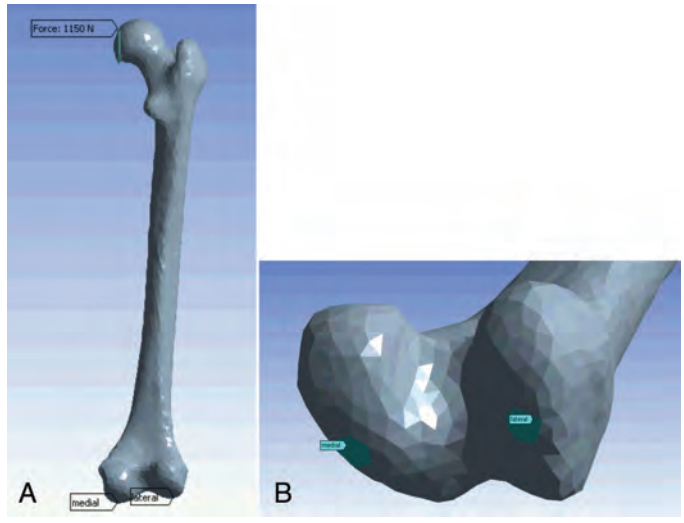

Figure 3. A) 1150 N load application point, B) medial and lateral fixation points

between IE and EE. While investigating the association of the reaction forces between lateral compartment of the distal femur (LCDF) and medial compartment of the distal femur (MCDF), the correlation coefficients and their significance were calculated using Spearman's test. P value <0.05 was considered statistically significant.

RESULTS

The highest force was recorded on LCDF, in which FNSA and FAV were 145° and -5°, respectively. The lowest force was recorded on LCDF, in which FNSA and FAV were 120° and 20°, respectively. The highest force was recorded on MCDF, in which FCSA and FAV were 120° and 20, respectively. The lowest force was recorded on MCDF, in which FCSA and FAV were 145° and -5°, respectively. Table 1 shows reaction force values in the MCDF and LCDF with all FCNA ranging from 120° to 145° and all FAV from -5° to 25° (Table 1).

A negative correlation was found between the lateral and medial parts of the distal femur after performing the correlation analysis of the reaction forces. That means when the load increases on one part of the knee, the load decreases on the other part and vice versa (Figure 6). A negative correlation was found between LCDF and FAV (r=-0.876; p=0.01), whereas a positive correlation was found between MCDF and FAV (r=896; p=0.006).

The standard femoral model (SFM), where FCSA was 135° and FAV was 10°, was chosen due to the close resemblance of its anatomic features to the human femur. On SFM, the MCDF load was 424.75 N, while the LCDF load was 725.25 N. When FAV was 5° and FNSA was 140°, the MCDF load was 638.94 N (a decrease of 12%) and the LCDF load was 511.06 N (an increase of 20%). Table 2 shows the force change between MCDF and LCDF at different angles as a percentage compared with SFM (Table 2).

FCNA is kept constant at 135°. Only the change in FAV leads to a maximum of 10% change in MCDF compared with the standard femur, while a maximum change of 18% in LCDF is observed.

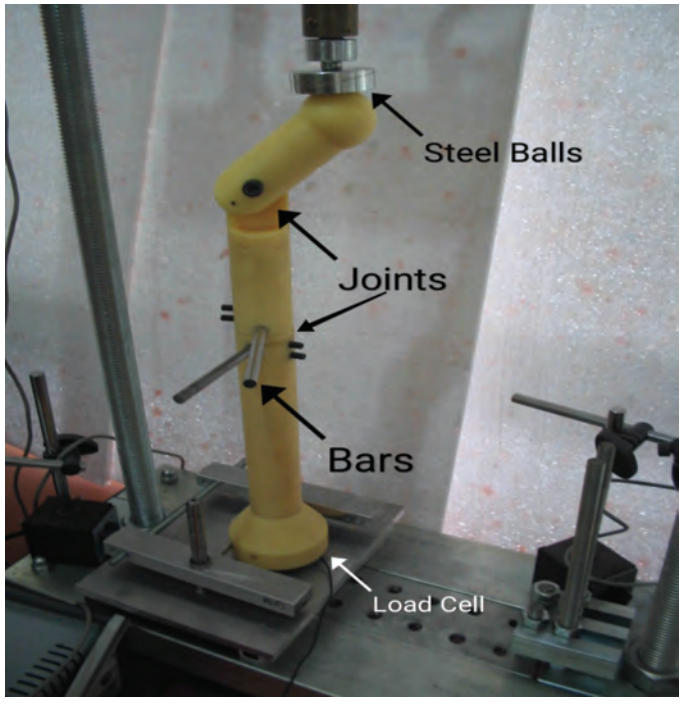

Figure 4. Polyamide femur model with bars and joints

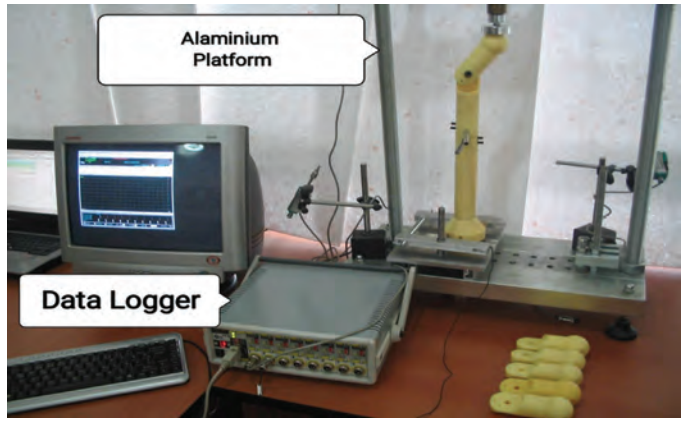

Figure 5. Aluminum platform and data logger

Table 1. Reaction force values of imaginary environment in the medial and lateral parts of the distal femur (N)

	120°		125°		130°		135°		140°		145°	
	Med	Lat	Med	Lat	Med	Lat	Med	Lat	Med	Lat	Med	Lat
-5°	767.84	382.16	756.89	393.11	706.25	443.75	649.14	500.86	586.13	563.87	524.53	625.47
0°	838.32	311.68	792.70	357.30	740.09	409.91	680.93	469.07	615.51	534.49	544.53	605.47
5°	868.12	281.88	821.19	328.81	767.12	382.88	706.38	443.62	638.94	511.06	566.11	583.89
10°	890.37	259.63	842.53	307.47	787.17	362.83	725.25	424.75	656.33	493.67	558.61	568.39
15°	904.69	245.31	855.91	294.09	800.04	349.96	736.91	413.09	667.36	482.64	592.46	557.54
20°	910.54	239.41	861.93	288.07	805.66	344.34	742.64	407.36	672.55	477.45	596.76	553.24
25°	908.51	241.49	860.09	289.91	803.72	346.28	741.28	408.72	670.55	479.45	594.66	555.34

Med: Medial, Lat: Lateral

In the 135° model of FCNA, the effects of MCDF and LCDF at different FAV are shown in the table (Figure 7).

FAV is kept constant at 10°. Only the change in FCNA leads to a maximum of 23% change in MCDF compared with the standard femur, while a maximum change of 39% in LCDF is observed. In the 10° model of FAV, the effects of MCDF and LCDF at different FCNA are shown in the table (Figure 8).

The values of biomechanical EE study are presented in Table 3. The reaction of forces gained from the real and virtual tests at 0°, 10°, and 15° anteversion angle, and 120°, 125°, 130°, 135°, 140°, and 145° shaft angle, were compared and contrasted using Mann-Whitney U test. There are no statistical differences found between the tests conducted in EE and the tests conducted in IE (p=0.12).

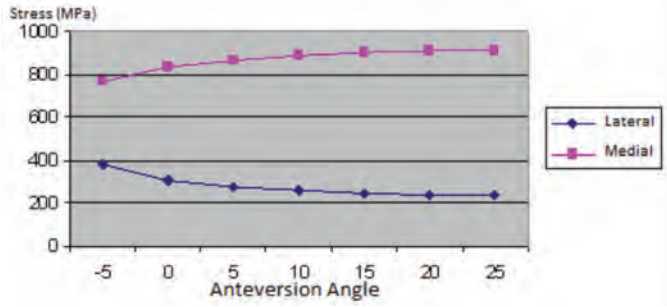

Figure 6. Negative correlation between the medial and lateral compartments

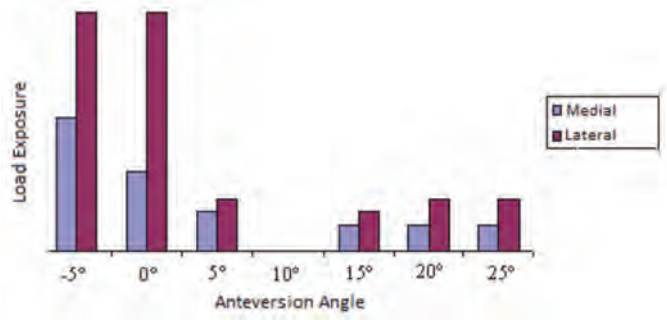

Figure 7. Medial and lateral effects when FNSA is fixed at 135° and FAV is variable
FNSA: Femoral neck shaft angles, FAV: Femoral anteversion

DISCUSSION

Many studies have supported that the tibiofemoral alignment is not only risk factor that affects compartment-specific knee OA. Malalignment of the lower leg, in either the varus or valgus direction, has influenced the distribution of load across the articular surfaces of the knee joint (20,21). In valgus alignment,

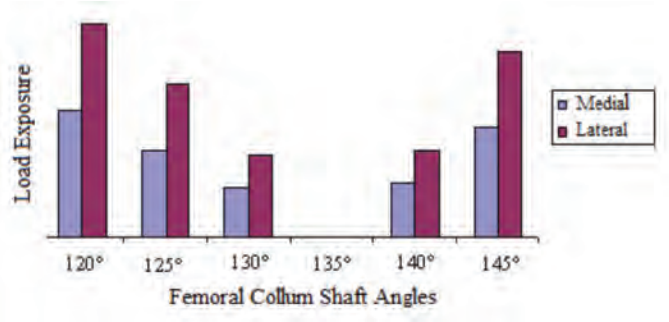

Figure 8. Medial and lateral effects when FAV is fixed at 10° and FNSA is variable
FAV: Femoral anteversion, FNSA: Femoral neck shaft angles

Table 2. Comparison of standard femur model with other models using percentage

	120°		125°		130°		135°		140°		145°	
	Med	Lat	Med	Lat	Med	Lat	Med	Lat	Med	Lat	Med	Lat
-5°	+%0.6	-%10	+%0.4	-%0.7	-%0.3	+%0.4	-%10	+%18	-%19	+%33	-%28	+%47
0°	+%16	-%27	+%0.9	-%16	+%0.2	-%0.3	-%0.6	+%10	-%15	+%26	-%25	+%43
5°	+%20	-%34	+%13	-%23	+%0.6	-%10	-%0.3	+%0.4	-%12	+%20	-%22	+%37
10°	+%23	-%39	+%16	-%28	+%0.9	-%15	SFM	SFM	-%10	+%16	-%20	+%34
15°	+%25	-%33	+%18	-%31	+%10	-%18	+%0.2	-%0.3	-%0.8	+%14	-%18	+%31
20°	+%26	-%44	+%19	-%32	+%11	-%19	+%0.2	-%0.4	-%0.7	+%12	-%18	+%30
25°	+%25	-%43	+%19	-%32	-%11	-%18	+%0.2	-%0.4	-%0.8	+%13	-%18	+%31

Med: Medial, Lat: Lateral, SFM: Standard femoral model

Table 3. Reaction force values of experimental environment (N)

	120° medial	125° medial	130° medial	135° medial	140° medial	145° medial
0°	363.7	327.5	323.3	277.0	255.8	221.1
10°	376.0	354.2	335.0	314.2	264.2	239.3
25°	379.7	360.0	352.1	320.5	288.0	250.1

the medial compartment continues to bear the load until excessive valgus occurs (22,23). Therefore, only valgus alignment affected the development and progression of OA in the knee (9). Alternatively, Felson et al. (24) found that valgus alignment increased the risk of knee OA and lateral cartilage damage.

There are studies supporting the association of hip and pelvic geometry with compartment-specific knee OA. Weidow et al. (17) evaluated the pelvic width, femoral offset, and femoral neck length in patients with lateral and medial knee OA. In the same study, they evaluated these features in a normal hip group and hip OA group separately. In the group without hip OA, lateral OA was associated with a wider pelvis and shorter femoral neck and femoral offset. They found a coexistence of hip OA with lateral knee OA and low incidence of hip changes in those with medial knee OA. Patients with lateral knee OA had increased FNSA. Their findings suggested that the occurrence of lateral and medial OA had a biomechanical background originating from the pelvis and hip anatomy (17). They also found an association between the presence of lateral knee OA and the biomechanics of the hip joint in gait analysis (18).

Boissonneault et al. (25) evaluated the association between tibiofemoral alignment, FNSA, femoral neck length, femoral offset, height of hip center, and abductor lever arm and compartment-specific knee OA. Lateral compartment OA was associated with increased abductor angle, increased FNSA (more valgus), and reduced femoral offset. Medial compartment OA was associated with reduced abductor angle and decreased FNSA (more varus) (25). In these studies, the anteversion was not evaluated.

In our study, we examined the relationship between FAV and FNSA regarding load transmission to the knee joint. Forty-two different femur models with six different FAV and seven different FNSA were investigated. The load on MCDF increased when FAV was decreased. The load on LCDF increased when FAV was increased. There is an increased load on MCDF when FNSA is decreased (more varus), and there is an increased pressure on LCDF when FNSA is increased (more valgus). FNSA was fixed at 135°, and FAV is reduced by -5°. The distribution of the load was down to 61% on the medial part of the knee and 39% on the lateral part. The equal distribution of the load on both parts of the knee is achieved at 140° and 145° including all the anteversion angles.

In SFM, 63% of forces transmitted to the medial part of the knee and 37% to lateral part. In the study, the forces transmitted disproportionally from the hip to the knee joint. FNSA is kept constant at 135°. Only the change in FAV leads to a maximum of 10% change in MCDF compared with the standard femur, while a maximum change of 18% in LCDF is observed. FAV is kept constant at 10°. Only the change in FNSA leads to a maximum of 23% change in MCDF compared with the standard femur, while a maximum change of 39% in LCDF is observed.

Table 2 is a different expression of the load change shown in Table 1 and provides a better understanding. When the increase or decrease in loads is considered to affect the lateral or medial side, the effect on the LCDF of the index is greater than MCDF. On examining the table carefully, LCDF numeric values are higher than those of MCDF.

Study Limitations

Our study has some limitations. First, when addressing FE models of bones, two key components, the geometry and material parameters, are essential. Both can be estimated from CT data but require a lot of approximation. Second, FE model did not consider the known local anisotropic behavior of the bone tissue. Third, even though inhomogeneus Young's modulus was represented different E (p) relations in the cortical and trabecular subregions by Yosibash et al. (26), in our study the bone tissue was accepted as a homegeneous, izotrophic and lineer material. It should be noted that there were no statistical differences found between the test conducted in the EE and the test conducted in IE (p=12). This statistical analysis showed that the EE study validated IE. Accurate methods for predicting and monitoring *in vivo* bone strength are of major importance in clinical applications. FEA is becoming a commonly used tool for the numerical analysis of the biomechanical response of human bones. Fourth, in this study, we need to mimic the joint contact force that is applied on the head of the femur during the complete gait cycle for the activities. The orientation and application of hip contact force are important because the dominant effect in the normal walking is hip contact force. A force of 2,460 N was expected to apply to the femoral head with an angle of 23° at the frontal plane, 6° at the sagittal plane, and a force of 1,700 N was expected with an angle of 24° at the frontal plane and 15° at the sagittal plane, related to the pull of abductor muscles at the trochanter major in the stance phase of the walking cycle. However, during the solid model experiments, the force applied to the femoral head caused the rotation of the model in the frame of measurement, and the optimum conditions cannot be obtained. We followed Peña et al. (27) and Sathasivam and Walker (19) studies, and a force of 1150 N was applied vertically to the femoral head to comply with the forces at the upper end of the femur.

Wright et al. (28) found a correlation between the proximal and distal femoral geometry. The medial trochlear inclination angle correlated with FNSA and mediolateral (ML) femoral offset. The absence of ML femoral offset and the distal femur morphology are the shortcomings of our study (28).

Changing FNSA, which is essential in hip biomechanics, affects the medial and lateral distributions of the force applied to the knee joint. In the alterations of FNSA and FAV, not only does the distribution of force on hip join change, but also the knee joint is affected. Coskun Benlidayi et al. (29) found that people with FNSA above 134.4° have an eightfold increased risk of developing severe knee OA.

Brouwer et al. (9) and Sharma et al. (21) found that valgus alignment affects the development and progression of knee OA. However, Felson et al. (24) found that valgus alignment increased the risk of knee OA. Neglecting hip and pelvic biomechanics while studying the effects of tibiofemoral alignment on compartment-specific knee OA may be the cause of this conflict.

CONCLUSION

This biomechanical study filled the gap in the literature by evaluating the load distribution on the distal femur by the hip anteversion effect. In the study, we found that the changed biomechanics of the hip had a significant effect on the knee joint, and LCDF was affected more than MCDF. Determining the forces that affect the knee during different FNSA and FAV help understand the difference between the lateral and medial knee OA. It is difficult to say that only the geometry of hip and pelvis is responsible for developing lateral knee OA. The geometry of hip and pelvis and valgus alignment may contribute to the development of lateral OA. Further dynamic studies, which evaluate hip and knee biomechanics together, are needed to better explain the occurrence of lateral OA.

Ethics

Ethics Committee Approval: Eskişehir Osmangazi University Faculty of Medicine Ethics Committee approved (date: 08.2.2007, project number: PR-07-02-08-17).

Informed Consent: Human studies were not conducted in this study therefore patient consent was not required.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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Is There a Relationship Between the Types of Nasal Septal Deviation and Morphologic Changes of Oropharyngeal Structures?

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Abstract

Objective: To evaluate the relationship between types of nasal septal deviation and other oropharyngeal structures that affected the upper airway respiratory tract.

Methods: A total of 120 participants were included in the study: 100 patients with nasal septal deviation and 20 healthy people who had no nasal septal deviation (control group). The oropharyngeal examination findings, modified Mallampati index, retroglossal space, tonsil size, and pharyngeal space were recorded for each patient. The types of nasal septal deviation were compared in terms of the aforementioned parameters.

Results: The types of nasal septal deviation were compared in terms of the Mallampati score, retroglossal space, tonsil grade, and pharyngeal space. Significant differences were present between the Mallampati scores and retroglossal space values and types of nasal septal deviation (p=0.001, p=0.001). Types of nasal septal deviation were divided into five groups as follows: Group 1, septal tilt; group 2, C-shaped anteroposterior deviation; group 3, C-shaped cephalocaudal deformity; group 4, S-shaped anteroposterior deformity; group 5, S-shaped cephalocaudal deformity. Group 6 was the control group. Groups 1, 2, and 4 had higher Mallampati scores than group 6. Group 3 and 5 did not differ compared to group 6. Groups 1, 2, 3, 4, and 5 had higher retroglossal space values than group 6. There was no difference between the other groups 1, 2, 3, 4 and 5. Tonsil grade and pharyngeal space values did not differ significantly between all groups (p>0.05).

Conclusion: Airway passage changes depend on various factors from childhood to adulthood. The change in airway resistance due to nasal septum deviation affects the airflow and oropharyngeal anatomical structures. In our study, it was observed that nasal septum deviation affected the Mallampati scores and retroglossal space values.

Keywords: Nasal septal deviation, Mallampati, tonsil grade

INTRODUCTION

The effects of respiratory function on craniofacial development have been studied for a long time. Various structural disorders of the upper airway induce mouth breathing and gradually lead to different maxillofacial and oropharyngeal morphologic changes (1). The shape and dimensions of the upper airway are involved in the pathogenesis of obstructive sleep apnea. Although the weight and neck thickness are critical in airway collapse, there is a multifactorial etiology involving the nose, palate, tonsils, and pharyngeal morphology (2,3).

One of the most common causes of mouth breathing, upper airway obstruction, and related sleep apnea is the nasal septal deviation. The most common reason for admission to otolaryngology outpatient clinics due to nasal obstruction is nasal septal deviation. It ranks first among nasal surgeries performed due to nasal congestion. This nasal resistance

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in respiratory pathologies plays an important role in the development of oropharyngeal and maxillofacial structures, especially in childhood. Although there is no known cause of nasal septal deviation, congenital deformities, prenatal, natal or postnatal traumas, and external traumas are the most common causes of nasal septal deviation. However, breathing through the mouth, applying pressure to the palate with the tongue, and finger sucking are also among the common causes of septal deviation (4).

So, it is possible to talk about a vicious circle in which structural deformities of different structures of the upper airway could lead to gradual deformation of the other pharyngeal structures. Both Nakata et al. (5) and Park et al. (6) reported in their studies that correction of nasal septal deviation had a functional influence on the improvement of obstructive sleep apnea.

In this study, we evaluated the relationship between types of nasal septal deviation and other oropharyngeal structures that had a positive effect on the upper airway respiratory tract.

METHODS

This prospective study enrolled 120 patients diagnosed with nasal septal deviation. A total of 100 patients with nasal septal deviation and 20 patients without nasal septal deviation (control group) were included in the study. The study was conducted between October 2018 and March 2019. The Okmeydanı Training and Research Hospital Ethical Committee Institutional Review Board approval were obtained (no: 48670771-514.10). Written informed consent was obtained from patients who participated in this study. Patients who attended an outpatient clinic with nasal congestion, snoring problems, and sleep apnea were included. Exclusion criteria included previous nasal and oropharyngeal surgeries, nasal polyposis, inferior turbinate hypertrophy, concha bullosa, allergic rhinitis, major nasal trauma in childhood, and chronic systemic diseases.

All patients underwent a complete history and otolaryngological examination, including nasopharyngoscopy and laryngoscopy. Computed tomography of the paranasal sinus was used to evaluate the type of septal deviation. The classification of nasal septal deviation was modified from that of Guyuron et al. (7). Deviations due to nasal septal spurs present in Guyuron classification were excluded in this study because they minimally affect the nasal airway resistance. Septal deviations were divided into five groups. Group 1 included septal tilts. The septal tilt was defined as a septum that had no curve; it was tilted to one side of the nose in relation to the sagittal plane as the maxillary crest remained straight. Group two included C-shaped anteroposterior deviation, where the septum had a curvature rather than being tilted. The maxillary crest and nasal spine have deviated. Group three included C-shaped cephalocaudal deformity. Group four included S-shape anteroposterior deformity. Group five included S-shape cephalocaudal deformity. In the S category, the septum had two curvatures next to each other in opposing directions. The oropharyngeal examination findings, modified Mallampati index, retroglossal space, tonsil size, and pharyngeal space were recorded for each patient. Oropharyngeal morphology was evaluated using modified Mallampati index. The modified Mallampati index was evaluated based on the visualization of the oropharynx (8). The patient was asked to open the mouth widely with the tongue left in place and oropharyngeal crowding was graded as follows: Grade 1: Tonsils, pillars, and soft palate were clearly visible; grade 2: The uvula, pillars, and upper pole were visible; grade 3: Only part of the soft palate was visible; grade 4: The tonsils, pillars, and base of the uvula could not be seen, and only the hard palate was visible. The tonsillar grade was assessed using a four-point ordinal scale (8,9). Grade 1 tonsils were in the tonsillar fossa, barely seen behind the anterior pillars. Grade 2 tonsils were visible behind the anterior pillars. Grade 3 tonsils extended three-quarters of the way to the midline. Grade 4 tonsils were completely obstructing the airway, also known as “kissing” tonsils. The retropharyngeal space evaluation was performed using the retroglossal grading system (9,10). We evaluated the retroglossal space using nasopharyngeal endoscopy. In grade 1, the retroglossal space is widely patent, allowing visualization of the larynx (normal). In grade 2, the retroglossal space allows visualization of the vocal folds, and the opposing walls are not in proximity (small). In grade 3, the retroglossal space allows only visualization of the posterior arytenoids (very small). In grade 4, the retroglossal space is in contact with the opposing walls (obstructed). The pharyngeal space (pharyngeal grade) was assessed using a four-point ordinal scale (9,11). The pharyngeal grading system is as follows. In class 1, the palatopharyngeal arch intersects at the edge of the tongue. In class 2, the palatopharyngeal arch intersects at 25% or more of the tongue diameter. In class 3, the palatopharyngeal arch intersects at 50% or more of the tongue diameter. In class 4, the palatopharyngeal arch intersects at 75% or more of the tongue diameter. Then, the relationship between types of nasal septal deviation and the morphology of the aforementioned oropharyngeal structures was evaluated.

Statistical Analysis

The sample size was calculated using the power and sample size analysis program. A sample size of 20 patients per group provided approximately 80% power to detect alpha: 0.05 level between the groups.

Statistical analyses of the data were conducted using IBM SPSS Statistics 22 (IBM SPSS, İstanbul, Turkey). The data were analyzed using descriptive statistical methods (mean and standard deviation). Shapiro-Wilk test was used to assess the normal distribution of the parameters. Kruskal-Wallis test was used for comparing two or more independent samples of equal or different sample sizes. Mann-Whitney U test was used for the post-hoc comparison test. Bonferroni correction was calculated for Mann-Whitney U test. The results were evaluated using the 95% confidence intervals, and the level of significance was set at $p<0.05$.

RESULTS

The study group included 120 consecutive patients. Seventy-two of them (60.0%) were males and 48 (40.0%) were females. The mean age was 34.19±13.22 years (range: 17-70 years). There was no significant difference between the septal deviation groups with respect to gender and age (p=0.367; p=0.191) (Table 1).

Table 1. The distribution of the patients according to age and gender

		Minimum-maximum	Mean ± SD
Age (years)		17-70	34.19±13.22
Age (years)	Females	17-68	34.04±13.28
	Males	17-70	34.29±13.27
		N	%
Gender	Females	48	40.0
	Males	72	60.0

SD: Standard deviation

The types of nasal septal deviation were compared in terms of the Mallampati score, retroglossal space, tonsil grade, and pharyngeal space. There were significant differences between Mallampati scores and retroglossal space values and types of nasal septal deviation (p=0.001; p=0.001) (Table 2). When the Mallampati scores were compared within the groups, groups 1, 2, and 4 had significantly higher scores than group 6. There was no difference between groups 3, 5, and 6 (Table 3). When retroglossal space values were compared between groups, groups 1, 2, 3, 4, and 5 had significantly higher values than the control group (group 6). There was no difference between the other groups 1, 2, 3, 4 and 5 (Table 3).

Tonsil grade and pharyngeal space values did not differ significantly between all groups (p=0.055; p=0.396) (Table 2).

DISCUSSION

Tongue base hypertrophy, tonsillar hypertrophy, hypertrophy in the lateral pharyngeal bands, and narrowing in retroglossal space occur in different degrees with aging. In childhood, oropharyngeal findings are generally normal, unlike the findings of sleep apnea syndrome in adults. As people get older, the soft tissues of the nose and pharynx change. Many environmental and genetic factors trigger this change, which are not fully addressed. Most of the studies focused on oropharyngeal and nasal pathologies in sleep apnea syndrome. Nasal septal deviation may have an indirect role in the growth of the maxilla that can affect the development of obstructive sleep apnea, together with other pharyngeal structures, such as the position of the palate, tonsils, fauces, and retropharyngeal space (8,9,12).

Table 2. Comparison between the types of nasal septal deviation in terms of the Mallampati score, retroglossal space, tonsil grade, and pharyngeal space

Septal deviation types	Group 1 (septal tilt) (n=20)	Group 2 (C-shaped anteroposterior deviation) (n=20)	Group 3 (C-shaped cephalocaudal deformity) (n=20)	Group 4 (S-shaped anteroposterior deformity) (n=20)	Group 5 (S-shaped cephalocaudal deformity) (n=20)	Group 6 (control) (n=20)		*p
	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	**(IQR: 25%-75%)	
Mallampati score	2.35±0.88 (2.00)	2.00±0.73 (2.00)	1.70±0.66 (2.00)	2.15±0.75 (2.00)	2.00±0.86 (2.00)	1.35±0.59 (1.00)	1.00-2.00	**0.001**
Retroglossal space	2.25±0.79 (2.00)	2.05±0.83 (2.00)	1.85±0.67 (2.00)	2.30±0.73 (2.00)	2.05±0.76 (2.00)	1.15±0.37 (1.00)	1.00-3.00	**0.001**
Tonsil grade	1.75±0.72 (2.00)	1.75±0.55 (2.00)	1.65±0.67 (2.00)	2.00±0.92 (2.00)	2.00±0.73 (2.00)	1.35±0.49 (1.00)	1.00-2.00	0.055
Pharyngeal space	2.05±0.99 (2.00)	1.85±0.75 (2.00)	1.70±0.66 (2.00)	2.00±0.92 (2.00)	2.05±0.95 (2.00)	1.55±0.69 (1.00)	1.00-2.00	0.396

*Kruskal-Wallis, **IQR: Interquartile range, p<0.05, SD: Standard deviation

Some studies have indicated that the nasal septal deviations affected total nasal resistance and airflow parameters in the nasal cavity (13). For this reason, the type of septum deviation may affect the development of oropharyngeal and nasal pathologies. Moreover, Park et al. (6) stated that correcting nasal pathologies and relieving nasal patency had an important role in the improvement of obstructive sleep apnea. However, Morinaga et al. (9) demonstrated that both palatal and pharyngeal morphologies were important factors for successful nasal surgery.

This shows the importance of getting a comprehensive evaluation and understanding of the relationship between different nasal septal deviations and pharyngeal morphology of the patients. In our study, we categorized patients according to the type of nasal septal deviation to compare between the types of nasal deviation in terms of the Mallampati score, tonsillar size, narrowness of the fauces, and retropharyngeal space.

Previous studies showed that the nasal airflow and amount of pharyngeal soft tissue were associated with each other (9,14). Our results revealed that retroglossal space differed in all types of septum deviations compared with the control group. However, the modified Mallampati index did not differ in S- and C-shaped cephalocaudal deviations. Tonsil grade and pharyngeal space did not differ between the groups (Table 2, 3). Anterior and posterior nasal septal deviations affect the nasal airflow through the nasal base more than the cephalocaudal deviations. Therefore, there was no significant change in modified Mallampati index scores in cephalocaudal septum deviation groups compared with the control group.

Table 3. Comparison of Mallampati score and retroglossal space within groups

	Mallampati score	Retroglossal space
	*p	*p
Groups 1 and 2	0.216	0.507
Groups 1 and 3	0.016	0.103
Groups 1 and 4	0.533	0.714
Groups 1 and 5	0.200	0.474
Groups 1 and 6	**0.001**	**0.001**
Groups 2 and 3	0.183	0.416
Groups 2 and 4	0.510	0.332
Groups 2 and 5	0.884	0.989
Groups 2 and 6	**0.004**	**0.001**
Groups 3 and 4	0.054	0.058
Groups 3 and 5	0.277	0.385
Groups 3 and 6	0.046	**0.001**
Groups 4 and 5	0.460	0.288
Groups 4 and 6	**0.001**	**0.001**
Groups 5 and 6	0.009	**0.001**

*Mann-Whitney U test (p value is calculated after Bonferroni correction p<0.0083)

Akbay et al. (15) stated that the septal deviation influenced the depth and curve of the palatal bone. Thus, posterior septal deviation and affected maxillo-palatal arch result in nasal obstruction. Friedman et al. (8) reported that both the retroglossal space and Mallampati score played an important role in the upper airway obstruction. In our study, it was observed that the Mallampati score was high, and the retroglossal space was narrower in those with septum deviation. Moreover, similar to the results of our study, Liistro et al. (2) found that the Mallampati and nasal obstruction scores were significant in patients with the risk of obstructive sleep apnea.

The etiology of tonsillar hypertrophy is not exactly known. However, diet, genetics, and humoral change may play a role (16). The recurrent and chronic inflammation of palatine tonsils sometimes result in hypertrophy (17) and, therefore, are not expected to be associated with types of septal deviation. In our study, we also did not observe a significant difference when we compared between types of septal deviation in terms of tonsil size.

Lateral pharyngeal band hypertrophy narrowed the pharyngeal space, which is the distance between two palatopharyngeal arches. The narrowing of this region increases with weight gain and causes obstructive sleep apnea syndrome. We did not see any difference between types of septal deviation in terms of the pharyngeal space. This showed that the septal deviation has no effect on the narrowing of the pharyngeal space.

CONCLUSION

The airway passage changes depend on various factors from childhood to adulthood. The change in airway resistance due to nasal septum deviation affects the airflow and oropharyngeal anatomical structures. Long-term prospective cohort studies involving the pediatric population are needed to understand this effect. In our study, it was observed that nasal septum deviation affected the Mallampati scores and retroglossal space.

Ethics

Ethics Committee Approval: The Okmeydanı Training and Research Hospital Ethical Committee Institutional Review Board approval were obtained (no: 48670771-514.10).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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10-year Analysis of Assisted Reproductive Technique Outcomes at a University Hospital

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Abstract

Objective: Our aim is to investigate the 10-year results of assisted reproductive technique (ART) cycles in our in vitro fertilization (IVF) clinic and to evaluate the effects of treatment protocols on ART outcomes.

Methods: Medical records of 2.795 IVF cycles of 1.964 infertile couples who were admitted to our IVF unit between 1998 and 2007 were evaluated retrospectively. A short or long protocol was performed with a gonadotropin-releasing hormone (GnRH)-analog and a GnRH-antagonist. Factors that may affect ART success or failure were evaluated and interpreted.

Results: The pregnancy rates per IVF cycle and per transfer were 21.07% and 24.4%, respectively. The highest pregnancy rate was attained when the cause of infertility was unexplained ($p<0.001$). Treatment with the long protocol resulted in a higher pregnancy rate than treatment with either the short or the long the antagonist protocol ($p<0.001$). The pregnancy rate was higher when the third-day step-down protocol was applied, compared with any of the fifth-day step-down, continuous-dose, and step-up protocols. The number of cycles, duration of infertility, age, follicle stimulating hormone level on the 3rd day of menstruation, E2 level measured on the day of human chorionic gonadotropin, total gonadotropin dose, total number of oocytes collected, and number of total embryos transferred affected the success rate of ART per cycle.

Conclusion: Unexplained infertility, use of the long protocol, application of the third-day step-down protocol, and application of intracytoplasmic sperm injection and luteal support are associated with higher pregnancy rates. The number of oocytes collected, number of embryos transferred, and the quality of the transferred embryos are important factors affecting pregnancy rates.

Keywords: Assisted reproductive technology, pregnancy, infertility

INTRODUCTION

Infertility is defined as failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility affects 10%-15% of couples in the reproductive age group (1). According to the findings of the Infertility Diagnosis and Treatment Group of the World Health Organization, the cause of infertility was attributed to the female in 37% of cases, the male in 8%, and the couple in 35%, while in 5% of cases, a cause was not found (unexplained infertility). Over the course of the study, 15% of the couples conceived (2). Female infertility may be caused by tuboperitoneal factors (25%-30%), ovulatory dysfunction (15%-20%), or cervical and uterine factors (5%-10%) (2).

A variety of treatment modalities are offered to infertile couples. In vitro fertilization (IVF) and embryo transfer (ET) is one such technique. It is generally applied after other treatment methods, but in some cases, it may be the first option. In 1978, Steptoe and Edwards obtained a single preovulatory human oocyte by a natural cycle, conducted IVF and transferred the resulting embryo to the uterus in the blastocyst stage, resulting in a term delivery

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(3). Over the years, significant improvements have been made to the techniques of ovulatory stimulation, oocyte collection, oocyte and embryo culture, embryos cryopreservation, and ET (4). IVF is a controlled ovarian stimulation performed by external gonadotropin administration, oocyte collection under transvaginal ultrasonography (USG), fertilization in the laboratory, and transcervical transfer of embryos to the uterus.

The aim of this study was to investigate the results of assisted reproductive technique (ART) cycles in our IVF unit and to investigate the factors confounding ART outcomes.

METHODS

In this study, 2.795 ART cycles performed in 1964 infertile couples were evaluated retrospectively in a 10-year period between January 1998 and December 2007. Indications for initiation of treatment of patients were classified as tubal factors, male factors, unexplained infertility, and ovarian failure. The study was conducted according to the Helsinki Declaration.

Patient histories were taken. Gynecological examinations were performed. Following gynecological examination, transvaginal USG was performed. Sperm analysis was performed prior to ART. In order to determine the ovarian reserve, venous blood was sampled on the third day of menstruation (early follicular phase); follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels were measured using enzyme immunoassay kits. Hysterosalphingography was routinely performed prior to treatment.

A short or long protocol was performed with a gonadotropin-releasing hormone (GnRH)-analog and a GnRH-antagonist.

1. Long protocol: Administration of a GnRH-analog was started on the 21st day of the menstrual cycle, and gonadotropin was added on the second to third day of the next cycle and continued until the day of human chorionic gonadotropin (HCG) administration.

2. Short protocol: Administration of a GnRH-analog was started on the first day of the menstrual cycle, and gonadotropin was added on the second to third day of the cycle and was continued until the day of HCG administration.

On the third day of ovulation induction, age and body mass index was taken into consideration, and 225-300 IU gonadotropin was started. Follicular development was followed by daily E2 evaluations and by transvaginal USG. It was decided that the dose of E2 in the late follicular phase should be increased by 50% compared with the previous day, and follicles increased by 1-3 mm/day. When at least 2 follicles passed 16 millimeters, and the E2 per follicle exceeded 150 pg/dL, for the LH peak 5,000 or 10,000 IU HCG was administered. Follicle aspiration was performed 36 hours after HCG administration. The follicles were collected with the help of transvaginal USG. Each follicle of 11 millimeters and above was aspirated.

Follicle aspiration was performed with transvaginal ultrasound. The vaginal mucosa was cleaned with warm saline prior to the procedure. Follicular aspiration was performed under intravenous analgesia. Follicle aspiration was performed by entering the vaginal side walls and fornices with a single-lumen aspiration needle, which could be attached to the vaginal ultrasound by an adapter. After this examination, the sperm were made ready for insemination or intracytoplasmic sperm injection (ICSI) by swim-up or rotating according to their density.

As luteal-phase support, oral, vaginal, or muscular progesterone supplementation or muscular HCG was administered up to 12 weeks of gestation.

Pregnancy was determined by serum β-HCG measurements at 12 days after ET. In patients with β-HCG levels above 10 mIU/mL, measurements were monitored at 7-14-day intervals. Clinical pregnancy was defined as the presence of at least one gestational sac with fetal cardiac activity, detected by transvaginal USG.

Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, (number: 4467, date: 05.02.2008).

Statistical Analysis

SPSS Statistics, Version 17 (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis. In the biostatistical analysis of the study, variables were defined by the mean, standard deviation, frequency, and percentages, and the chi-square and Fisher exact tests were used to compare frequencies and percentages. The Mann-Whitney U test was used for non-parametric variables. In order to compare the mean of the variables with the normal distribution, a t-test was used in the two groups. Multivariate stepwise logistic regression analysis was used for regression analysis. $P<0.05$ was considered as statistically significant.

RESULTS

A total of 1964 cases were evaluated. The total number of cycles was 2,795. A total of 2,405 ETs were performed. The total number of pregnancies was 589. The pregnancy rate per cycle was 21.07%. The rate of pregnancy per ET was 24.4%.

Cases of patients admitted to our inpatient clinic due to infertility were examined according to their etiological factors: 1,982 (70.9%) had a male factor, 487 (17.4%) had a tuboperitoneal factor, 282 (10.1%) had unexplained infertility, and 44 (1%) had

ovarian failure. In these groups, the rates of pregnancy per cycle were 22.5% in the male factor group (41.9% in ET), 18.6% in the tuboperitoneal factor group (21.5% in ET), 31.5% in the unexplained infertility group (35% in ET), and 10.7% (13.6% pregnancy rate per ET) in the ovarian failure group. In the group with unexplained infertility, the pregnancy rate per cycle was significantly higher than that in the other groups ($p<0.001$).

In 2.795 cycles, the GnRH-analog long protocol was used in 1.713 cycles, the GnRH-analog short protocol in 954 cycles and the GnRH-antagonist protocol in 128 cycles. The pregnancy rates per cycle in these groups were 24.3%, 16.0%, and 14.8%, respectively. In the GnRH-analog long protocol group, the pregnancy rate was found to be significantly higher than that in the other groups ($p<0.001$).

In 1.105 cycles, a step-down gonadotropin protocol was applied with dose reduction on the third day. A total of 281 (25.4%) pregnancies were obtained in this group. In 152 cycles, a stepwise decreasing gonadotropin protocol was applied, and dose reduction was applied on the fifth day. A total of 29 (19.1%) pregnancies were obtained in this group. In 1,390 cycles, a fixed-dose gonadotropin protocol was applied, and 258 (18.6%) pregnancies were obtained in this group. The step-up gonadotropin protocol was applied in 148 cycles. A total of 21 (14.2%) pregnancies were obtained in this group. The pregnancy rates per cycle in the third-day decreasing group were found to be significantly higher than those in the other group treatment protocols ($p<0.001$).

Out of 2.795 cycles, 1.051 (37.7%) cycles were treated with human menopausal gonadotropin (HMG), 1.566 (56%) with pure FSH, 113 (4%) with urinary FSH, and 65 (2.3%) with different drugs. The pregnancy rates per cycle in these groups were 21%, 21%, 23.8%, and 18.4%, respectively. There were no statistically significant differences in pregnancy rates according to these ratios ($p>0.05$).

A GnRH-analog was used in 2,656 (95.4%) cycles and GnRH-antagonists in 129 (4.6%) cycles. The pregnancy rate per cycle was 21.4% and 14.7%, respectively. Pregnancy rates among the GnRH-analog and GnRH-antagonist groups were significantly higher in the Leuprolid asetat group ($p=0.002$). In addition, when only GnRH-analog agents were compared, pregnancy rates were significantly higher in the Leuprolid asetat group ($p=0.002$).

Oral progesterone, intramuscular (IM) progesterone, HCG, and vaginal progesterone were used as luteal-phase support. Pregnancy rates per cycle were 24.1% in the group using oral progesterone, 26.7% in the IM progesterone group, 24.9% in the vaginal progesterone group, 24.2% in the HCG group, and 24.1% in the HCG and progesterone group. There were no statistically significant differences between the groups ($p>0.05$).

No difference was found in LH, PRL, E2, and thyroid stimulating hormone levels between the clinically positive and negative patients. Infertility duration, age, and the FSH level on the third day of menstruation were higher in the group that did not achieve clinical pregnancy (Table 1).

The total number of ART cycles, serum E2 level on the day of HCG administration, total gonadotropin dose, total number of oocytes collected, number of oocytes used for ICSI, number of oocytes used for IVF, total number of oocytes fertilized for ICSI, total number of oocytes fertilized for IVF, number of total embryos transferred, number of grade 1 embryos transferred, number of grade 2 embryos transferred, number of metaphase 2 oocytes, and number of prophase 1 oocytes (germinal vesicle) were significantly higher in the group that achieved clinical pregnancy (Table 2).

In logistic regression analysis, the number of transferred embryos [$p=0.06$, odds ratio (OR): 1.38] was found to be poorly correlated with pregnancy success, although not statistically significant; the relation between the use of the ICSI method ($p=0.03$, OR: 1.13) and pregnancy success was found to be the most statistically significant, among all the variables tested (Table 3).

DISCUSSION

The rate of pregnancy per ART cycle in our clinic was 21.1%. The rate of pregnancy per ET was 24.4%. These rates are close to those reported by the European Society of Human Reproduction and

Table 1. Demographic and clinical features of the patients

	Clinical pregnancy negative (n=1.375)	Clinical pregnancy positive (n=589)	p value
Age	33.43±4.82	31.84±3.98	**<0.001**
Infertility duration (years)	8.91±3.23	7.80±2.84	**<0.001**
BMI (kg/m^2)	25.70±4.87	24.17±4.66	**<0.001**
FSH (mIU/mL)	7.98±3.43	6.75±3.23	**<0.001**
LH (mIU/mL)	5.57±2.66	5.62±2.76	0.794
Estradiol (pg/mL)	54.87±12.54	49.66±12.98	0.227
Prolactin (ng/mL)	20.96±7.44	20.94±6.98	0.994
TSH (µIU/mL)	2.14±1.12	2.13±1.32	0.930
Total number of cycles	1 (1-2)	1 (1-2)	**0.028**

BMI: Body mass index, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone

Embryology (ESHRE) for ET in 2005 (28.8%) (5). The society for ART (SART) reported in 2001 that the pregnancy rate per ET was 40% (6). The success rate of our clinic is consistent with the pregnancy rate reported by ESHRE, but lower than that reported by the SART.

Table 2. Comparison of clinical pregnancy-positive and -negative groups

	Clinical pregnancy negative (n=2.206)	Clinical pregnancy positive (n=589)	p value
Induction duration (days)	8.64±2.32	8.76±1.54	0.154
LH level at HCG day (mIU/mL)	3.46±1.55	3.84±1.67	0.550
Estradiol level at HCG day (pg/mL)	1853.37±846.44	2230.20±987.22	**<0.001**
Progesterone level at HCG day (ng/mL)	1.22±0.66	0.94±0.55	0.563
Endometrial thickness at HCG day (mm)	10.42±2.67	10.52±2.33	0.794
Total number of oocytes	8 (5-11)	11 (7-15)	**<0.001**
Number of fertilized oocytes	3 (4-6)	5 (3-7)	**<0.001**
Number of transferred blastocytes	0 (0-1)	0 (0-1)	0.811
Number of metaphase 1 oocytes	0 (0-1)	0 (0-1)	0.862
Number of metaphase 2 oocytes	2 (1-3)	2 (1-4)	**<0.001**
Number of prophase 1 (germinal vesicle) oocytes	0 (0-1)	0 (0-1)	0.065
Total number of transferred embryos	2 (1-4)	4 (2-6)	**<0.001**
Number of transferred grade 1 embryos	1 (0-2)	2 (1-3)	**<0.001**
Number of transferred grade 2 embryos	1 (0-2)	2 (1-3)	**<0.001**
Number of transferred grade 3 embryos	0 (0-1)	0 (0-1)	0.294
Number of transferred grade 4 embryos	0 (0-1)	0 (0-1)	0.332
Number of postmature oocyte	3 (1-5)	5 (3-8)	**<0.001**

LH: Luteinizing hormone, HCG: Human chorionic gonadotropin

A variety of reasons may account for this difference. These include differences in ovulation induction protocols, variability between patient groups, and different ET techniques of physicians working in our IVF unit. Pregnancy rates per cycle are different between patient groups and between different treatment protocols. Male factor infertility was the major etiological reason for patient admission to our IVF unit. This was followed by tuboperitoneal factors and unexplained infertility. When the pregnancy rates per cycle according to etiological factors were evaluated, we found that the highest success rate was with unexplained infertility [31.5% (pregnancy rate per ET 35%)] group. This was followed by male factor [22.5% (pregnancy rate 41%)] and tuboperitoneal factor [18.6% (21.5% per ET)]. Qublan et al. (7) reported 891 ART cycles with the following etiologies: Male factor (17.8%), endometriosis (17.6%), tubal factor (31.6%), and unexplained infertility (41.1%). They found that patients with unexplained infertility had higher pregnancy rates.

There are many reports suggesting that there is no difference in randomized studies comparing ART protocols. Similar

Table 3. Multivariate stepwise logistic regression analysis

	OR	p
Number of transferred embryos	1.38 (0.98-1.94)	0.062
ICSI method	1.13 (1.01-1.26)	**0.031**
Number of fertilized oocytes	2.26 (1.04-4.87)	**0.045**
Age	1.34 (0.98-1.85)	0.061
Infertility duration	0.94 (0.79-1.12)	0.559
Induction duration	2.10 (0.96-4.56)	0.067
LH level at HCG day	0.79 (0.58-1.08)	0.143
Estradiol level at HCG day	1.02 (0.74-1.40)	0.904
Endometrial thickness at HCG day	1.35 (0.67-2.72)	0.392
Number of transferred blastocytes	0.39 (0.02-2.20)	0.287
Number of metaphase 1 oocytes	0.97 (0.93-1.01)	0.255
Number of metaphase 2 oocytes	0.77 (0.44-1.34)	0.398
Number of prophase 1 (germinal vesicle) oocytes	0.80 (0.28-2.30)	0.686
Total number of transferred embryos	1.43 (0.92-2.23)	0.105
Number of transferred grade 1 embryos	1.31 (0.90-1.90)	0.147
Number of transferred grade 2 embryos	1.33 (0.94-1.89)	0.109
Number of transferred grade 3 embryos	0.76 (0.33-1.75)	0.534
Number of transferred grade 4 embryos	0.26 (0.04-1.62)	0.152
Number of postmature oocyte	0.80 (0.35-1.83)	0.605

ICSI: Intracytoplasmic sperm injection, LH: Luteinizing hormone, HCG: Human chorionic gonadotropin, OR: Odds ratio

pregnancy rates have been found in clinical studies comparing standard long GnRH-analog protocols with GnRH-antagonist protocols (8,9). In a clinical study comparing the GnRH-antagonist protocol with the standard long GnRH-analog protocol, Firouzabadi et al. (10) did not find a clinically significant difference between these two groups. Al-Inany and Aboulghar (11) compared GnRH-analog long protocol cycles with GnRH-antagonist cycles and found that the GnRH-antagonist group had significantly lower pregnancy rates than the GnRH-analog group (10). However, studies have also found the GnRH-antagonist group to be more successful (11,12). In a meta-analysis comparing the GnRH-analog long agonist protocol with the short GnRH-analog protocol, higher pregnancy rates were obtained with the GnRH-analog long protocol (13). We used the long GnRH-analog protocol, the short GnRH-analog protocol, and the GnRH-antagonist protocols, and the long GnRH-analog protocol was more successful. We have used the short GnRH-analog and GnRH-antagonist protocols frequently in patients with poor responses. Therefore, lower success rates may have been achieved.

A meta-analysis comparing urinary FSH with purified FSH in the literature showed similar pregnancy rates (14). In a study comparing urinary FSH with purified FSH, no significant difference was found between the two groups in terms of the clinical pregnancy rate and mean number of collected oocytes (15). However, in the meta-analysis of a large number of different studies, purified FSH was associated with a higher pregnancy success rate than urinary FSH (16). In a study comparing urinary FSH with purified FSH, the clinical pregnancy rate per ET was higher in the purified FSH group (17). In a meta-analysis of five similar studies, urinary FSHs were found to be more successful (18). In a study comparing HMG with purified FSH, the live birth rate with HMG was significantly higher (19). These results show that there is no consensus on the superiority of any drug against another. In our retrospective study, we found that there was no difference in pregnancy rates between pure gonadotropins and urinary gonadotropins.

A wide variety of agents have been proposed in the literature for luteal-phase support after ET. These include progesterone, HCG, and GnRH analogs. In a meta-analysis of 30 randomized studies comparing the use of progesterone and the use of supplemental HCG in the literature, it was found that vaginal use of progesterone was associated with a higher implantation rate than oral use (20). It was determined that IM use of progesterone was associated with higher clinical pregnancy rates, compared with non-use, and no difference was found between oral and vaginal progesterone use. It was observed that HCG administration was associated with higher clinical pregnancy rates, compared with those in the untreated group and the groups treated with oral progesterone, and there was no difference between vaginal and IM use of progesterone (20). The efficacy of HCG compared with progesterone showed similar results, but it has been suggested that HCG increases the ovarian hyperstimulation syndrome risk (21). It has been reported that IM progesterone use results in higher pregnancy success rates than vaginal progesterone use (20). In our study, we found that there were no differences between the various routes of administration of HCG and progesterone after ET.

Increased treatment cycles of ART appear to be associated with poor prognosis and increased maternal age (22,23). In a retrospective study by Martin-Johnston et al. (22) with 2.167 ART cycles, pregnancy rates decreased significantly after the second cycle, and even this decrease was more prominent after 3-5 cycles. They observed that the probability of success decreased with each new treatment cycle. The most significant reduction in pregnancy rates occurred after the third cycle. Therefore, patients who experience three failed cycles should be informed about other treatment options. In a study by Silberstein et al. (23), pregnancy rates and implantation rates decreased in second cycle and reach a plateau in 3-5 cycles. In our study, we found that increasing the number of cycles decreased the ART success and pregnancy rate per cycle.

The gonadotropin dose used is also an important factor affecting the pregnancy rate. We found that increasing the dose of gonadotropin negatively affects pregnancy outcomes. The response to gonadotropin treatment is an indication of the ability of the ovaries to develop follicles directly. In a retrospective study by Martin et al. (24), they found an inverse relationship between the gonadotropin dose and pregnancy rates. This study shows that success in ART cycles depends on the ability of the ovaries to develop an appropriate follicle. The high-dose gonadotropins used are indicative of the inability of the ovaries to develop follicles.

We showed that the number of oocytes collected, number of embryos transferred, and the quality of the transferred embryos are important factors affecting conception. We found that the number of collected oocytes, the number of embryos transferred, and the quality of the transferred embryos increased pregnancy rates. Kably Ambe et al. (25) found in their study that the number of collected oocytes, especially when this number was above 13, was associated with high pregnancy rates, in support of our findings.

CONCLUSION

In summary, the number of ART cycles performed, duration of infertility, maternal age, FSH level on the third day of menstruation, E2 level measured on the day of HCG, total gonadotropin dose, total number of oocytes collected, number of oocytes used for ICSI, number of oocytes used for IVF, total number of oocytes fertilized by ICSI, total number of oocytes fertilized as a result of IVF, number of total embryos transferred, number of grade 1 embryos transferred, number of metaphase 2 oocytes, number of prophase 1 oocytes (germinal vesicles) affect the success of ART per cycle. The limitation of our study is its retrospective design. Future prospective randomized trials with large patient populations evaluating ART success are needed.

Ethics

Ethics Committee Approval: Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, (number: 4467, date: 05.02.2008).

Informed Consent: Informed consent is not obtained due to the retrospective nature of this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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Correlation of Risk Factor of Pressure Ulcer Using the Braden Risk Assessment Scale

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Abstract

Objective: Pressure ulcers (PUs) are a common problem in intensive care units (ICUs) and lead to prolonged hospital stay and increased mortality and treatment cost. The Norton and Braden Risk Assessment scales (BRAS) were developed for this purpose. However, in recent years, it has been suggested that BRAS is insufficient.

This study aimed to investigate the correlation between BRAS and risk factors of PU in patients treated in the ICU.

Methods: This retrospective, single-center study was conducted between February and July 2017 and enrolled 200 patients with standardized PaO_2/FiO_2 ratio and BRAS scores, and all possible risk factors including age, sex, serum hemoglobin (Hb), albumin, bilirubin, creatinine, platelet, mechanical ventilation support, Glasgow Coma scale (GCS) scores, Nutritional Risk Screening (NRS2002) scores, Acute Physiology and Chronic Health Evaluation (APACHE) 2 scores, hypotension, and expected mortality were evaluated.

Results: The ages of the patients included the study were between 18 and 95 years, with a mean age of 62.84±17.98 years [88 (44%) women and 112 (56%) men]. A positive correlation was noted between BRAS measurements and albumin, Hb, GCS, hypotension, and PaO_2/FiO_2 measurements. Also, a negative correlation was noted between BRAS measurements and NRS2002 values, direct bilirubin levels, APACHE 2, and expected mortality values.

Conclusion: Low albumin and Hb values, GCS, and PaO_2/FiO_2 values, hypotension, and high indirect bilirubin levels, NRS2002, and APACHE 2 scores are risk factors for developing PU. It is inferred from our study that these symptoms and standard laboratory results should be used as additional indicators in determining the risk of PU, and BRAS should be modified by considering these risk factors.

Keywords: Braden Risk Assessment scale, pressure ulcer, albumin

INTRODUCTION

Pressure ulcers (PUs) are localized tissue injuries of the skin and subcutaneous tissues covering bone protrusions and usually result from factors such as pressure, friction, tear, and others (1). It is a common problem in intensive care units (ICUs) and leads to prolonged hospital stay and increased mortality and treatment cost (2). The success of preventive intervention and treatment methods depends on thoroughly understanding etiological methods. However, the multiplicity of risk factors and differences in the results of the study on the subject impedes a complete consensus on the prevention and treatment of PU (3). Hence, it is necessary to define the presence of predisposing factors in the etiology of PU in such an important tissue. For this purpose, several scales have been developed, and the Norton and Braden Risk Assessment scales (BRAS) are the most important ones. The Norton Scale is the simplest and evaluates mental state, activity, mobility, and incontinence. The BRAS has a more detailed questioning and risk rating. However, it has low calibration power in predicting the risk of PU development.

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Additionally, it cannot predict serum albumin levels because of malnutrition, which is an important part of predisposing factors (4-7).

Our study aimed to investigate the validity and reliability of BRAS in determining the risk groups in patients treated in the ICU.

METHODS

This retrospective, single-center study was conducted between February and July 2017 and enrolled 200 patients. When patients were admitted in the ICU, demographic data (age and sex) and initial values of BRAS, hemoglobin (Hb), serum albumin, bilirubin (direct and indirect), creatinine, platelet, Glasgow Coma scale (GCS), Nutritional Risk Screening (NRS2002), Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation (APACHE) 2 were recorded. If the patient is given mechanical ventilation support, the first PaO_2/FiO_2 ratio, hypotension, and expected mortality were evaluated.

Statistical Analysis

Statistical analysis was conducted using the Number Cruncher Statistical System 2007 (Kaysville, UT, USA) program. Student's t-test was used to compare descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) and two groups of variables that showed normal distribution in the comparison of quantitative data. The Kruskal-Wallis test was used to compare groups of three and more with no normal distribution, and the Mann-Whitney U test was used to determine the group that caused the difference. Pearson and Spearman correlation analyses were used to evaluate the relationships between variables. Significance was evaluated at $p<0.05$ levels.

RESULTS

The ages of the patients included the study were between 18 and 95 years, with a mean age of 62.84±17.98 years. There were 88 (44%) female and 112 (56%) male patients (Table 1). The distributions of the descriptive characteristics of the cases are shown in Table 2.

There was no statistically significant relationship between BRAS measurements and age distributions, indirect bilirubin, creatinine, and platelet count ($p>0.05$). A significant correlation was noted between BRAS and serum albumin measurements (the albumin levels increased as the BRAS values increased), and 31.5% relationship was statistically significant ($r=0.315$, $p=0.001$). There was also a positive correlation between BRAS measurements and Hb levels (the Hb levels increased as the BRAS values increased). The statistical significance of the relationship has been found weak ($r=0.198$, $p=0.005$). A positive correlation between BRAS measurements and GCS values was found (the GCS values increased as the BRAS values increased), and 62.6% relationship was statistically significant ($r=0.626$, $p=0.00$). There was a positive relationship between BRAS and hypotension

Table 1. Distribution of demographic characteristics

		Minimum-maximum (median)	Mean ± SD
Age (year)		13-95 (66)	62.84±17.98
GCS		3-15 (14)	12.36±3.38
		n	**%**
Gender	Female	88	44.0
	Male	112	56.0

SD: Standard deviation, GCS: Glasgow Coma scale

Table 2. Distribution of descriptive properties

	Minimum-maximum (median)		Mean ± SD
Albumin	0.20-4.60 (3)		2.98±0.81
Direct bilirubin	0.01-4.72 (0.21)		0.47±0.72
Indirect bilirubin	0-2.46		0.35±0.32
Creatinine	0.15-6.40 (0.88)		1.16±0.97
Platelet count ($x10^3$)	10-979 (230)		249.16±133.75
Hb	2.50-18 (10.8)		10.99±2.13
NRS2002	0-6 (3)		2.54±1.51
APACHE 2	3-49 (12)		15.13±9.16
Expected mortality (%)	4-97 (15)		26.13±23.22
BRDs	9-23 (19)		17.98±3.30
Hypotension	11-160 (91)		90.67±21.63
PaO_2/FiO_2	88-660 (311)		321.91±134.03
		n	**%**
Mechanical ventilation	(-)	154	77.0
	(+)	46	23.0
SOFA score	0-6	164	82.0
	7-9	21	10.5
	10-12	11	5.5
	13-14	3	1.5
	15	1	0.5
Expected mortality (%)	0-20	165	82.5
	20-40	20	10.0
	40-60	12	6.0
	60-80	2	1.0
	80-100	1	0.5

SD: Standard deviation, Hb: Hemoglobin, NRS2002: Nutritional Risk Screening, APACHE 2: Acute Physiology and Chronic Health Evaluation 2, SOFA: Sequential Organ Failure Assessment, BRDs: Bromodomains

measurements (increased hypotension values were observed as the BRAS measurements increased). About 27.5% relationship was found to be statistically significant (r=0.275, p=0.01). BRAS measurements were positively correlated with PaO_2/FiO_2 measurements (the increased PaO_2/FiO_2 values were noted as the BRAS values increased), and 45.2% relationship was found to be statistically significant (r=0.452; p=0.001). There was a negative correlation between BRAS measurements and NRS2002 values (decreased NRS2002 values were measured as the BRAS values increased). The correlation was statistically significant (r=0.450, p=0.001). BRAS measurements were negatively correlated with direct bilirubin levels (the direct bilirubin levels decreased as the BRAS values increased), and 27% relationship was found to be statistically significant (r=-0.270; p=0.001). BRAS measurements were negatively correlated with APACHE 2 and expected mortality values (decreased APACHE 2 and expected mortality values were noted as the BRAS values increased). A 61.9% relationship was statistically significant (r=-0.619; p=0.001; Table 3, Figure 1).

There was no statistically significant difference between BRAS measurements of the cases according to gender (p>0.05). The BRAS measurements of non-intubated patients were significantly higher than intubated ones (p=0.001). A statistically significant difference was found between the BRAS measurements of the patients according to SOFA score (p=0.001). According to the results of the Mann-Whitney U test performed to determine the differences, the BRAS values of patients with SOFA scores between 0 and 6 were significantly higher than those with SOFA scores of 7-9 and 10-12 (p=0.001 for each). Similarly,

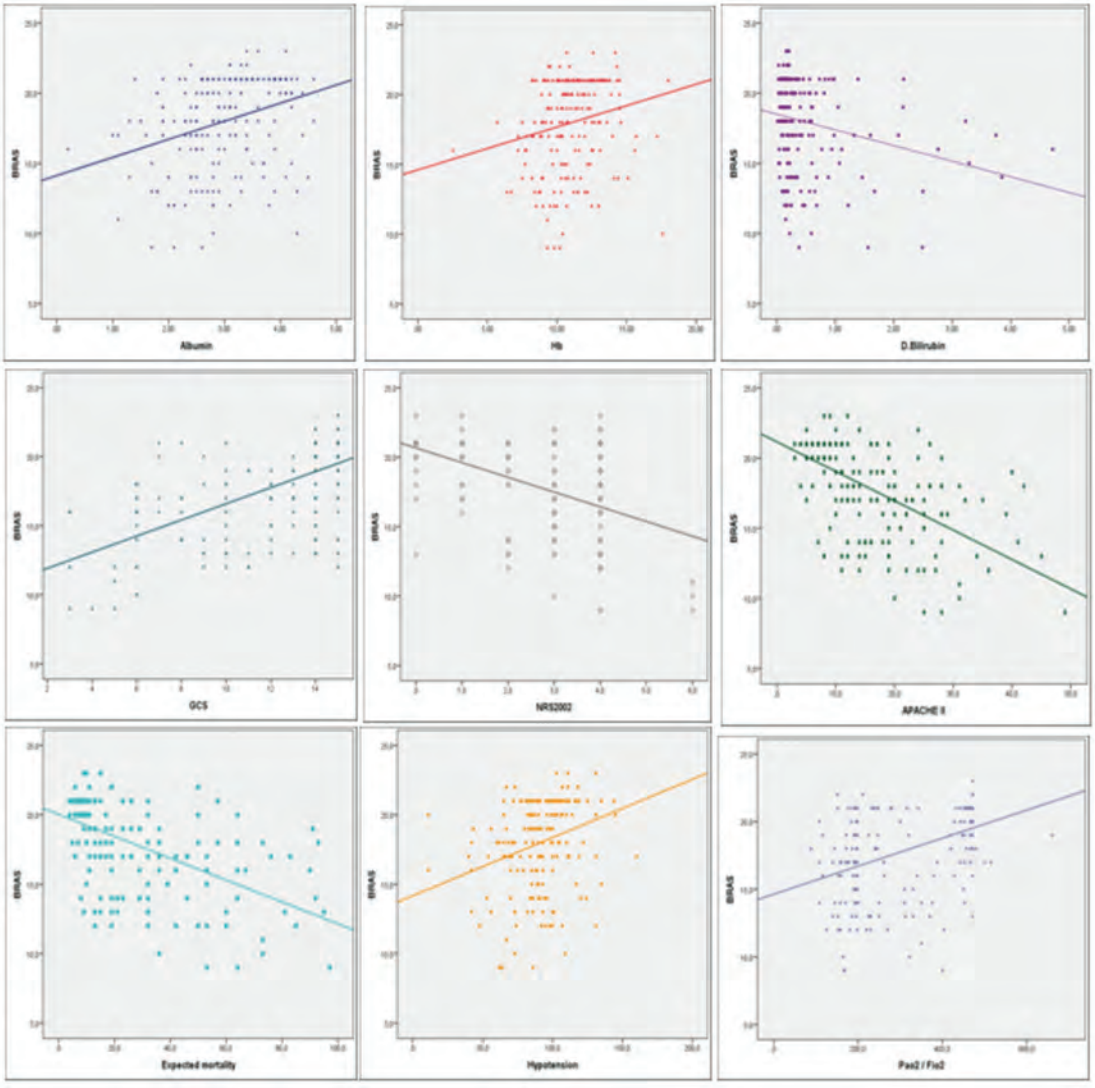

Figure 1. The correlation between BRAS measurements and albumin, Hb, direct biluribin, GCS, NRS2002, APACHE 2, expected mortality, hypotension, and PaO_2/FiO_2 ratio

BRAS: Braden Risk Assessment scale, Hb: Hemoglobin, GCS: Glasgow Coma scale, NRS2002: Nutritional Risk Screening, APACHE 2: Acute Physiology and Chronic Health Evaluation 2

the BRAS values of patients with SOFA scores between 7 and 9 were significantly higher than those with SOFA scores between 10 and 12 (p=0.049). A statistically significant difference was found between the BRAS measurements of the cases according to mortality. According to the results of the Mann-Whitney U test performed to determine the difference, the BRAS values of patients with an expected mortality of 0-20% were significantly higher than those with expected mortality of between 20-40% and 40-60% (p=0.001 for each, Table 4).

Table 3. Evaluation of the relatoinship between BRAS and other variables

	BRAS	
	r	p
Age	-0.124	0.080[a]
Albumin	0.315	0.001[a*]
Direct bilirubin	-0.270	0.001[b*]
Indirect bilirubin	-0.004	0.951[b]
Creatinine	-0.125	0.077[b]
Platelet count (x10^3)	-0.024	0.733[a]
Hb	0.198	0.005[a*]
GCS	0.626	0.001[b*]
NRS2002	-0.450	0.001[b*]
APACHE 2	-0.619	0.001[b*]
Expected mortality	-0.619	0.001[b*]
Hypotension	0.275	0.001[a*]
PaO_2/FiO_2	0.452	0.001[b*]

[a]r: Pearson correlation coefficient, [b]r: Spearman's correlation coefficient, *p<0.01, BRAS: Braden Risk Assessment scale, Hb: Hemoglobin, GCS: Glasgow Coma score; NRS2002: Nutritional Risk Screening, SOFA: Sequential Organ Failure Assessment, APACHE 2: Acute Physiology and Chronic Health Evaluation 2

DISCUSSION

In 1997, the first reliability and validity study of the scale developed by Braden and Bergstrom was conducted by Oguz in Turkey. In 1998, Pınar and Oğuz (8) examined the reliability and safety of the Norton Risk Assessment scale and BRAS. The reliability and validity of the scales were high in both studies and other studies (8-10). The scale includes six subdimensions, including sensory perception, moisture, activity, movement, nutrition, and friction and shear (11).

The total score of the scale is obtained by collecting the subdimension score. The values ranged from 6 to 23. Based on the total score, 12 points and below indicate high risk, 13-14 points indicate risk, 15-16 points indicate low risk, and 15-18 points indicate low risk in patients older than 75 years (7,9).

According to Karadağ (12), BRAS is the most reliable and valid scale for patients in the wide age range and is currently the most widely used scale in the United States. Balzer et al. (13) reported that it is the risk assessment tool with the best sensitivity-specificity balance. It is recommended for use in intensive care and long-term care units, but the subdimensions of the perception of moisture, nutrition, and stimulus should be more

Table 4. Evaluation of BRAS measurement by gender, intubation, SOFA score, and mortality

		BRAS		Test value
		Minimum-maximum (median)	Mean ± SD	p
Gender	Female (n=88)	9-23 (19)	18.07±3.26	t: 0.353
	Male (n=112)	9-23 (18)	17.9±3.34	**0.724**[a]
Intubation	No (n=154)	12-23 (20)	18.81±2.84	t: 7.397
	Yes (n=46)	9-21 (16)	15.17±3.20	**0.001**[a**]
SOFA score	0-6 (n=164)[1]	12-23 (20)	18.63±2.96	χ^2: 30.895
	7-9 (n=21)[2]	10-20 (17)	16.00±2.66	**0.001**[b**]
	10-12 (n=11)[3]	9-18 (14)	13.64±3.38	**p=0.001**[1, 2**]
	13-14 (n=3)[#]	13-17 (14)	14.67±2.08	**p=0.001**[1, 3**]
	15 (n=1)[#]	9-9 (9)	9.00±0.00	**p=0.049**[2, 3*]
Expected mortality (%)	0-20 (n=165)	12-23 (20)	18.62±2.95	χ^2: 30.482
	20-40 (n=20)	10-20 (16.5)	15.95± 2.72	**0.00**[b**]
	40-60 (n=12)	9-18 (15)	13.92±3.37	**p=0.001**[1, 2**]
	60-80 (n=2)[#]	13-14 (13.5)	13.5±0.71	**p=0.001**[1, 3**]
	80-100 (n=1)[#]	9-9 (9)	9.00±0.00	**p=0.084**[2, 3]

[a]Student t-test, [b]Kruskal Wallis test, *p<0.05, **p<0.01, [1]SOFA score (0-6), [2]SOFA score (7-9), [3]SOFA score (10-12), [#]The number of people is not included in the comparison because of insufficient number.
BRAS: Braden Risk Assessment scale, SOFA: Sequential Organ Failure Assessment, SD: Standard deviation

clearly defined (14,15). In the study of Kottner and Dassen (16) in patients in the ICU, BRAS is a more reliable risk measurement tool than the Waterlow scale, but using these scales coexistencely is recommended. BRAS is the most widely used scale and has also been used in many studies conducted in our country (3,17-19).

Previous studies have shown that patients categorized as high risk according to BRAS have a higher incidence of pressure sores. However, BRAS can be used to determine the risk of developing PU in hospitalized patients, although it may be insufficient for risk assessment in patients in the ICU (19,20). In a retrospective study conducted by Sardo et al. (21), PU developed in 153 (2.3%) of 6.652 patients, and other than nutrition, assessment factors such as mobility and activity were accepted as independent risk factors for developing PU. In our study, there was a positive correlation between BRAS measurements and serum albumin levels (the albumin levels increased as the BRAS values increased). A 31.5% relationship was found to be statistically significant. However, Kurtuluş and Pınar (22) showed that 18.3% of pressure wound incidences are noteworthy despite hypoalbuminemia.

Hypoalbuminemia, which is widely accepted as a risk factor for PU development, seems to have lost its importance against conditions such as changing position every 2 h, assessing the skin every position change, preventing excessive humidity, pressure, and irritation of the sheets and clothes, and using pressure-reducing devices (23). Increased risk of PU is related to factors such as previous stroke, trauma, cognitive function decline, poor GCS, and delayed enteral nutrition. It has been shown that there was a significant correlation between PU and 21-day mortality and 3-month recovery in patients with traumatic cerebral injury. Hence, early nutritional support and Hb level monitoring should be considered important parts of nursing care interventions in patients with high risk of developing PU (23,24). In our study, there was a positive correlation between BRAS measurements and Hb levels (the Hb levels increased as the BRAS values increased). A weak 19.8% relationship was found. BRAS measurements were significantly correlated with GCS values (the GCS values increased as the BRAS measurements increased). A 62.6% relationship was found to be statistically significant.

The retrospective study by El-Marsi et al. (25) has been conducted in a university hospital with 420 bed capacity and included 145 patients with newly developed PU. Variables such as gender, age, inotropic agent usage, primary disease, comorbidity, and weight (entry and exit weights in the ICU) were compared with BRAS measurements. The length of ICU stay, use of vasopressors, and duration of hypotension were found as prominent factors in the development of PU. In our study, a 27.5% positive relationship between BRAS measurements and hypotension levels was significant. There was also a 45.2% positive and statistically significant relationship between BRAS measurements and PaO_2/FiO_2 values (the PaO_2/FiO_2 values increased as the BRAS values increased) ($r=0.452$; $p=0.001$; $p<0.01$).

CONCLUSION

BRAS can be eligible in determining the risk of developing PU in hospitalized patients but is insufficient in determining the risk of critical patients in the ICU. Low albumin and Hb values, GCS, PaO_2/FiO_2 values, hypotension, and high indirect bilirubin levels, NRS2002, and APACHE 2 score are risk factors for developing PU.

It is inferred from our study that these symptoms and standard laboratory results should be used as additional indicators in determining the risk of PU, and BRAS should be modified by considering these risk factors.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

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Axillary Approaches to Brachial Plexus Block: A Comparison of Stimulator-guided Peripheral Nerve Block with and Without Ultrasonography Techniques

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Abstract

Objective: This study aims to compare stimulator-guided peripheral nerve block with and without ultrasonography techniques to investigate the block procedure time, sensory and motor block onset time, pain related to the block procedure-related pain, and anesthesia-related complications.

Methods: Patients were randomized into two groups: The nerve stimulator (NS)-guided technique group (n=30) and the NS with ultrasound (NU)-guided technique group (n=30). One-quarter of the solution prepared with prilocaine 2% and lidocaine 2% with the height/5 formula was injected around each nerve after receiving a motor response between 0.3-0.5 mA.

The block procedure time, sensory and motor block onset time, the number of skin punctures, procedure-related preoperative complications, procedure-related postoperative complications, and visual analog scale (VAS) (0-10) scores were recorded.

The heart rate, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, and peripheral oxygen saturation values were noted at 0, 5, 10, 15, 30, 45, 60, 120, and 180 minutes.

Results: The block procedure time was similar between them ($p>0.05$). The number of skin punctures ($p=0.001$) and VAS ($p<0.045$) were significantly higher in the NS group. The sensory and motor block onset times were significantly similar ($p>0.05$) except for the motor block of musculocutaneous nerve onset time ($p<0.05$). Although the success rate was higher in the NU group, there was no statistically significant difference between the groups ($p>0.05$). The number of complications was significantly higher in the NS group ($p<0.05$).

Conclusion: Using ultrasonography with the NS in the axillary approach to brachial block improves the success rate with a lower incidence rate of complications.

Keywords: Brachial plexus block, motor block, nerve stimulator, sensory block, ultrasound

INTRODUCTION

A brachial block via the axillary approach is a common technique to provide anesthesia for upper extremity surgery. Peripheral nerve blocks offer numerous advantages, such as providing better postoperative pain scale scores, lower incidences of nausea and vomiting, shorter recovery time, early mobilization, decreased hospital stay, more stable hemodynamic results, and greater patient satisfaction. For the past decades, the nerve stimulator (NS) had been the gold standard for nerve localization in regional anesthesia. However, with recent developments in high-frequency imaging, using ultrasound (US) technology has significantly increased nerve localization.

A US-guided peripheral nerve block can be applied more successfully, easily, safely, and painlessly. This technique

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enables direct visualization of nerves and surrounding anatomy, continuous observation of the needle tip, and local anesthetics distribution. However, complications occur during the US alone. Therefore, using a combination of different techniques is recommended.

This study aims to compare peripheral nerve block guided with the NS with and without ultrasonography to investigate the time to perform the block, sensory and motor blocks onset time, pain related to the block procedure, and complications related to anesthesia.

METHODS

After obtaining Institutional Ethics Committee approval was received for this study from the Local Ethics Committee of İstanbul University, Medical Faculty of İstanbul (decision date: 12/04/2013, decision no: 412), a total of 60 patients undergoing elective upper extremity surgery between 18-70 ages and American Society of Anesthesiologists (ASA) I-IV status were enrolled in this prospective randomized study. Before conducting the study, all patients provided their informed consent. Then, they were randomly divided into two groups according to a randomization table: the NS-guided technique group and the NS with ultrasound (NU)-guided technique group. Patients with coagulation disorders, a history of allergy to local anesthetics, and neuromuscular and psychiatric diseases, a history of peripheral neuropathy, and patient refusal were the study's exclusion criteria.

After arrival at the operating room, standard monitoring was used, including non-invasive arterial blood pressure, heart rate (HR), and pulse oximetry, and an intravenous catheter was placed to the forearm contralateral to the operating arm 30 min before the block, standard premedication was given intravenously (2 mg) to all the patients. Then, the patients were placed supine with the arm abducted 90 degrees.

The skin sterilization was made with chlorhexidine antiseptic solution.

In all patients, the block procedure was done by an experienced anesthesiologist applying the axillary approach technique.

Systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, HR, and peripheral oxygen saturation (SPO_2) was recorded in 0^{th}, 5^{th}, 10^{th}, 15^{th}, 30^{th}, 45^{th}, 60^{th}, 120^{th}, and 180^{th} seconds.

In the NS group, after palpating the axillary artery's pulse at the attachment of the major pectoral muscle, the nerve was localized using a 21 gauge, 100 mm needle connected to the negative lead of the NS (Stimuplex® HNS B/BRAUN). The NS was set at a pulse duration of 0.1 ms, a current intensity of 1.5 mA, and a frequency of 2 Hz. The stimulator flow was deducted after receiving the proper muscle contraction (wrist flexion for the nervus medianus, ulnar deviation for the nervus ulnaris, wrist extension for the radial nerve, and elbow flexion for the nervus musculocutaneous).

In cases of motor responses between 0.3-0.5 mA, after determining that there was no blood aspiration, an equal amount of a prepared solution containing a mixture of prilocaine 2% and lidocaine 2% was injected around each nerve by the axillary artery. This volume was one-quarter of the solution prepared earlier, with prilocaine 2% and lidocaine 2% using the height/5 formula.

In the NU group before the procedure, the US settings were set at depth: 3-5 cm, frequency: 8-14 Hz, and the stimulator parameter was set at 1.5 mA, 2 Hz, and 0.1 ms. The US probe was covered with a sterile sheath, coated with a sufficient amount of gel, and placed on the short axis of the humerus' insertion point on the pectoralis major muscle.

After recognizing the pulsatile axillary artery by gentle suppression of the probe, a 100 mm 21 G needle was inserted into the skin at a 45° angle with the long axis approach.

When the needle was visible under the probe, it was directed to the target nerves. After obtaining the proper muscle contraction (wrist flexion for the nervus medianus, ulnar deviation for the nervus ulnaris, wrist extension for the nervus radialis, elbow flexion for the nervus musculocutaneous), the flow of the simulator was deducted. In cases of motor responses between 0.3-0.5 mA, after determining that there was no blood aspiration, an equal amount of a prepared solution containing a mixture of prilocaine 2% lidocaine 2% was injected around each nerve by the axillary. This volume was one-quarter of the solution prepared earlier, with prilocaine 2% and lidocaine 2% using the height/5 formula.

In all patients, the block procedure time, onset time of sensory and motor blocks, the number of skin punctures, procedure-related preoperative complications, procedure-related postoperative complications, visual analog scale (VAS) (0: No pain; 10: Worst imaginable) scores were recorded.

The block procedure time: Time from skin contact with either the US probe or the needle to the injection of the local anesthetic solution.

The onset time of the sensory and motor block: From the end of the injection of the local anesthetic solution, the onset time

for the sensory block was evaluated with the pinprick test. For the motor block, the radial, ulnar, median, and musculocutaneous nerves were evaluated with the medical research council scale at 3, 5, 10, 15, 20, 25, 30, and 40 min, respectively.

Sensory Block

0: Normal sensation, 1: Decreased sensation (analgesia), 2: Complete sensory block (anesthesia).

Visual Analog Scale Score

When the sensory and motor blocks were completely performed, pain levels were assessed during the verbal pain scale.

0-2: No pain, 3-4: Mild pain, 5-6: Moderate pain, 7-8: Severe pain, 9-10: Excruciating pain.

Complications

Procedure-related preoperative complications: vascular puncture, hematoma, paresthesia, allergic reaction.

Procedure-related postoperative complications: After 24 hours, neurological complications, such as paresthesia and motor weakness, were evaluated.

Block Success was Evaluated as

Successful block: The operation was completed under block without any additional analgesia.

Partial block: The need for additional analgesia.

Failed block: General anesthesia was needed, or the procedure duration exceeded 20 min.

Insufficient block: In pain during the surgery, sedo-analgesia was administered with a bolus of 0.03 mg kg^{-1} midazolam IV and remifentanil infusion 0.05 mcg kg^{-1} h^{-1} under 3 L min^{-1} oxygen. If SPO_2 <90% or apnea was longer than 20 sec^{-1} under sedo-analgesia, general anesthesia was administered.

Statistical Analysis

All data were evaluated with Statistical Package for Social Sciences for Windows v. 16.0 program. Data are given as mean ± standard deviation. Categorical data were compared with the chi-square test and continuous data with Fisher's exact test. P values <0.05 were considered significant.

RESULTS

During the study, 70 patients were scheduled. Four patients refused to participate in the study, six patients did not meet the inclusion criteria, and 60 patients were enrolled in this investigation (Figure 1). Demographic data of the patients were not significantly different between the two groups (Table 1).

Table 1. Patient demographic data

	NS group (n=30)	NU group (n=30)	p value
Age	44.8±12.8	48.2±13.4	0.32
Weight (kg)	76.3±9.9	78±14.7	0.61
Height (cm)	163.9±11.2	167.6±11.9	0.22

Data were given as mean ± standard deviation. NS: Nerve stimulator, NU: Nerve stimulator with ultrasound

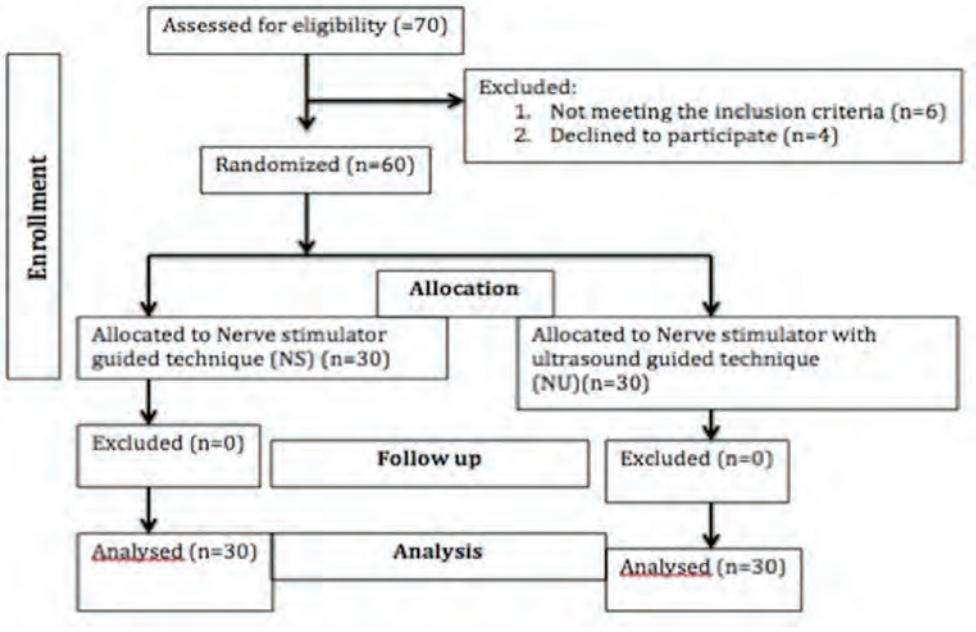

Figure 1. Flow diagram of the study

There were no significant differences in operation time and time to perform the block between the two groups (Table 2).

The number of skin punctures and VAS scores was significantly higher in the NS group than in the NU group (p=0.001, p<0.05) (Table 2).

There was not a statistically significant difference between the two groups in the usage of a total local anesthetic volume (p>0.05) (Table 2).

While there was no statistically significant difference in sensory and motor onset times of the ulnar nerve, the median nerve, and the radial nerve (p>0.05) in the NU group, there was a significant difference in the motor onset time of the musculocutaneous nerve in the NS group (p<0.05) (Figure 2).

There were no differences in the patients' hemodynamic values between the two groups during the procedure (p>0.05).

Although the success rate was higher in the NU group, there was no statistically significant difference between groups (p>0.05) (Table 3).

While a total of 19 complications were seen in the NS group during the block procedure, four complications were observed in the NU group (p=0.0001) (Table 3); and complete recovery of sensory and motor function was observed in all studied patients.

DISCUSSION

In this study comparing the peripheral nerve block guided with the NS with and without ultrasonography, no significant difference was observed to perform the block between the two groups. While the two groups' data consistently showed similar success rates, the complication rates and VAS scores were better in the US group.

In recent clinical studies, it was demonstrated that, in peripheral nerve blocks, the success rate was influenced by the local anesthetic solution type, concentration, and volume, and by patients' demographic data (1-3). In our study, patients' demographic data were similar, and we administered equal doses of the local anesthetic solution to each patient to provide the standardization between the groups.

Table 2. Data on the axillary approach to brachial plexus block

	NS group (n=30)	NU group (n=30)	p value
Operation time (min)	72.3±35.5	59.3±29.8	0.13
Time to perform the block (min)	10.7±5.4	9±3.6	0.15
The number of skin punctures	2.3±1 (1-4)	1.5±0.7 (1-3)	0.001*
Usage of total local anesthetic volume (mL)	33.5±2.3	33.5±2.3	0.47
VAS score (0-10)	3.8±2.4	2.6±2.1	0.045*

*Data are given as mean ± standard deviation and minimum-maximum. NS: Nerve stimulator, NU: Nerve stimulator with ultrasound, VAS: Visual analog scale

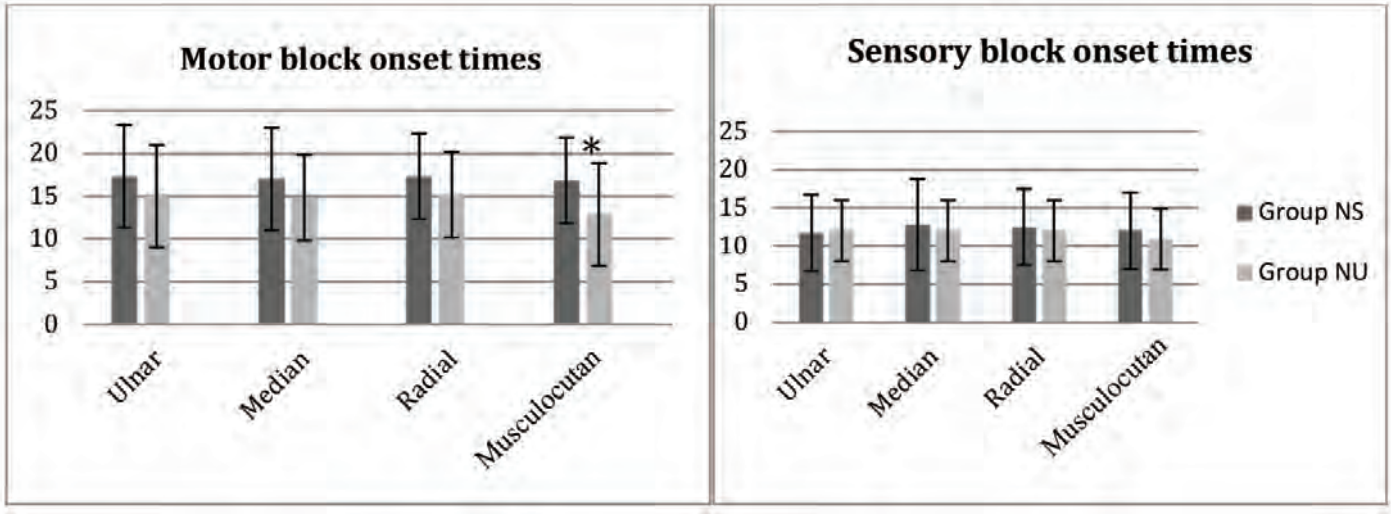

Figure 2. Motor and sensory block onset times of groups
*p<0.05 The motor onset time of the musculocutaneous nerve in the NU group was significantly shorter than the NS group.
NS: Nerve stimulator, NU: Nerve stimulator with ultrasound

Table 3. The success rate and complications observed in groups		
	NS group (n=30)	NU group (n=30)
Success rate		
Successful block	23 (76.6%)	28 (93.2%)
Partial block	7 (23.3%)	2 (6.6%)
Failed block	0	0
Complications		
Vascular puncture	8	0
Hematoma	2	0
Paresthesia	9	4

Values are numbers of patients. NS: Nerve stimulator, NU: Nerve stimulator with ultrasound

Our study found no significant difference in the time to perform the block between the two groups. Cataldo et al. (4) showed that using the time was faster using the US popliteal block than with the NS. In Chan et al.'s (5) study, US was used with the NS to perform the block. They observed that an additional technique extended the time to perform the block.

The application time to perform the block varied with the different approaches used (6). Song et al. (7) demonstrated that performing the brachial block via the infraclavicular approach was faster than the axillary approach. This difference in the processing time was explained by fewer injection requirements in the infraclavicular approach. Imasogie et al. (8) performed the US-guided axillary approach brachial plexus block using four nerve injections in 10.9 min and with two nerve injections in 7.86 min.

Our study performed four nerve injections in 10.7 min in the NS group and 9 min in the NU group.

In our study, the number of skin punctures and VAS scores was significantly higher in the NS group than in the NU group. While VAS scores were not an objective criterion, the relationship between the skin punctures was demonstrated in different studies (9,10). On the other hand, Cataldo et al. (4) observed that while the number of skin punctures was higher in the US group, patient satisfaction was much better. This finding is likely because the time to perform the block was shorter when using the US.

Several trials demonstrated that the onset times of motor and sensory blocks were shortened by utilizing the US in peripheral nerve blocks (11,12). Our results showed that while the onset times of motor and sensory blocks were shorter in the US group, there was no significant difference except musculocutaneous nerve block. The smaller diameter of the musculocutaneous nerve than other nerves can make localization difficult with NS alone. It is possible to obtain a similar effect on onset times as in our study with US and NS technique in experienced hands (9).

The local anesthetic solution's characteristics used, dose, and concentration affect the onset time of action. Casati et al. (9) using 20 mL ropivacaine 0.75%, the sensory and motor block action onset times were 18±6 and 25±8 min, respectively, while 14±6 and 24±8 min in the ultrasonography group. In our study, sensory and motor block action time was 12.8±5.5 and 17.3±5.4 min in the NS group, 12±4.3 and 15.2±5.2 min in the NU group. It was showed that sensory and motor block effect onset times are shorter in our study. This is due to the usage of a higher volume of lidocaine and 2% prilocaine in our study.

Training is essential for US techniques and takes longer than other techniques. Sandhu and Capan (13) stated that at least 20 procedures should be performed for successful block by ultrasonography. Therefore, all ultrasonographic blockage procedures were performed by an experienced anesthesiologist in our study.

Auroy et al. (14) stated that there is a possibility of developing systemic complications in the range of 0 to 25 at 10,000 according to the applied block type. In contrast, Zetlaoui et al. (15) reported developing generalized seizures in the axillary approach with brachial nerve block using ultrasonography. In this study, the short-term clinical picture after drug injection suggests that intravascular injection was performed.

Liu et al. (16) stated that they did not see systemic and local complications using ultrasonography. In our study, 26.6% of vascular pneumonectomy was performed in the NS group, and 25% of these patients had hematomas in their axillary region. In contrast, the vascular puncture was not performed in the NS group. Nevertheless, no systemic complications were encountered in any of our patients.

The frequency of nerve injury in the axillary approach to peripheral block ranges from 0.2% to 19% (17,18). In our study, paresthesia was observed in four patients (13.3%) in the NU group but nine patients (30%) in the NS group. Less skin fouling affects paresthesia frequency in the NU group. Nevertheless, none of the patients had neurological complications after the operation.

Study Limitations

The limitation of our study was that we did not perform a neurological follow-up for a long time after the operation.

CONCLUSION

In our study, while ultrasonography was associated with decreased pain and complications associated with the procedure, though not statistically significant, a higher success rate was obtained. Our study results support the routine use of ultrasonography with the NS.

Ethics

Ethics Committee Approval: Institutional Ethics Committee approval was received for this study from the Local Ethics Committee of İstanbul University, Medical Faculty of İstanbul (decision date: 12/04/2013, decision no: 412).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.A., M.T., Design: D.A., Data collection or Processing: D.A., M.S.K., E.A.Ş., G.D., Analysis or Interpretation: D.A., M.T., Literature Search: D.A., M.S.K., E.A.Ş., Writing: D.A., G.D.

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

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Prognostic Value of Systemic Immune Index in Patients with Metastatic Gastric Cancer

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Abstract

Objective: Immune indexes are used to predict prognosis and survival in patients with cancer. Systemic immune-inflammation index (SII) is an index that is calculated using neutrophils (N), lymphocytes (L), and platelet (P) counts (SII=N x P/L). SII is shown to be associated with prognosis in many tumors. The objective of this study is to evaluate the relationship between SII and prognosis in patients with metastatic gastric cancer.

Methods: In this study, the data of 187 patients who were followed up with the diagnosis of metastatic gastric cancer in the medical oncology outpatient clinic of the tertiary training and research hospital were retrospectively reviewed. SII was calculated using the formula N x P/L and the optimal cut-off was determined as 600, which was the median value. Values below 600 were grouped as low SII and values above 600 were grouped as high SII. The effect of SII on survival was evaluated by the log-rank test and the Kaplan-Meier curve.

Results: For the study, medical files of 253 patients who were diagnosed with metastatic gastric cancer were scanned. Patients who had no follow-up and whose pre-treatment hemogram data were not available at that time were excluded. Finally, this study included 187 patients. In total, there were 63 (33.7%) female and 124 (66.3%) male patients, with a median age of 63 (27-88) years. Although survival was shorter in patients with SII above 600, no statistical significance was detected (9 months vs. 12 months; p=0.13). In primary surgically resected patients, survival was significantly better (13 months vs. 4 months p<0.001), but there was no difference in SII between the operated and non-operated groups.

Conclusion: Our study suggests that a high SII may be a poor prognostic factor in patients with metastatic gastric cancer, despite no statistical significance. Well-designed prospective studies with a larger number of patients are needed to evaluate the prognostic significance of SII and determine the optimal cut-off value before its inclusion into the clinical routine in this group of patients.

Keywords: Gastriccancer, prognosis, systemicimmune-inflammation index (SII)

INTRODUCTION

Gastric cancer is the fifth most common cancer in the world and ranks third among all cancer-related deaths. Globally, more than one million patients were diagnosed with gastric cancer in 2018, resulting in over 780,000 deaths. Despite the decreasing incidence and mortality of gastric cancer in recent years, it is still a major public health challenge (1,2). The highest cancer incidence in the world is found in East Asia, Eastern Europe, and South America, followed by Japan and Korea, where the incidence is also quite high (3).

Gastric cancer is still a high mortality disease with a poor prognosis despite the new developments in treatment such

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as new surgical techniques, chemotherapy, radiotherapy, and immunotherapy (4). Because gastric tumors exhibit late clinical manifestations, they are usually diagnosed at an advanced stage, with only around 10% of patients diagnosed at an early stage with the five-year survival rate of 10-30% (5,6).

Surgery combined with adjuvant chemotherapy and radiotherapy when diagnosed at an early stage increases survival chances, whereas systemic chemotherapy and radiotherapy aim to improve the survival and palliation of symptoms in patients diagnosed at the metastatic stage (5,7).

Systemic inflammation is known to play an important role in the development of many cancers, including gastric cancer. Chronic inflammation and chronic atrophic gastritis, especially due to *Helicobacter pylori* infection, increase the developmental risk of gastritis cancer (8,9). Cancer-related inflammation is a vital component of the tumor microenvironment, and inflammatory cells play an essential role in tumor development and progression. Researchers have shown that systemic inflammatory responses include DNA damage, angiogenesis, and tumor invasion and migration (10). Furthermore, another group of researchers have assessed the use of some histological and immunological markers in evaluating the prognosis of gastric cancer; however, many of these markers require tissue, cost, and time (6,11). Inflammatory cells such as white blood cells, neutrophils (N), lymphocytes (L), monocytes, platelets (P) and parameters such as N/L ratio, monocyte/L ratio, P/L ratio, are used routinely and believed to be indicators of systemic inflammatory and recommended as a prognostic factor in many types of cancers (6,10,12-14).

Recently, systemic immune-inflammation index (SII) based on N, P counts, and L counts in the peripheral blood has been used for a better reflection of the balance between host immune response and inflammation. Prognostic value of the results obtained from this calculation has been confirmed in many solid tumors such as colon, esophagus, hepatocellular and lung cancers (15-18).

SII has been reported to be associated with prognosis in patients operated for gastric cancer, as well as in patients with locally advanced gastric cancer who receive neoadjuvant chemotherapy. However, its prognostic use in patients with metastatic gastric cancer is not clear (6,19). The objective of this study is to evaluate whether the systemic immune index has a prognostic significance in patients with metastatic gastric cancer.

METHODS

Our study included 187 patients who were diagnosed with pathologically confirmed metastatic gastric cancer between 2006 and 2017 at the Medical Oncology Clinic of Kayseri Training and Research Hospital. In addition, their pre-treatment hemogram values and follow-up data were also recorded. Patients with steroid use that may affect hemogram parameters or patients with autoimmune disease, systemic inflammatory disease, and active infection at the time of diagnosis were not included in the study. Consent was obtained from the patients that the file information would be used before the study. Participating patients' gender, age, pathological tumor type, metastasis regions, type of surgery, hemogram, and tumor marker levels were then determined and evaluated. SII was calculated with the hematological parameters of the patients with the formula P x (N/L), and the median SII value of 600 was accepted as the cut-off value. Those with the SII cut-off value ≥600 were considered as high and those with <600 as low.

Statistical Analysis

All analyses were performed using Statistical Package for Social Sciences version 22.0 software (SPSS Inc, Chicago, IL).

Categorical variables in the clinicopathological database were presented as frequency and percentage (%) and compared using the chi-square test or Fisher exact test. The basic characteristics of the patients were expressed as median for qualitative variables. Independent t-test was used in the analysis of numeric parameters that do not comply with normal distribution and cases who did not have a normal distribution were evaluated using Mann-Whitney U test.

The Kaplan-Meier curve was used for determining the effect of SII on overall survival (OS), whereas the log-rank test was used for the comparison of survival rates.

Ethical Approval

Ethical approval, dated 23/07/2020/07 decision number 126, was obtained from the Ethics Committee of Kayseri Training and Research Hospital.

RESULTS

For the study, the medical files of 253 patients who were diagnosed with metastatic gastric cancer were scanned. Patients who had no follow-up and whose pre-treatment hemogram data were not available were excluded. Finally, this study included 187 patients. In total, there were 63 (33.7%) female and 124 (66.3%) male patients, with a median age of 63 (27-88) years. Surgery was performed for primary gastric cancer in 150 patients (69.5%) before staging the patients and the most common surgery was total gastrectomy (37%). As for the pathological subtypes, adenocarcinoma was the

most frequently observed at a rate of 73.8%, among which 28.3% were poorly differentiated, 24.1% were moderately differentiated, 3.7% were well-differentiated tumors according to the differentiation status.

Evaluation of the metastasis sites revealed that the most common metastasis sites were liver (25%) and peritoneum (24%), whereas 20.3% of the patients had multiple metastases at the time of diagnosis. Tumor marker elevation was observed in 114 (61%) patients at the time of diagnosis (Table 1).

The median white blood cells, hemoglobin, N, P, and L counts in blood parameters were $7x10^3$ µ/dL, 11.9 g/dL, $4.44x10^3$ u/dL, and $1.615x10^3$ u/dL, respectively. A significant relationship was observed between hemogram parameters and SII when the optimum SII cut-off value was determined as the median SII value (Table 2).

Patients were divided into two groups according to SII levels: Those with SII <600 were accepted as the low group, and those with SII >600 as the high group. There were 60 patients in the low SII group and 127 patients in the high SII group. Although the median OS was 10 (8.2-11.7) months in the whole study group, there was no significant relationship among age (p=0.61), gender (p=0.97), pathological subtype (p=0.28), serum tumor elevation (p=0.06), and survival. However, survival was statistically significantly better in patients undergoing primary surgery (p<0.001) (Table 3, Figure 1).

Evaluation of the relationship between SII and survival showed that the median OS was 12 (9.5-14.4) months in the low SII

Table 1. Clinical characteristics of the study group

Age	**(Mean ± SD) 61.6±12.26**	**Median (min-max) 63 (37-75)**				
Gender	Male	Female				
n (%)	124 (66.3)	63 (33.7)	-	-	-	-
Histologic subtype	Signet ring cell	Adenocarcinoma	Mucinous	Mixed		
n (%)	46 (24.6)	138 (75.4)	1 (0.5)	1 (0.5)		
Surgery	Yes	No	NA	-	-	-
n (%)	130 (70)	27 (14.4)	30 (15.6)	-	-	-
Metastasis site	Lung	Liver	Lymph node	Bone	Peritoneum	Multiple
n (%)	10 (5.3)	47 (25.1)	28 (15)	6 (3.2)	45 (24.1)	38 (20.3)
BMI	Mean ± SD 22.5±4.14	Median (min-max) 22.0 (17-32)	-	-	-	-

SD: Standard deviation, min: Minimum, max: Maximum, BMI: Body mass index

Table.2. Clinico-pathologic characteristics of the patients according to SII groups.

Category	**SII <600**	**SII >600**	**p value**
n (%)	60 (32.1%)	127 (%67.9)	
Age (mean ± SD)	61.5±12.23	63±12.27	$p=0.94^t$
Gender (male/female) (%)	54/28 (38.3/61.7)	114/57 (31.5/68.5)	$p=0.89^{x^2}$
Surgery (total/subtotal) (n/%)	26 (43.3)/20 (33.7)	44 (34.6)/29 (22.8)	$p=0.51^{x^2}$
BMI (mean ± SD)	22.8±3.67	22.3±4.37	$p=0.88^t$
Pathology adenocarcinoma/signet ring cell (n/%)	47 (78.3)/13 (21.7)	91 (71.7)/33 (26.0)	$p=0.39^{x^2}$
Operated/non-operated (n/%)	66 (78.3)/10 (16.7)	118 (65.4)/19 (13.4)	$p=0.88^{x^2}$
Differentiation (good/moderate/poor) (n/%)	4/21/20	8/49/58	$p=0.26^{x^2}$
Hemoglobin (g/dL) (IQR 25-75)	12 (11-13)	11.8 (10-13)	$p=0.27^z$
Lymphocyte (u/dL) (IQR 25-75)	1790 (410-4370)	1595 (470-4500)	$p=0.13^z$
Neutrophil (u/dL) (IQR 25-75)	2795 (1975-3457)	5750 (4105-7587)	$p<0.001^z$
Monocyte (u/dL) (IQR 25-75)	430 (330-579)	600 (440-837)	$p<0.001^z$
Platelet (u/dL) (IQR 25-75)	224000 (181500-281000)	354500 (277750-450250)	$p<0.001^z$

SD: Standard deviation, ^{t}: Independent t-test, ^{z}: Mann-Whitney U test, $^{x^2}$: Chi-square test, SII: Systemic immun infalammation index, BMI: Body mass index, IQR: Interquartile range

group and 9 (6.9-11.0) months in the high SII group. Although no statistically significant difference was observed in survival, it was 3 months longer in the low SII group (Figure 2).

No significant difference was found in age, gender, body mass index, histological subtype, previous gastric surgery, and pre-treatment elevation in markers between the patients in the low and high SII groups (Table 2).

DISCUSSION

In our study, we found that a low SII value was associated with a better survival in patients with metastatic gastric cancer, even though it was not statistically significant.

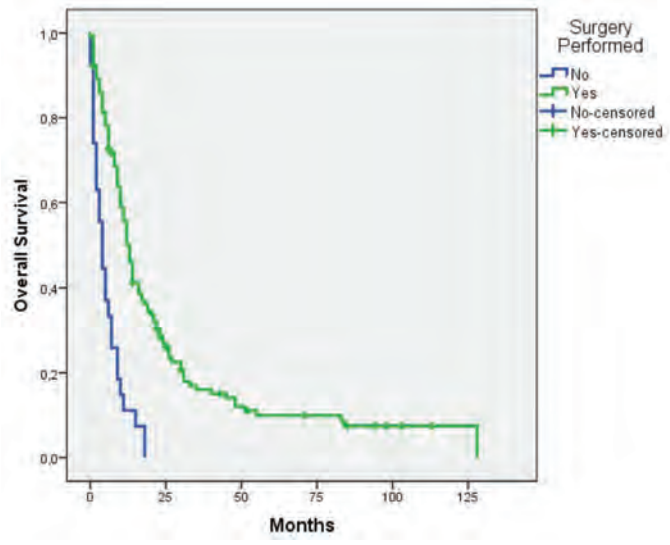

Figure 1. Kaplan-Meier survival curve according to the surgical procedure

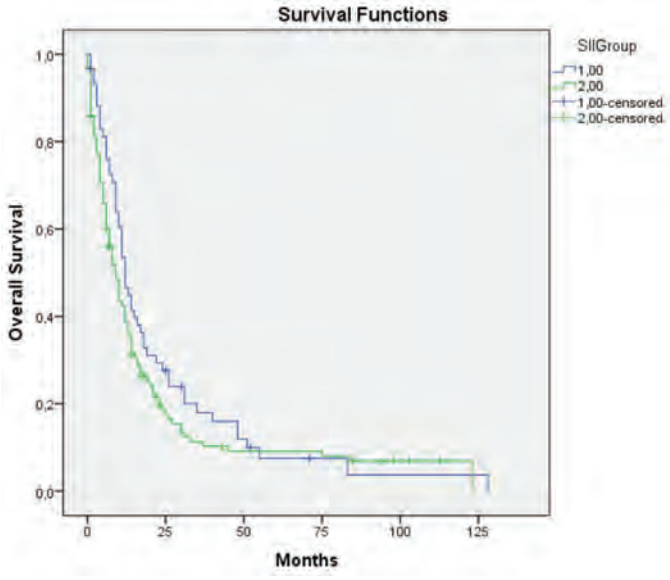

Figure 2. The effect of SII on OS in metastatic gastric cancer
SII: Systemic immune-inflammation index, OS: Overall survival

Recent studies have shown that systemic immune response stimulates malignant tumor development, is associated with a more aggressive clinical course and shorter survival, and predicts prognosis in patients with malignant tumors. SII is used in practice and has been reported to show immune and inflammatory status in various tumors in the preoperative period and can predict prognosis (20-22). SII is calculated with the formula - P x (N/L). It is known that N help tumor cells escape immune surveillance and, thus, the development of invasion, proliferation, and metastasis while inhibiting the proliferation and migration of tumor cells in L. With this mechanism, a high SII value shows a stronger inflammatory response but a weaker immunity and can be used as an applicable inflammation index in clinical practice that can predict cancer prognosis.

Previous studies showed that SII is associated with prognosis during the preoperative and neoadjuvant treatment period in patients with gastric cancer, but as far as we know, there is no study evaluating SII focused on a patient group with metastatic gastric cancer.

Table 3. Clinical characteristics and survival of the study group

	n	Median OS (95% confidence interval)	p value
Gender			
Female	63	10 (8.32-11.6)	p=0.97*
Male	124	10 (7.52-12.4)	
Age (years)			
<65 years	115	12(8.6-15.3)	p=0.61*
>65 years	72	9 (6.5-11.4)	
Pathology			
Adenocarcinoma	138	11 (8.7-13.2)	p=0.28*
Signet ring cell	46	9 (5.43-12.5)	
Mucinous	1	26 (8.23-11.7)	
Differentiation			
Good	7	21 (0.36-41.6)	p=0.26*
Moderate	45	10 (5.7-14.2)	
Poor	53	12 (9.06-14.9)	
SII			
<600	60	12 (15.3-30.6)	p=0.13*
>600	127	9 (13.9-25.8)	
Marker elevation			
Yes	140	12 (11.3-22.6)	p=0.06*
No	107	17 (9.3-14.6)	
Surgery			
Yes	130	13 (11.1-14.8)	p<0.001*
No	27	4 (2.3-5.6)	

*Kaplan-Meier survival analysis, OS: Overall survival

The study conducted by Wang et al. (20) in patients with gastric cancer found that a high SII value was associated with poor prognosis in stage 1-3 patients with cancer. It also showed that high SII values were associated with advanced age, advanced stage, poor histological subtype, increased local lymph node involvement, and distant metastasis. Again, this study revealed no significant relationship between SII and survival in stage 4 patients. Similarly, in our study, no statistically significant relationship was found between survival and SII in patients with metastatic gastric cancer. However, survival was shorter in the high SII group (20).

Chen et al. (6) evaluated the prognostic significance of SII in the pre-neoadjuvant period in patients with advanced gastric cancer, where patients with metastatic cancer were not included. Moreover, they found that patients with low SII levels had a higher survival rate and were better in terms of 1-3 and 5-year disease-free survival compared to the group with high SII. They also showed that SII is an independent prognostic factor (6).

A meta-analysis conducted by Sun et al. (23) on patients with metastatic gastric cancer who underwent palliative gastric surgery concluded that gastrectomy significantly and positively affected survival. In our study, in line with the results of this meta-analysis, the median survival was statistically significantly better in patients who underwent primary surgery than those who did not (13 months vs. 4 months; $p<0.001$).

Serum tumor markers are tests used in the evaluation of response to the treatment and during the follow-up in patients with gastric cancer. Various studies have reported that high carcinoembryonic antigen (CEA) levels at the time of diagnosis are an independent prognostic factor and associated with a shorter survival (24,25). In our study, patients with high serum CEA levels exhibited shorter survival as compared to the group with low levels, but they did not reach the limit of significance, which was attributed to the low number of cases.

Study Limitations

There were several limitations to our study. First, it was designed as a retrospective, single-center study and had a limited number of patients. Second, although SII is an independent predictor in many tumors, its sensitivity and specificity are not high. In future, prospective, randomized, and well-designed studies are needed to optimize the appropriate cut-off value.

CONCLUSION

SII is an effective, easily applicable, reproducible, and inexpensive marker, and can be used in patients at an early and advanced stage cancer to show prognosis. In our study, we found that a high SII value was associated with poor survival, although not statistically significant. It was also found that patients with metastatic gastric cancer who underwent primary surgery exhibit higher survival. However, larger prospective studies are needed to clarify the prognostic value of SII in patients with metastatic gastric cancer.

Ethics

Ethics Committee Approval: Ethical approval, date: 23/07/2020/07, decision number: 126, was obtained from the Ethics Committee of Kayseri Training and Research Hospital.

Informed Consent: Consent was obtained from the patients that the file information would be used before the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.D., Design: H.D., M.İ., Data Collection or Processing: H.D., İ.B., Y.K., Analysis or Interpretation: H.D., İ.B., Literature Search: H.D., S.K.E., M.İ., Writing: H.D.

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Correlation of Sleep Disorders with Suicidal Ideation in Patients with Major Depressive Disorder

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Abstract

Objective: This study aimed to investigate the correlation of subjective sleep disorders with suicidal ideation in patients with major depressive disorder (MDD).

Methods: The study included 60 patients attending at University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital, Clinic of Psychiatry with diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders-V diagnostic criteria. Cases completed a sociodemographic data form, Beck Depression Inventory (BDI), Suicidal Ideation scale (SIS), and Pittsburgh Sleep Quality Index (PSQI).

Results: Correlation analysis identified positive significant correlations between number of disease attacks with PSQI and SIS points. Positive significant correlations were found between SIS total points and PSQI-1, PSQI-5, PSQI-6, PSQI-T, and BDI points. Regression analysis identified that PSQI-5 and PSQI-T points were each a predictor for SIS values.

Conclusion: Data obtained in this study confirmed that sleep disorders may have an effect on suicidal thoughts among MDD cases.

Keywords: Major depressive disorder, sleep disorder, suicidal ideation

INTRODUCTION

Major depressive disorder (MDD) is the most common mood disorder included under the heading of depression disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V classification, which seriously disrupts functioning and may occur as a single attack or recurring attacks (1). It is a serious mental disorder that may be observed commonly, with high rates of becoming chronic and recurrence, causing physical and psychosocial disability (2). Risk factors for suicide in MDD are reported to be hopelessness, alcohol dependence or alcohol abuse, low social and occupational functioning levels, and poor perceived social support (3). In addition, an association is reported between sleep disorders with suicidal ideation and behavior (4). Risk factors in terms of suicide are accepted as insomnia, hypersomnia, nightmares, and panic attacks during sleep (5).

In Turkey, the correlation between sleep disorder and suicidal thoughts in MDD is limited to studies by Ağargün et al. (6) Agargun and Cartwright (7) stated that sleep disorders were associated with suicidal ideation in depression. This led to the curiosity about the relationships between disease attack frequency and disease duration, which may determine the progress of MDD, with both sleep disorders and suicidal ideation.

This study aimed to investigate the relationship between sleep disorders with suicidal ideation in patients with MDD. Our main hypothesis is that sleep disorder in MDD is associated with suicidal ideation. Our secondary hypothesis is that sleep disorder is a determinant for suicidal ideation.

METHODS

The study included 60 patients diagnosed with MDD according to the DSM-V diagnostic criteria, who are attending

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at Prof. Dr. Cemil Taşçıoğlu City Hospital Psychiatric Clinic. The research was permitted by the Clinical Research Ethics Committee (12.10.2020/396) of the hospital and abided by the principles stated in the Helsinki Declaration. Participants were informed about this study and verbal and written consent were obtained.

Patients with past or current bipolar disorder, psychotic disorders, alcohol and substance abuse disorders, or severe neurological diseases were excluded from the study. Diagnosis of patients included in the study was confirmed with the semi-structured clinical interview form for DSM (SCID)-5 interview. Patients completed the Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI), and Suicidal Ideation Scale (SIS).

Scales Used

SCID-5: This is a structured interview form developed by First (8). Turkish adaptation and reliability studies were performed by Elbir et al. (9).

Sociodemographic information form: This form includes questions about the patients' demographic characteristics (age, sex, educational status, year of onset of depression, number of time depression was experienced, and hospital admissions due to depression).

BDI: This scale measures the bodily, affective, and cognitive symptoms observed in depression. It is a self-report scale containing 21 symptom categories. Highest point that can be obtained is 63. High total points show the severity of depression. It was developed by Beck et al. (10), and validity and reliability studies for our country were performed by Hisli (11).

SIS: It comprises 17 questions in which the questions are answered as yes/no, and the total score from the scale varies between 0-17. The SIS is a self-reported test that was developed in 1989 by Levine et al. (12). This scale aims to determine the intensity of suicidal ideation and Turkish validity, and reliability studies were performed by Dilbaz et al. (13). It comprises 17 questions with yes/no answers, and total points vary from 0 to 17. High points indicate the presence of pronounced suicidal ideation.

PSQI: The PSQI was developed by Buysse et al. (14). PSQI is a sleep survey assisting to determine the quality of sleep, amount of sleep, and presence and severity of sleep disorders experienced by a person within the last month. Turkish validity and reliability studies were performed by Ağargün et al. (15). This scale contains 19 items and comprises seven subcomponents of subjective sleep quality (PSQI-1), sleep latency or the duration to fall asleep (PSQI-2), sleep duration (PSQI-3), habitual sleep efficiency (PSQI-4), sleep disturbance (PSQI-5), sleep medication use (PSQI-6), and daytime functioning (PSQI-7). Total PSQI score is obtained by adding the seven subscores, and is between 0 and 21. PSQI total score definitively differentiates those who sleep well (PSQI total score of ≤5) from those who sleep poorly (PSQI of >5).

Statistical Analysis

When analyzing findings obtained in the study, statistical analyses used the International Business Machines Corporation Statistical Package for the Social Sciences Statistics 22 program (IBM SPSS, Turkey). Pearson correlation analysis was used to investigate the correlations between parameters which fit normal distribution. Spearman correlation analysis was used to investigate the correlations between parameters without normal distribution. Linear regression analysis was used to assess the effect of PSQI subscales on SIS.

RESULTS

The study included 38 female and 22 male patients with MDD. Mean age of patients was 38.24±10.28 years with mean educational duration of 11.24±4.36 years.

Correlations of PSQI total, SIS total, BDI total, and disease onset age, disease attack numbers (DAN), and disease duration for patients with MDD are given in Table 1. Positive significant correlations were identified between DAN with PSQI-T, SIS, and BDI points.

Table 1. Correlations between PSQI, and BDI points of patients with MDD with disease characteristics

	PSQI	SIS	BDI	DAN	DD
PSQI	1	0.316*	0.462**	0.284*	0.098
SIS	0.316*	1	0.582**	0.308*	0.102
BDI	0.462**	0.582**	1	0.535**	0.462**
DAN	0.284*	0.308*	0.535**	1	0.567**
DD	0.098	0.102	0.462**	0.567*	1

*p<0.05, **p<0.01 (pearson correlation), SIS: Suicidal Ideation scale, PSQI: Pittsburgh Sleep Quality Index, BDI: Beck Depression Inventory, DAN: Disease attack number, DD: Disease duration, MDD: Major depressive disorder

Correlations between SIS subscales and total points, PSQI subscales and total points, and BDI for patients with MDD are given in Table 2. Positive significant correlations were identified between SIS total points with PSQI-1, PSQI-5, PSQI-6, PSQI-T, and BDI points.

Only PSQI-5 and PSQI-T dimensions was statistically significant when the effect of PSQI subscale points on SIS total points is assessed with linear regression analysis. Analysis of these dimensions identified R^2 0.416 and corrected R^2 0.216, and these were statistically significant (F: 18,630, p=0.001) (Table 3).

DISCUSSION

In this study, disrupted sleep quality in patients with MDD is identified to be associated with suicidal ideation.

With recurrent depression, insomnia may worsen just before the next depressive episode begins. Insomnia can also pose a significant risk for new depression attacks. Armitage stated that permanent sleep problems, especially insomnia, elevated the risk of requiring increased medication, in addition to the risk of recurrence and poor progression (16). In our study, DAN was identified to be significantly correlated with both disrupted sleep quality and suicidal ideation. Additionally, a significant correlation was identified between the PSQI-6 dimension with depression and severity of suicidal ideation. The high risk of recurrence of the disease in depression, where sleep disorders are at the forefront, is a factor that increases the suicide attempt of sleep disturbance independent to the disease (17). In this context, in the cycle of insomnia and depression which may have double-sided effects (18), treatment of sleep disorders may reduce the number of recurrences (19).

Poor sleep quality, early insomnia, and lack of restful sleep were reported to be associated with suicide risk (20). In addition, studies investigating the correlations between sleep, depression, and suicidal tendency variables reported that sleep disorders like difficulty falling asleep, early waking, poor sleep quality, and nightmares were associated with depressive mood and suicidal ideation (21,22). In our study, disruption of both subjective sleep quality and total sleep quality were identified to be correlated with suicidal ideation in patients with MDD in accordance with the literature. It was reported that sleep onset insomnia problems were associated with suicidal ideation in patients with MDD (23). In our study, when early insomnia symptoms as assessed by the PSQI-5 dimension are evaluated, they were identified to be correlated with suicidal ideation, supporting this data. In this context, the correlation of sleep disorders with suicidal ideation may be explained by patients having difficulty falling asleep due to thoughts like continuous guilt and worries, in addition to frequent disturbance of sleep (24). Moreover, nighttime is an active time due to disrupted

Table 2. Correlations between BDI and SIS subscales and total points with PSQI subscales and total points for patients with MDD

	SIS	PSQI-1	PSQI-2	PSQI-3	PSQI-4	PSQI-5	PSQI-6	PSQI-7	PSQI-T	BDI
SIS	1	0.248*	0.132	-0.028	0.122	0.486**	0.422**	0.072	0.386*	0.582**
PSQI-1	0.248*	1	0.484**	0.424**	0.292*	0.302*	0.226*	0.442**	0.628*	0.424**
PSQI-2	0.132	0.484**	1	0.382*	0.432*	0.397*	0.493**	0.382*	0.728**	0.385*
PSQI-3	-0.028	0.424**	0.382*	1	0.562**	0.197	0.202	0.224	0.528**	0.123
PSQI-4	0.122	0.292*	0.432*	0.562**	1	0.325*	0.302*	0.256	0.667**	0.286
PSQI-5	0.486**	0.302*	0.397*	0.197	0.325*	1	0.198	0.467**	0.534**	0.592**
PSQI-6	0.422**	0.226*	0.493**	0.202	0.302*	0.198	1	0.182	0.425**	0.482**
PSQI-7	0.072	0.442**	0.382*	0.224	0.256	0.467**	0.182	1	0.578**	0.145
PSQI-T	0.386*	0.628*	0.728**	0.528**	0.667**	0.534**	0.425	0.578**	1	0.462**
BDI	0.582**	0.424*	0.385*	0.123	0.286	0.592**	0.482	0.145	0.462**	1

*p<0.05, **p<0.01 (pearson correlation), SIS: Suicidal Ideation scale, PSQI: Pittsburgh Sleep Quality Index, BDI: Beck Depression Inventory, MDD: Major depressive disorder

Table 3. Linear regression analysis results for variables predicting SIS total points

Dependent variable	Predictors	B	Std E	Beta	T	p
SIS	PSQI-5	1.398	0.322	0.524	3.423	0.001
	PSQI-T	2.424	0.566	0.237	3.752	0.001

SIS: Suicidal Ideation scale, PSQI: Pittsburgh Sleep Quality Index

circadian rhythms in depression (25) along with inadequate problem-solving capacity caused by lack of sleep (26) which may increase suicidal ideation.

Regression analysis in our study identified the PSQI-5 (sleep disturbance) subdimension and PSQI-T points were each predictors of suicidal ideation. This finding supports previous studies. That is, the deterioration of sleep quality in MDD may affect suicidal thoughts through mood dysregulation (4,7).

CONCLUSION

Our results revealed a correlation between disrupted sleep quality and suicidal ideation in MDD. Sleep disorder in MDD may be a predictor for passive suicidal ideation. Additionally, disrupted sleep quality in patients with MDD was associated with the number of disease attacks in the past.

Sleep disturbances may be associated with clinically significant suicidal thoughts and specific suicidal plans, especially in outpatients with active suicidal thoughts and depressive disorder. Therefore, sleep disorders should be taken into account in the clinical evaluation of depressive patients in terms of suicide risk. Improving sleep quality may prevent the development of depressive symptoms and reduce the likelihood of suicidal ideation. Moreover, it is not possible to determine the cause-outcome relationship due to the cross-sectional design of our study.

Ethics

Ethics Committee Approval: The research was permitted by the Clinical Research Ethics Committee (12.10.2020/396) of the hospital and abided by the principles stated in the Helsinki Declaration.

Informed Consent: Participants were informed about this study and verbal and written consent were obtained.

Peer-review: Externally peer-reviewed.

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ORIGINAL ARTICLE

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Correlation Between Patient-reported Outcome Scores and Objective Functional Assessments Following Surgical Treatment of Achilles Tendon Ruptures

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Abstract

Objective: The purpose of this retrospective study was to investigate the correlation between patient-reported outcome scores and objective functional assessments following surgical treatment of Achilles tendon ruptures (ATR).

Methods: A retrospective review of 53 patients with acute ATR who underwent primary surgical repair was performed. Patient-reported functional outcomes were evaluated with the ATR score (ATRS). Calf atrophy was assessed using the difference between the maximum calf circumference on the involved and healthy sides. The objective functional capacity of the lower leg was assessed using a single-leg standing heel-rise fatigue test. The limb symmetry index (LSI) was calculated as the ratio between the injured and uninvolved limbs. The correlation between variables was tested using the Spearman correlation test.

Results: There were 53 patients (50 males and three females) with a mean age of 40.8±7.7 years (range, 27-59 years). The mean follow-up duration was 35.6±16.6 months (range, 12-80 months). The mean ATRS ranged from 88 to 100 points with a mean of points. There was a mean of 1.15±0.6 cm (range, 0-2 cm) calf circumference difference between the limbs. Calf atrophy was present in 46 (86.7%) patients. The mean LSI (%) was 87.5%±9.3% (range, 61%-100%). No correlation was detected between the ATRS score and calf atrophy and LSI.

Conclusion: The ATRS overestimates the objective functional capacity of the Achilles tendon. New scoring systems that combine both subjective and objective measures are required to assess the overall outcome following an ATR.

Keywords: Achilles tendon rupture, surgical repair, patient-reported outcome scores, functional recovery

INTRODUCTION

Achilles tendon ruptures (ATR) are the most common tendon injuries seen in the adult population (1). They frequently occur in active young males during sporting activities. Although the exact etiology is unknown, chronic degenerative tendinopathy is the significant risk factor (2,3). An acute ATR might be managed either with surgical or conservative treatment methods. However, the optimal treatment of ATR remains controversial. Some authors advocated surgical treatment because of the decreased risk of re-rupture. Others favored conservative treatment because both treatment methods result in similar functional recovery with a lower complication rate. One of the most important reasons for obtaining different results is that the outcome scores and evaluations vary considerably among these studies (4-8).

The most popular patient-reported outcome score for evaluating Achilles tendon functions is the ATR score (ATRS). It is a simple questionnaire comprising 10 questions. Each item is rated between 0 (worst) and 10 (best) with a maximum cumulative score of 100 (9,10). The reliability and validity of ATRS have been shown in previous studies (11-13). However, ATRS only provides

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subjective data of the patients' own opinions about the results. We hypothesized that objective and subjective assessments on the functional outcomes of ATR are variable, and patient-reported outcome measures might overestimate the actual functional capacity following surgical treatment of ATR. The purpose of this retrospective study was to investigate the correlation between residual functional deficits and patient-reported outcome scores following surgical treatment of ATR.

METHODS

Patients and Study Design

A retrospective review of patients who underwent primary repair of acute ATR in authors' institutions between 2013 and 2019 was performed. Patients treated with mini-open or closed techniques, chronic ATR admitted later than four weeks, patients who had missing clinical data and followed less than one year were excluded from the study. During the study under investigation, 67 cases were identified. Of these patients, 14 were excluded, and 53 patients were eligible for study inclusion. This research was undertaken in compliance with the ethical principles set out in the Helsinki Declaration of 1964 and its later modifications. Also, the Institutional Review Board at Antalya Training and Research Hospital approved the study protocol (approval date/issue: 4.3.2021/1.34). All patients provided consent to participate in the study.

Surgical Technique and Postoperative Rehabilitation

All patients underwent open primary repair using either the Krakow or Kessler end-to-end suture technique with non-absorbable sutures. A short or long leg cast was performed in the neutral position of the ankle for three weeks postoperatively, and the patients were mobilized with crutches without weight-bearing. Afterward, the cast was removed, and active ankle exercises were started without weight-bearing. Full-weight-bearing was encouraged at the end of the sixth week. Participation in recreational sporting activities was allowed after the sixth postoperative month.

Functional Evaluations at the Final Follow-up

All patients were followed for at least 12 months. At the final follow-up, the Turkish version of the ATRS was used to evaluate the patient-reported functional outcome (14). The functional capacity of the lower leg was assessed using the single-leg standing heel-rise fatigue test. The patients were asked to perform repetitive heel-rises as many and as quickly as possible until reaching fatigue. The total number of repetitions was counted and recorded. First, the healthy side and then the injured side were tested. The limb symmetry index (LSI) was calculated as the ratio between the injured and uninvolved limbs and expressed as a percentage. The maximum calf circumference was measured on both sides, and the difference was recorded as an objective measure of calf atrophy. Finally, the ankle range of motion was evaluated.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics Base v.23 for Windows. Descriptive statistics of the continuous and categorical data are presented as the mean ± standard deviation, range, and frequency distribution. The Kolmogorov-Smirnov test was used to determine whether the data were distributed normally. The correlation between variables was tested using the Spearman correlation test. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

There were 53 patients (50 males and three females) with a mean age of 40.8±7.7 years (range, 27-59 years). The right side was involved in 29 (54.7%) patients and left in 24 (45.3%) patients. The mean follow-up duration was 35.6±16.6 months (range, 12-80 months). Superficial wound infection was seen in six (11.3%) patients and was treated with oral antibiotics. Permanent sural nerve injury was seen in three (7.5%) patients. Ankle dorsiflexion was limited to four patients (10° in three and 20° in one). Two (3.7%) patients had re-rupture and underwent revision surgery. No other complications were recorded. A summary of the demographic and clinical characteristics of patients is presented in Table 1.

The mean ATRS ranged from 88 to 100 points with a mean of points. There was a mean of 1.15±0.6 cm (range, 0-2 cm) calf

Table 1. Demographic and clinical characteristics of patients

Variable	Mean ± SD	Range
Age (years)	40.8±7.7	27-50
Height (cm)	177.3±7.3	160-193
Weight (kg)	87.2±12.5	60-125
BMI (kg/m^2)	27.6±2.9	22.7-38.5
Follow-up (months)	35.6±16.9	12-80
Injured side single-leg rise test (n)	21.7±7.3	6-38
Healthy side single-leg rise test (n)	24.6±7.5	8-40
LSI (%)	87.5±9.3	61.1-100
Calf atrophy (cm)	1.15±0.6	0-2
ATRS (points)	97.6±2.4	88-100

BMI: Body mass index, ATRS: Achilles tendon rupture score, LSI: Limb symmetry index, SD: Standard deviation

circumference difference between the limbs. Calf atrophy was present in 46 (86.7%) patients. The mean LSI (%) was 87.5%±9.3% (range, 61%-100%). No correlation was detected between the ATRS score and calf atrophy, and LSI (Table 2, Figure 1). Patients were divided into two groups according to their LSI score. The first group consisted of patients who had LSI scores less than 90%, and the second group had scores greater than 90%. Although the LSI was significantly different between groups (80.6±8.6 vs. 94.2±2.9, p=0.001), the ATRS was similar (97.6±2.0 vs. 97.5±2.7, p=0.798).

DISCUSSION

In the current study, no relationship was found between patient-reported outcome measures and objective measures following surgical treatment of ATR. Although significant residual functional limb asymmetry was detected in half of the patients, ATRS remained similar. Based on our findings, it can be proposed that ATRS does not reflect the actual functional status of the patients. Accordingly, there is an obvious need for better outcome measurement based on patient outcomes and objective functional measures.

In general, two criteria are used to evaluate the results after Achilles tendon injuries. The first depends on the physician's measurements through the physical examination and certain specific tests. The other is a set of patient-reported outcome measurements (PROM) that has become increasingly important in recent years. ATRS is the most commonly used PROM after Achilles tendon injuries (15). However, the minimal detectable change value is 18.5 points for ATRS (13). Therefore, the ATRS has a low discriminative capacity.

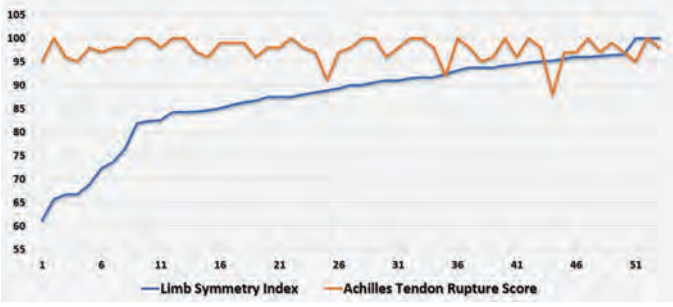

Figure 1. Graph showing the correlation between LSI and ATRS
ATRS: Achilles tendon rupture score, LSI: Limb symmetry index

Table 2. Correlation between the ATRS score and calf atrophy and LSI

		ATRS	LSI	Calf atrophy
ATRS	Correlation coefficient	1.000	-0.090	0.042
	Sig. (2-tailed)	-	0.521	0.765
LSI	Correlation coefficient	-0.090	1.000	0.169
	Sig. (2-tailed)	0.521	-	0.227
Calf atrophy	Correlation coefficient	0.042	0.169	1.000
	Sig. (2-tailed)	0.765	0.227	-

ATRS: Achilles tendon rupture score, LSI: Limb symmetry index, Sig: Significance

Few published studies support our findings. Keene et al. (16) compared the potential benefit of platelet-rich plasma (PRP) injection with conservative treatment of ATR. There was no significant difference in ATRS between patients at the end of 24 weeks, but the LSI was significantly better in the PRP group. Westin et al. (17) evaluated the factors affecting the outcome one year after ATR in 391 patients. Although the older age at injury was a predictive factor for concentric Achilles power, no significant predictor was related to the ATRS. Brorsson et al. (18) examined calf muscle performance deficits seven years after ATR in 66 patients. Eighty-five percent of their patients scored more than 85 points on the ATRS, but only 29% of the patients had an LSI higher than 85% in calf muscle endurance and calf muscle concentric power. Kastoft et al. (19) compared early versus delayed weight-bearing in the non-operative treatment of acute ATR in 37 patients. At the end of 4.5 years, ATRS showed no association with heel-rise work or heel-rise height (19). Silbernagel et al. (20) examined the functional deficits in 78 patients with ATR using the heel-rise endurance test in the sixth and twelfth months. The authors found no significant correlations between ATRS and heel-rise endurance at the 6- or 12-month evaluations (20). All these previous findings show that ATRS is not a sensitive outcome measure to evaluate the objective functional capacity of the Achilles tendon.

Study Limitations

The current study has some limitations. First, the functional capacity of the Achilles tendon was measured with a simple fatigue test. Although this is accepted as a good indicator of functional capacity, other sophisticated methods such as isokinetic muscle strength measurements were not available (21). The study assessed a relatively limited number of patients; however, the follow-up period was sufficiently long.

CONCLUSION

ATRS, which is the most commonly used PROM in ATR research, cannot show differences in the objective functional capacity following surgical treatment of the ATR. Future studies should focus on developing more accurate scoring systems that combine both objective and subjective measures.

Ethics

Ethics Committee Approval: The Institutional Review Board at Antalya Training and Research Hospital approved the study protocol (approval date/issue: 4.3.2021/1.34).

Informed Consent: All patients provided consent to participate in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Perioperative and Early Renal Functional Outcomes of Laparoscopic and Open Partial Nephrectomy in Clinical T1 Renal Carcinoma

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Abstract

Objective: To compare the perioperative and postoperative outcomes of open partial nephrectomy (OPN) and laparoscopic partial nephrectomy (LPN) in clinical T1 renal carcinoma.

Methods: We examined the records of patients who underwent partial nephrectomy at our clinic between January 2016 and May 2020. The records of 20 patients who underwent LPN were compared with the records of 50 patients who underwent OPN. The demographic findings, tumor size, operation time, warm ischemia time (WIT), PADUA nephrometry score, complications, blood loss, preoperative and early postoperative estimated glomerular filtration rate (eGFR), creatinine, and hemoglobin (Hb) values, surgical margins, and hospital stay time of both surgical techniques were compared. Student's t-test and Mann-Whitney U test were used in the statistical analysis. A p value ≤0.05 was considered significant.

Results: Of the 70 patients, 45 were men and 25 were women, with 42 patients diagnosed with right-sided renal cell carcinoma (RCC) and 28 patients diagnosed with left-sided RCC. The median age was 55 years. Fifty-four patients were diagnosed with clinical T1a RCC, and 16 patients were diagnosed with clinical T1b RCC. The median WIT was shorter in the LPN group. The median tumor size was larger in the OPN group. There was a statistically significant difference between PADUA score and operation time in OPN, while there was no significant difference between OPN and LPN in terms of preoperative and early postoperative eGFR, creatinine, and Hb values. In OPN group, the postoperative creatinine increase was statistically significant compared with preoperative value. This difference was not statistically significant in the LPN group. Clavien-Dindo complications and hospital stay time were higher in OPN.

Conclusion: LPN is an alternative technique to OPN for treatment of clinical T1 RCC when performed by experienced urologists in experienced clinics. It was concluded that postoperative early renal function is better in LPN.

Keywords: Partial nephrectomy, RCC, laparoscopic surgery, acute kidney injury

INTRODUCTION

Renal cell carcinoma (RCC) constitutes 2%-3% of all cancers (1). Radiologic imaging techniques have recently advanced, and due to this development, we can diagnose kidney tumors in early stages compared with previous times (2,3). Recently, partial nephrectomy (PN) is considered the most prominent method for treating CT1 kidney tumors (3).

The main purpose of PN in RCC treatment is to protect the kidney parenchyma as much as possible and reduce the decrease in glomerular filtration. In approximately 20% of patients, acute kidney injury (AKI) develops after PN (4).

Laparoscopic PN (LPN) has become the standard surgical treatment for T1a and some T1b tumors in recent years (5). There are many studies comparing the oncologic and functional results

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of LPN and open PN (OPN) for renal masses in the literature. It was found that the results of both techniques are comparable, and LPN has some advantages over OPN (6-9).

According to the recent literature, there was no definite superiority between OPN, LPN, and robotic PN methods in terms of perioperative outcomes and AKI (10).

We analyzed the perioperative and early renal functional outcomes regarding AKI in our patients who performed LPN and OPN for treatment of clinical T1 RCC.

METHODS

This is a retrospective single-center study (Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Turkey), including 86 patients who underwent either OPN or LPN between January 2016 and May 2020. Seventy patients (45 patients were males and 25 patients were females) with clinical T1N0M0 RCC are included in this study. Patients with missing data (n=7), multiple tumors (n=1), and benign lesions (oncocytoma n=4, angiomyolipoma n=2, and benign cyst n=2) were excluded from the study.

The study followed the ethical recommendations of the Declaration of Helsinki and was approved by the Ethics of Research Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (14.04.2020; number: 119). All the participants in this study have signed an informed consent form.

The mass was diagnosed with computed tomography or magnetic resonance imaging and was treated with OPN or LPN. Fifty patients underwent OPN, and 20 patients underwent LPN.

Renal function was assessed by measuring serum creatinine and estimated glomerular filtration rate (eGFR). The severity of surgical complications was graded according to the modified Clavien classification system. Postoperative histopathology of the tumors, Fuhrman grade, and surgical margin status were recorded. LPN was performed by one experienced urologist, while OPN was done by another two experienced urologists.

Our primary aim was to compare OPN and LPN techniques in terms of the demographic findings, tumor size, PADUA nephrometry score, warm ischemia time (WIT), intraoperative complications, blood loss, operative time, postoperative Clavien-Dindo complications, surgical margins, and hospital stay time. Our secondary aim was to compare the two techniques in terms of AKI (eGFR and creatinine values before the operation and on the postoperative third day).

Statistical Analysis

Number Cruncher Statistical System (2007) (Kaysville, Utah, USA) was used to perform the statistical analysis with a significance level of $p \leq 0.05$.

We used Student's t-test (years and WIT), Mann-Whitney U test (operation time, PADUA score, hospital stay time, eGFR, creatinine, urea, and hemoglobin (Hb), Pearson's chi-square test (side, male-to-female ratio), Fisher's exact test (bleeding and pathology), Fisher-Freeman-Halton test (Clavien classification and Fuhrman grade), Wilcoxon signed-rank test (creatinine, urea, eGFR, and Hb) in our study.

RESULTS

Demographics

The study included 70 patients, of which 20 patients (28.6%) underwent LPN and 50 patients underwent OPN (71.4%). Fifty-four patients (77.1%) were diagnosed with clinical T1a RCC and 16 patients (22.9%) were diagnosed with clinical T1b RCC. 60% (n=42) of the patients had right-sided lesions, while 40% (n=28) had left-sided lesions. The descriptive characteristics of the 70 patients who underwent either OPN or LPN are reported separately in Table 1.

In the OPN group, the operation time and WIT are longer, and the size of the tumor is bigger. Of 70 patients, 19 (27%) had Clavien-Dindo complications, grades 1-3 [14 patients (28%) in the OPN group; 5 patients (20%) in the LPN group; p=0.451]. Forty-five patients (64.3%) had a PAUDA score of six to seven, 17 patients (24.3%) had a score of eight to nine, and eight patients (11.4%) had a score ≥10.

There is no statistically significant difference between the two techniques in terms of operation time (p=0.973), WIT (p=0.824), size of tumor (p=0.865), PAUDA score (p=0.195), Clavien-Dindo complications (p=0.451), hospital stay time (p=0.206), preoperative Hb (p=0.274), and postoperative Hb values (p=0.553).

The difference between pre- and postoperative Hb values is statistically significant in OPN and LPN groups (p=0.01 in OPN; p=0.043 in LPN).

Creatinine and eGFR values of patients who underwent either OPN or LPN are shown in Table 2.

Postoperative creatinine increase is statistically different in OPN (p=0.001) and postoperative eGFR decrease is statistically different in both approaches (OPN: p=0.001; LPN: p=0.001).

The relationship between PADUA score and WIT, operative time, and Clavien complications is reported in Table 3.

There is a statistically significant difference between PADUA score and operation time in OPN (r=0.311; p=0.028). There is no statistically significant difference between PADUA score and operative time, WIT, and Clavien complications in LPN (p>0.05).

We found surgical margin positivity in two patients who underwent OPN, although we did not see a recurrence during eight and fourteen months of follow-up.

In the OPN group, three patients underwent a transperitoneal PN, and five patients had 12th rib resection. One patient with a PADUA score of 12 had undergone nephrectomy because of bleeding during the operation. Perioperative ultrasonography was performed to locate the tumor in two patients.

In the LPN group, we opted for OPN in one patient with a PADUA score of 11 because of colon injury. The urinary fistula occurred and lasted 18 days in one patient who underwent LPN, and it lasted for 21 days in another patient, who underwent OPN.

Table 1. Descriptive characteristics of patients who underwent either OPN or LPN

		OPN N (%)	LPN N (%)	p value
Age (y)	Min-max (median)	26-81(55)	44-77(59)	0.176
BMI (kg/m^2)		23-30 (25)	22-28 (24)	0.45
Sex	Male Female	31 (62) 19 (38)	14 (70) 6 (30)	0.528
Side of involvement	Right Left	29 (58) 21 (42)	13 (65) 7 (35)	0.589
Clinical T stage	T1a T1b	38 (76) 12 (24)	16 (80) 4 (20)	0.964
Operation time (min)	Min-max (median)	120-300 (174)	120-300 (162)	0.973
Warm ischemic time (min)	Min-max (median)	8-35 (19)	10-28 (18)	0.824
Size of tumor (cm)	Min-max (median)	1.5-6.5 (3.2)	1-7 (2.5)	0.865
PADUA score	Grade 1 Grade 2 Grade 3	6-12 (7)	6-11 (7)	0.195
Clavien-Dindo complication (n=19)	Min-max (median)	3 (21.4) 8 (57.1) 3 (21.4)	0 (0) 2 (40) 3 (60)	0.451
Hospital stay time (day)	-	3-21 (6)	4-16 (5.5)	0.206
Pre-op hemoglobin Post-op hemoglobin	Min-max (median) Min-max (median)	12-15.8 (14.1) 8.8-14.8 (11.9) p=0.01	13.2-16 (15) 10.0-13.7 (13) p=0.043	0.274 0.553
Difference between postop and preop values	Min-max (median)	-6.1/-0.2 (-2)	-13.2/-2 (-2.4)	0.118

OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy, min: Minimum, max: Maximum

Table 2. Creatinine and eGFR values of patients, who underwent either OPN or LPN

		OPN (n=50)	LPN (n=20)	p value
Pre-op creatinine (mg/dL)	Min-max (median)	0.4-2 (0.8)	0.6-2.1 (0.9)	0.112
Post-op creatinine (mg/dL)	Min-max (median)	0.5-11 (0.9)	0.6-1.9 (1)	0.466
p value	-	0.001	0.184	-
Difference between postop and preop values (mg/dL)	-	-0.4-10.4 (0.2)	-1.3-1 (0.1)	0.349
Pre-op eGFR (mL/min/1.73 m^2)	Min-max (median)	40-115 (92.5)	53-108 (94.5)	0.995
Post-op eGFR (mL/min/1.73 m^2)	Min-max (median)	23-110 (84.5)	41-104 (81.5)	0.672
p value	-	0.001	0.001	-
Difference between postop and preop values (mL/min/1.73 m^2)	Min-max(median)	-30-11 (-8.5)	-30-13 (-11.5)	0.558

eGFR: Estimated glomerular filtration rate OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy, min: Minimum, max: Maximum

The transfusion rate (intra- and postoperatively) in LPN and OPN group was 10% and 16%, respectively (p=0.761).

Of 86 patients, eight (9.3%) had benign lesions (oncocytoma n=4; angiomyolipoma n=2; benign cyst n=2).

Of 70 patients, 42 (60%) had clear cell RCC, 17 (24.4%) had papillary RCC, and 11 (15.7%) had chromophobe RCC.

Thirteen (18.6%) patients had grade 1 Fuhrman, 35 (50%) patients had grade 2 Fuhrman, and 22 (31.4%) patients had grade 3 Fuhrman.

DISCUSSION

Previously, the conventional treatment of kidney tumors was radical nephrectomy. However, PN was performed in patients with small masses with solitary kidney or multiple bilateral tumors.

Today, the success rates, oncological results, and complication rates of PN are comparable with the results of radical nephrectomy for treating renal tumors. PN can be an open, laparoscopic, or robotic surgery. Due to the need for technical experience and devices to perform a laparoscopic surgery, it took some time for LPN to become an alternative to OPN. We observed that surgical and functional outcomes of LPN and OPN were comparable in our study. Tumor size, operative time, WIT, blood loss, Clavien complications, hospital stay time, eGFR decrease, and creatinine increase were higher in the OPN group, but the difference between the two approaches was not statistically significant in our study cohort.

In the study by Gill et al. (7), in the LPN group, blood loss was less and hospital stay time was shorter, while WIT was longer. In the study by Minervini et al. (11), the median operative time in OPN and LPN is 131.2 min and 143.0 min, respectively, while, in our study, the median operative time in OPN and LPN is 174 min and 162 min, respectively. Shorter operation time and hospital stay time reduce the perioperative and postoperative morbidity in patients (12). Hospitalization time is shorter in all LPN groups in the literature (13), which agrees with our results.

Table 3. The relationship between PADUA score and warm ischemia time, operation time, and Clavien-Dindo complications in OPN and LPN

		Total	OPN (n=50)	LPN (n=20)
Clavien-Dindo complications (n=19)	r	0.055	0.195	0.354
	p	0.824	0.504	0.559
Warm ischemic time (min)	r	-0.035	0.067	-0.287
	p	0.776	0.644	0.220
Operation time (min)	r	0.205	0.311	-0.029
	p	0.088	0.028*	0.905

OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy

In our study, Clavien-Dindo complications were higher in the OPN group, which is probably is related to higher PADUA scores and bigger size of tumors.

In Marszalek's study, the overall complication rate in OPN and LPN groups was 22% and 24%, respectively (13). Overall, the complication rates in the LPN group in the literature range from 9% to 33% and in the OPN group range from 4.1% to 38.6% (14).

Total complications were not statistically significant between OPN and LPN groups, but intraoperative surgical complications were higher for the OPN group in A. Minervini's study (11,13).

WIT (minimum-maximum-median) in the OPN and LPN groups was 8-35 (19) min and 10-28 (18) min, respectively (p=0.824) in our study group. The LPN groups had a significantly longer WIT in many studies in the literature (11), although some studies reported shorter WIT in the LPN groups (7,13). Bravi et al. (15) showed that LPN and robotic PN had a longer ischemia time than OPN. In our study, shorter WIT in the LPN group may be related to the surgeon's experience and complexity of the tumor.

The surgical margin was positive in two patients who underwent OPN in our study. A higher PADUA score and a larger size of tumor can affect this finding. A multicenter analysis of LPN showed positive surgical margins (PSM) in 1.8%-2.4% of the patients (16). In Kwon's et al. (17) study, the PSM rate of OPN is 7%. In Andrea Minervini's study, the incidence of PSM was not significantly different between both groups (3.5% for OPN and 3% for LPN) (11). Bravi et al. (15) showed that minimally invasive approaches did not affect the risk of PSM when compared with open surgery. Only 4% of patients with PSM will develop a local recurrence (17). Our two patients with PSM did not experience recurrence during the eight and fourteen months of followup. However, we must follow up these patients closely.

In our study, the difference between the two approaches in terms of pre- and postoperative Hb values is statistically significant (p=0.001 in OPN and p=0.043 in LPN). The decrease in Hb values postoperatively in both approaches is not statistically different (p=0.118). These findings correlate with the literature.

In Marszalek et al.'s (13) study, the transfusion rate was 6% in the LPN group and 11.0% in the OPN group (p=0.2). The transfusion rate in our LPN group was 10% and in the OPN group 16% (p=0.761). In Minervini et al.'s (11) study, the mean intraoperative blood loss was slightly higher for the OPN group,

but it was not statistically significant (221 cc vs. 164 cc). In White et al.'s (18) study, the median blood loss was 200 mL (100 mL-375 mL) in patients who underwent robotic PN.

The increase in postoperative creatinine ($p=0.001$; $p<0.01$) and decrease in eGRF ($p=0.001$; $p<0.01$) are statistically different in our OPN group. Preoperative and postoperative creatinine and eGFR values are not statistically different in OPN and LPN groups (creatinine: $p=0.349$; eGRF: $p=0.558$; $p>0.05$).

AKI develops in approximately 20% of patients after PN (4). AKI can be temporary and may take up to 24-72 h or can be persistent (19). Bravi et al. (15) demonstrated that AKI is associated with long-term renal function and duration of the injury. The longer the duration of AKI (specifically exceeding the third day), the more reduced the long-term renal function (15).

Jimenez-Romero et al. (20) showed that, in the LPN group, patients weighing more than 84 kg, the tumor size being larger than 4 cm, WIT exceeding 26 min, operation time exceeding 200 min are more likely to cause renal function impairment after the operation. In their study, 18 patients (37.5%) preserved their renal function and 30 (62.5%) had a renal function impairment postoperatively (20).

Martín et al. (21) stated that if WIT exceeds 25 min, each additional minute increases renal function deterioration (RFD) by 5%-6%. The protected renal parenchyma is an important factor in RFD (21). The median size of the tumors in patients with deteriorated renal function was 1.1 cm larger than that in patients without RFD (20).

Marszalek et al. (13) found that the decrease in eGFR rate in both groups was similar ($p=0.8$). Minimally invasive techniques (both laparoscopic and robotic) had a lower risk of AKI than open surgery (both $p<0.0001$) (15). Our findings in the LPN group are correlated with this study.

White et al. (18) found median eGFR decrease of 11.1 mL/mm/1.73 M2 in his robotic PN group, whose patients had renal masses with a nephrometry score of ≥7. In our study, the median GFR decrease is 8.5 and 11.5 in OPN and LPN groups, respectively. The mechanisms determining AKI after PN is not fully understood (22).

The age of the patient, preoperative kidney function, renal perfusion during surgery, WIT, operative time, operation technique, intraoperative blood loss, resected tumor volume, type and-duration of anesthesia, and surgeon's experience may affect AKI. If AKI is not transient (≥3 day), the kidney's function can be worse in the long-term.

There is a statistically significant difference between PADUA score and operative time in the OPN group ($r=0.311$; $p=0.028$) in our study cohort. The other relationships in both approaches are comparable.

The possibility of having a positive trifecta in patients who have a PADUA score <10 and treated robotically was higher than in patients who underwent OPN and LPN (15).

Altunrende et al. (23) found a correlation between total RENAL nephrometry score and WIT after robotic PN (Spearman's correlation coefficient: 0.54; $p<0.0001$). In this study, they declared that posteriorly located tumors require complete mobilization of the kidney, and this increases the adjacent tissue damage (23).

When PADUA score increases, the complexity of the tumor and complications, operation time, hospital stay time, and bleeding increase. PN in patients with high PADUA score (≥10) is usually performed by open surgery (15). The rate of converting from PN to radical nephrectomy during the operation was approximately 5% regardless of the surgical technique (24). The rate of converting to open surgery in LPN and robotic PN was 7 (1%) and 1 (<1%), respectively, in this study (15).

We changed the decision from PN to radical nephrectomy in one patient in the OPN group because of bleeding and a PADUA score of 12. We converted LPN to OPN in one patient because of bleeding and injury of the colon with a PADUA score of 11.

The urinary fistula occurred and lasted 18 days in one patient, who underwent LPN, and lasted 21 days in another patient, who underwent OPN.

CONCLUSION

LPN is an alternative technique to OPN for treatment of clinical T1 RCC by experienced urologists in experienced clinics. Postoperative creatinine increase in OPN is more obvious. All perioperative outcomes in OPN and LPN are comparable to each other in T1 RCC.

Ethics

Ethics Committee Approval: The study followed the ethical recommendations of the Declaration of Helsinki and was approved by the Ethics of Research Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (14.04.2020; number: 119).

Informed Consent: All the participants in this study have signed an informed consent form.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

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Perilunate Injuries as an Important Cause of Hand Morbidity

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Abstract

Objective: Perilunate injuries are rare but highly overlooked injuries among hand injuries. These injuries, primarily seen in the young population after high-energy trauma, cause significant disability or loss of labor. We aimed to share the 2-year follow-up results of patients who were operated on for perilunate injury.

Methods: Twelve patients diagnosed with perilunate injuries were included in the study. Seven patients had trans-scaphoid, three patients had trans-scaphoid and trans-radial, and two patients had trans-scaphoid and transcapitate fractures. Five cases were operated on using the dorsal approach, three cases with the volar, and the remaining four cases using the combined approach.

Results: The patients were followed for an average of 25.7 (range, 17-34) months. At the end of the follow-up period, scaphoid avascular necrosis was observed in two patients and lunate avascular necrosis in one patient. Three patients were in stage 4 wrist osteoarthritis; two patients were in stage 3; six patients were in stage 2, and one patient was in stage 1. Four cases were evaluated as good, five cases were fair, and three were poor according to the modified Green and O'Brien clinical evaluation scale.

Conclusion: Perilunate injuries are rare and the most important step in making the suspected diagnosis. Early treatment prevents carpal arthrosis and loss of wrist motion. Care should be taken during diagnosis and treatment. Also, patients should be informed at every stage because perilunate injuries cause permanent morbidity in young patients.

Keywords: Perilunate, fracture, ligament dissociation

INTRODUCTION

High-energy injuries to the wrist are most common in patients under 40 with high functional demand expectations. Depending on the position of the wrist at the time of trauma and the direction of the trauma forces, one or more conditions may occur: distal radius fracture, radiocarpal or perilunate dislocations (PLDs), or other intercarpal dislocations (scaphoid, capitate, trapezium, or hamate) (1). Among these conditions, PLDs are relatively less common and often overlooked during the first examination. PLDs constitute 7% of all carpal bone traumas (2). PLDs and perilunate fracture dislocations (PLD-PLFDs) are often difficult to diagnose. The main problem with carpal ligament injuries is that they cause arthrosis in the medium or long term (starting from the radiocarpal joint and extending to the intercarpal joints (3). Early treatment of perilunate injuries to restore wrist motion and function prevents complications, such as chronic carpal instability and posttraumatic arthrosis, because reconstructive procedures are limited. Our study aims to share the 2-year follow-up results of patients operated on for perilunate injury.

METHODS

Patients diagnosed with perilunate injuries were among the patients admitted to the emergency department because of hand trauma between January 2015, and January 2018 were included in this retrospective study. Fifteen patients were selected for inclusion in the study because of a diagnosis of perilunate injury. Three patients did not participate in the study because they were out of follow-up visits. Twelve patients were included in the study. This article complies with the Ethical Principles for Medical Research Involving Human Subjects of the

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World Medical Association Declaration of Helsinki. University Health Science Turkey, Prof. Dr. Cemil Taşçıoğlu Hospital Ethical Committee (no: 48670771-514.10).

All patients were male. The mean patient age was 32.4 (range, 24-43) years. All cases were due to high-energy trauma occurring after a fall. Falling was due to sports in five patients, whereas the remaining seven patients fell from a certain height due to an accident. The average time from trauma to surgery was 3.4 (range, 1-9) days. Three patients were misdiagnosed at the initial examination but were operated on when they re-applied more than five days after the trauma (six days, eight days, and nine days). The remaining nine patients were operated on as acute cases within the first five days after trauma (Table 1). All patients were evaluated with preoperative and postoperative standard wrist anteroposterior (AP), and lateral (LAT) radiographs, and computed tomography (CT) examinations were performed for patients warranting confirmation.

According to the Herzberg classification, seven patients had trans-scaphoid, three patients had trans-scaphoid and trans-radial, and two patients had trans-scaphoid and transcapitate (TC) fractures (4,5). Five cases were operated using the dorsal approach, three cases using the volar, and the remaining four cases were operated on using the combined approach. Herbert screws or K-wires were used to treat scaphoid fractures. The scapholunate, capitolunate, and lunotriquetral joints were stabilized with K-wires. Mini anchors were used in patients who underwent ligament repair (Figure 1).

Statistical Analysis

SPSS (Statistical Package for Social Sciences) 21.0 and Microsoft Office Excel 2016 programs were used for statistical analysis. Shapiro-Wilk test was used to determine whether the study findings were normally distributed. Comparisons between groups were made using an independent t-test or analysis of variance.

RESULTS

The patients were followed for an average of 25.7 (range, 17-34) months. At the end of the follow-up period, scaphoid avascular necrosis and then scaphoid non-union advanced collapse in two patients, and lunate avascular necrosis was observed in one patient. According to the osteoarthritis classification, the radiological wrist evaluations indicated that (6) three patients were in stage 4, two patients were in stage 3, six patients were in stage 2, and one patient was in stage 1. According to the modified Green and O'Brien clinical evaluation scale, three cases were evaluated as good, five were fair, and three

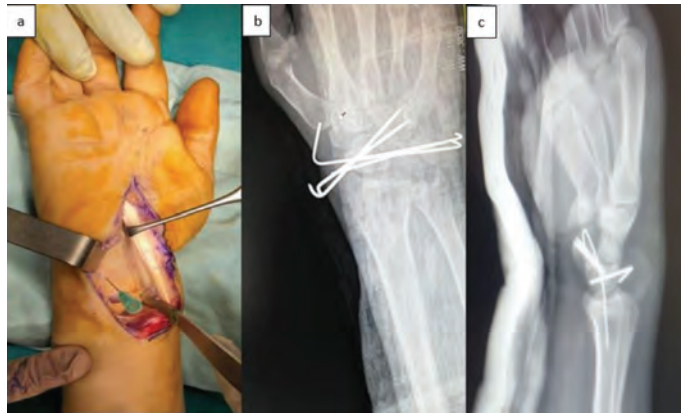

Figure 1. (a) Stage 3 perilunate injury treated with the volar approach and (b, c) postoperative X-ray images

Table 1. Statistical data of the patients included in the study

Patients	Age (years)	Fracture type	Approach	Trauma to surgery (days)	Follow-up time (months)
1	43	T-S	Dorsal + volar	6	25
2	34	T-S	Volar	3	18
3	25	T-RS-S	Dorsal + volar	2	32
4	30	T-S	Dorsal	2	27
5	23	T-S	Volar	9	25
6	26	T-RS-S	Volar	3	23
7	42	T-S	Dorsal	2	34
8	24	T-S-C	Dorsal + volar	1	33
9	35	T-RSç-S	Dorsal	2	17
10	34	T-S	Dorsal	8	27
11	39	T-S-C	Dorsal + volar	1	17
12	34	T-S	Dorsal	2	31

T-S: Transschaphoid, T-RS-S: Transscaphoid and transradial, T-S-C: Transscaphoid and transcapitate

were poor. All the poor cases were delayed cases. The clinical findings of two patients who complained of numbness in their fingertips showed that their median nerve compression regressed postoperatively.

DISCUSSION

PLDs constitute 7% of all carpal bone traumas (2). Axial load that occurs due to falling on an outstretched hand causes hyperextension and ulnar deviation of the wrist. The resulting intercarpal supination causes progressive perilunar instability. These injuries occur sequentially because of progressive ligamentous disruption. The load starts from the radial side and begins to transmit through the scaphoid or scapholunate ligament interval. This force causes a trans-scaphoid fracture or scapholunate ligament dissociation. The force then spreads toward the midcarpal area and ends at the ulnar part of the wrist (Figure 2) (7).

The severity of the trauma determines the pathways of two clinical situations: Either a PLD or PLFD on the posteroanterior or AP view. Mayfield et al. (8) demonstrated that progressive perilunate injuries occur in four stages because the disorientation of the carpal bones around the lunate creates the PLD. The scapholunate and radioscaphocapitate ligaments are disrupted in stage 1. The lunocapitate ligament disruption occurs in stage 2. The lunotriquetral joint disruption (the entire carpus separates from the lunate) in stage 3 and volar lunate dislocation due to weakness in the volar capsule into the carpal tunnel occurs in stage 4.

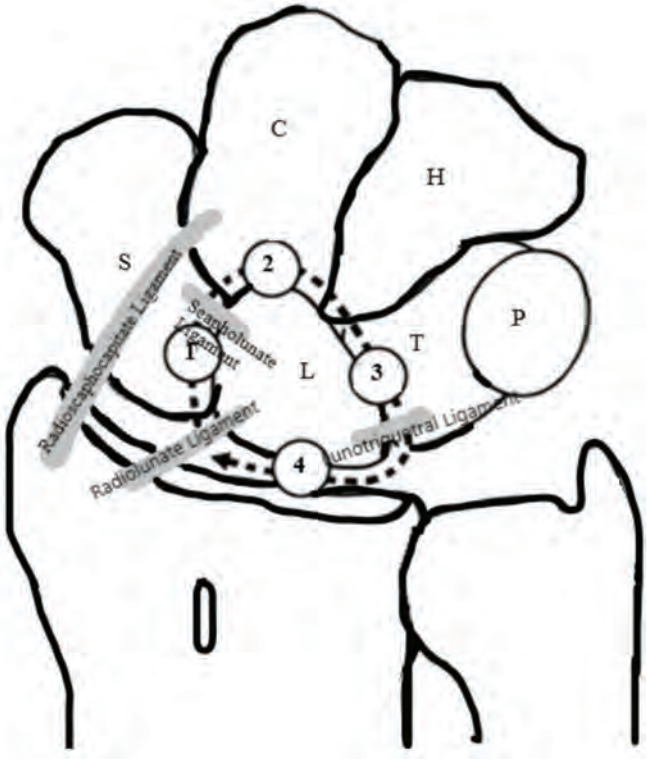

Figure 2. The force applied to the wrist, starting from the radial side, is transmitted through the ligaments toward the ulna

Gilula's (9) arcs are formed by the proximal and distal articular surfaces of the proximal row and the proximal cortical margins of the capitate and the hamate. Perilunate instability can be described in the form of the lesser arc and greater arc injuries. Lesser arc injuries occur because of pure and complete ligamentous disruption, which occurs on the second and third Gilula's (9) arc. Greater arc injuries occur at the most proximal arc among the three radiographic arcs described by Gilula (9) in the posteroanterior or AP wrist radiographs. These injuries are ligamentous and osseous. This group includes intact scaphoid [transradial-styloid (TRS), TC, transtriquetrum (TT), and combinations], and the trans-scaphoid, PLFD, and their variants (TS-TRS, TSTC, TS-TT, and combinations). The most commonly seen perilunate instability is the trans-scaphoid PLFD (10). In our study, trans-scaphoid PLFD was the most common and was observed in seven patients.

In the first examination and radiographic evaluation, 25% of the cases can be missed (5). A study has revealed that the lack of experience is the most important determining factor in the missed diagnosis of perilunate injuries (11). Although there is no obvious deformity, edema, pain, limited movement of the wrist joint, and even symptoms related to acute median nerve compression in 24%-45% of patients can be observed (12,13). Among our patients, three patients were operated on as delayed cases because they were not diagnosed during the first examination. These patients had the worst Green and O'Brien clinical evaluation scores.

Since perilunate injuries are frequently overlooked, the functional results of patients who undergo delayed surgery are poor. Studies have shown that patients undergoing surgery have progressive, permanent damage to the radiocapitate and midcarpal joints even two months after the first injury (14). For this reason, poor postoperative results are thought to be associated with delayed surgery, overlooked initial diagnosis, and concomitant carpal bone injuries (15).

Standard wrist PA and LAT radiographs are usually sufficient for diagnosis. The gapping in the carpal bone joint faces, distortions in the continuation of the Gilula (9) arcs, overlapping of the carpal bones, and loss of carpal height may help make a diagnosis. CT may help to detect occult fractures and fracture type. Occult fractures, bone bruises, and ligamentous disruptions can be seen with magnetic resonance imaging (MRI). CT or MRI,

if necessary, will prevent cases from being overlooked, especially for suspected cases.

Historically, although the treatment of perilunate injuries has been cast after closed reduction, studies have shown that anatomic reduction of the intercarpal relationship is the key to avoid carpal instability and avascular necrosis (13,16-18). Inadequate reduction of the carpal bones is associated with arthritis, chronic persistent pain, scapholunate advanced collapse, carpal instability, and loss of wrist motion (7). Although it does not restore anatomical carpal alignment, the closed reduction should attempt to reduce the pressure on the median nerve for every patient waiting in the emergency room for definitive treatment. A closed reduction maneuver has been tried in all our acute cases, from diagnosis to surgery. The primary treatment should be surgery because 59% reduction loss was detected within six weeks in patients who had a plaster cast after closed reduction (19).

The volar approach, dorsal approach, combined approach, or arthroscopic-assisted open surgery may be preferred. The optimal surgical approach is still controversial. The dorsal approach has advantages, such as better reduction of the scapholunate interval, allowing the repair of the dorsal ligaments, and better visualization of the proximal carpal row and midcarpal row. The high probability of developing avascular necrosis of the scaphoid and lunate is its most important disadvantage (20). The volar approach has the advantages of carpal tunnel decompression, better repair of volar ligaments (especially the lunortriquetral ligament) but has disadvantages such as difficult access to distal scaphoid fractures (21). The type of injury is important in addition to the surgeon's experience in determining the surgical approach. In our study, surgery was performed using the combined approach in four patients, the volar approach in three patients, and the dorsal approach in five patients. Especially in patients whose distal scaphoid fractures could not be reached by the volar approach, either the combined approach was preferred or started with the dorsal approach.

CONCLUSION

Perilunate injuries are rare and the most important step in making the suspected diagnosis. Early treatment prevents carpal arthrosis and loss of wrist motion. The risk of posttraumatic arthritis is high in the long term due to chondral damage that occurs depending on the severity of the trauma despite appropriate treatment. Care should be taken during diagnosis and treatment. Also, patients should be informed at every stage because perilunate injuries cause permanent morbidity in young patients. Such injuries should not be overlooked to avoid medical and legal problems.

Ethics

Ethics Committee Approval: This article complies with the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association Declaration of Helsinki. University Health Science Turkey, Prof. Dr. Cemil Taşçıoğlu Hospital Ethical Committee (no: 48670771-514.10).

Informed Consent: An informed consent form was signed by all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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CASE REPORT

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Lipofibromatous Hamartoma of the Upper Extremity: Report of Two Cases

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Abstract

Lipofibromatous hamartoma is a rare, slow-growing, benign, fibrofatty tumor-like condition. The upper extremity nerves are commonly involved. It is characterized by thickened axonal bundles with epineural and perineural fibrosis and fatty infiltration around the axonal bundles. Macrodactyly is a characteristic symptom in one-third of cases. Treatment options are differentiated according to the symptomatology. The diagnosis can be made by ultrasonographic and magnetic resonance imaging findings for those obviating diagnostic biopsy.

Keywords: Macrodactyly, median nerve, ulnar nerve, lipofibromatous hamartoma

INTRODUCTION

Lipofibromatous hamartoma (LFH) is a rare condition caused by fibroadipose tissue proliferation within peripheral nerves. Endoneural and perineural fibrosis thicken the axonal bundles. Fat tissue infiltrates the nerves separating the axonal bundles. Macrodactyly is associated with LFH in about one-third of cases (1).

LFH is a non-hereditary, congenital condition that is often seen in young patients. The most commonly affected nerve is the median nerve. In the literature, the involvement of other peripheral nerves is also reported (2).

We present two cases with LFH, one in the median nerve, the other in both the median and ulnar nerves.

CASE PRESENTATIONS

Case 1

An 11-year-old boy presented to our institution with a complaint of mass-like swelling on the palmar aspect of his left hand and first finger. According to his parents, the mass presented in infancy and has grown slowly as the boy grows.

He had a palpable mass on the thenar side of his left hand extending to the volar aspect of his first and second fingers in physical examination. Macrodactyly was seen in the first finger (Figure 1). There was tenderness to palpation.

On sonography, the extremely thick median nerve was seen at the distal forearm, wrist, and midhand extending to the fingers. Lipomatous tissue infiltration was seen in the median nerve, at the thenar site, and the first finger's volar aspect, seen as echogenic structures (Figure 2, 3).

On magnetic resonance imaging (MRI), the thickened median nerve was seen with serpiginous hypointense nerve fibers surrounded by fatty tissue giving the pathognomonic "coaxial cable-like appearance" at axial images.

Case 2

An 11-year-old girl presented to our institution with a complaint of soft tissue swelling at the palmar aspect of her left hand, especially on the fourth metacarpal.

On MRI, median and ulnar nerves were thickened at wrist and mid hand, typical "coaxial cable-like appearance" was seen at axial images, "spaghetti-like appearance" at coronal

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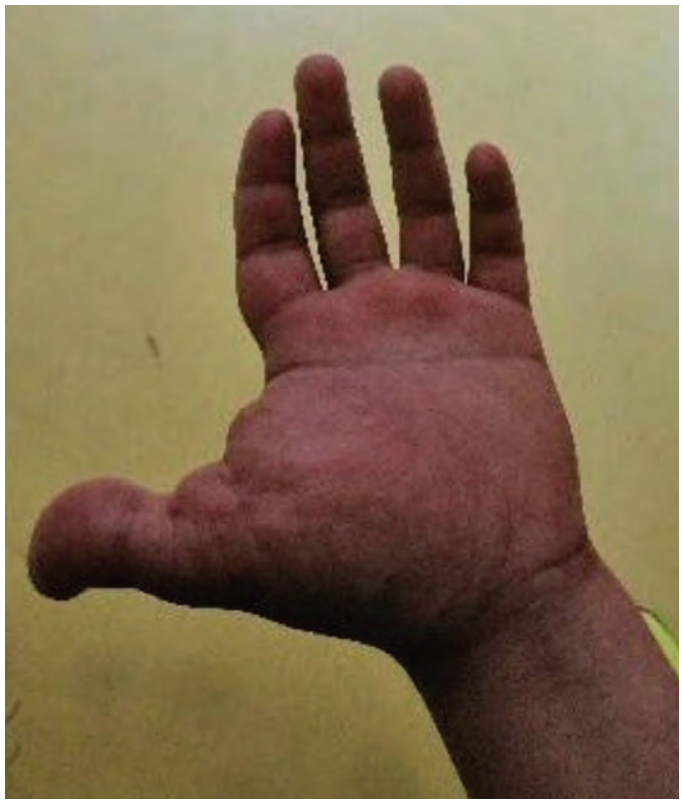

Figure 1. An 11-year-old boy with LFH of the median nerve. Enlargement of the thenar side of the left hand and macrodactyly at the first finger is seen
LFH: Lipofibromatous hamartoma

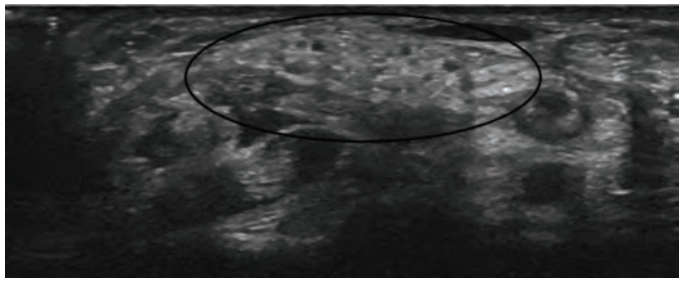

Figure 2. An 11-year-old boy with LFH of the median nerve. The extremely thick median nerve (circle) is seen in axial planes of sonography of the wrist
LFH: Lipofibromatous hamartoma

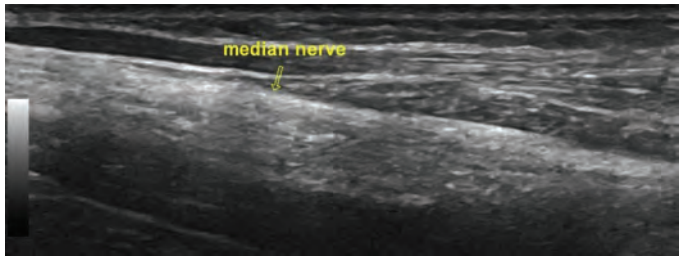

Figure 3. An 11-year-old boy with LFH of the median nerve. The extremely thick median nerve (arrow) is seen in sagittal planes of sonography of the distal forearm
LFH: Lipofibromatous hamartoma

images, indicating fibrolipomatous infiltration of both nerves (Figure 4, 5).

DISCUSSION

LFH is a rare, slow-growing, tumor-like condition formed by the infiltration of the peripheral nerves by fibroadipose tissue (3).

The etiology is unknown. It is congenital, and the vast majority of cases are seen in childhood and young adulthood (4).

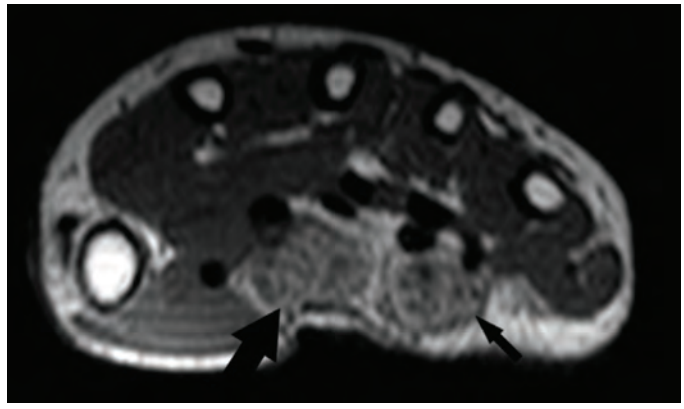

Figure 4. An 11-year-old girl with LFH of the median and ulnar nerves. Axial T1-weighted images through the wrist. The coaxial cable-like appearance of both the median (thick arrow) and ulnar nerve (thin arrow)
LFH: Lipofibromatous hamartoma

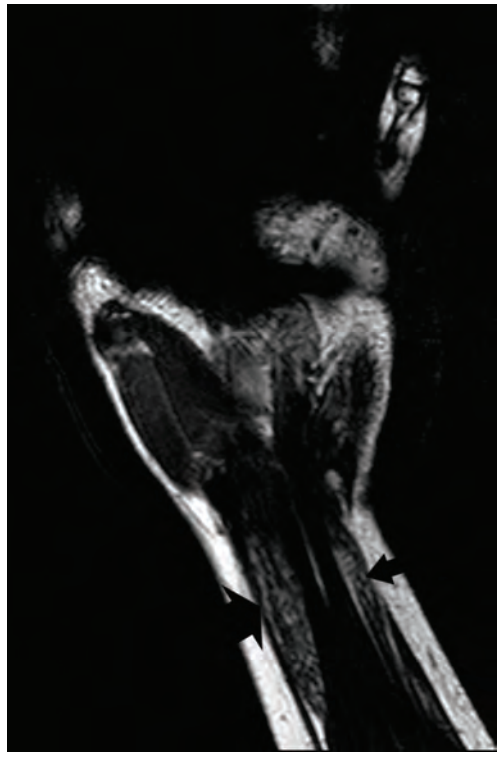

Figure 5. Coronal T1-weighted images of the wrist and distal forearm. The spaghetti-like appearance of both the median nerve (thick arrow) and ulnar nerve (thin arrow)

According to a 2019 literature review by Marek et al. (2) there have been 329 cases of LFH with 220 median and 22 ulnar nerve involvement. In seven cases, both the median and ulnar nerves were involved. Other nerves reported were plantar foot, sciatic, brachial plexus, tibial, radial, lumbosacral plexus, obturator, and femoral (2). Median nerve involvement was seen in one of our cases, while both the median and ulnar nerve involvement was seen in the other case.

The typical presentation of median nerve involvement is carpal tunnel syndrome (5). Symptoms are often seen in the third or fourth decade. There is a long history of painless swelling since childhood. Macrodactyly is the most common characteristic finding of LFH, seen in approximately 30% of cases (1). Carpal tunnel symptoms were not present in our cases. We think it may be due to the young age of the patients.

MRI is the first choice for imaging (6). The pathognomonic findings are "coaxial cable-like appearance" in axial planes, "spaghetti-like appearance" in sagittal planes (7). This is formed by the thickening of axonal bundles with fibrosis and fatty infiltration. The sonographic findings consistently correspond to the MRI findings. Sonography may be helpful for the complete viewing of extensive lesions. Sonographic and MRI findings are accurate for diagnosis and may obviate diagnostic biopsy (1). The imaging findings were typical for the diagnosis in our cases. We did not need a biopsy for the diagnosis.

The treatment choices are different according to the symptomatology. Asymptomatic patients are observed. Prophylactic carpal tunnel release or total nerve resection are performed in symptomatic patients. For macrodactyly, available treatment choices include debulking overgrown tissue, digital amputation, and middle phalangectomy with arthroplasty (8). We decided to observe the patients for probable carpal tunnel symptoms that may manifest in the future.

CONCLUSION

LFH is a rare, slow-growing, benign, fibro-fatty, tumor-like lesion that most commonly manifests in the upper extremity nerves, mainly the median nerve. LFH must be considered in the differential diagnosis of macrodactyly. Radiological findings are characteristic and accurate for the diagnosis, thus obviating diagnostic biopsy.

Ethics

Informed Consent: Consent was obtained from the parents of the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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CASE REPORT

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Eur Arch Med Res 2021;37(2):124-8

Single Brain Metastasis of Uterine Sarcoma Irradiated with Robotic Assisted LINAC-based Stereotactic Radiosurgery (Cyberknife): A Case Report

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Abstract

Brain metastasis in uterine leiomyosarcoma (ULMS) is very rare. Reported here is a 41-year-old woman with ULMS history who presented with multiple lung metastases, as she had undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy, solitary lung metastasectomy, and 4 cycles of adjuvant chemotherapy. A multi-targeted tyrosine kinase inhibitor pazopanib was administered orally for recently developed multiple lung metastases. She has been followed for nearly 2 years without any treatment. With complaints of headaches, magnetic resonance imaging revealed a metastatic lesion in the vermis. The lesion was inaccessible, thus, neurosurgery could not be performed, and radiosurgery with Cyberknife was instead elected to be performed. She died due to massive hepatic and lung metastases after the brain radiosurgery completion.

Keywords: Uterine leiomyosarcoma, brain metastasis, radiosurgery, Cyberknife

INTRODUCTION

Uterine leiomyosarcoma (ULMS) is a rare tumor that represents 1-5% of all malignancies (1). ULMS is a highly aggressive tumor, thus, it frequently metastasizes to peritoneal cavity and omentum, lung, pelvic and paraaortic lymph nodes, and liver parenchyma (2). The incidence of brain metastasis is extremely rare (2,3) and is strongly associated with lung metastasis (1,4). We presented an uncommon case with brain metastasis from ULMS who was treated with stereotactic radiosurgery (SRS).

CASE PRESENTATION

In June 2014, a 41-year-old woman with a history of total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy due to ULMS applied to our clinic. She had presented menorrhagia in September 2013, and uterine myomatosis was detected. She underwent TAH, and the histopathological diagnosis with leiomyosarcoma was made. The tumor diameter was 10 cm and mitosis was >15/10 high-power field (Figure 1). After the operation, thoracic and abdominopelvic computed tomographies (CTs) were performed for staging, and a solitary lung metastasis was found. Following pulmonary metastasectomy, 4 cycles of adjuvant chemotherapy with cisplatin and etoposide combination was performed. After 1 year, during her routine control, a 6x8 cm mass was found in her left ovary, thus bilateral oophorectomy was performed, whereupon the pathology was reported as serous cystadenoma. In October 2014, CT of the thorax and abdomen revealed multiple metastatic lesions in the lung, with the largest one at 15 mm in diameter. Afterwards, oral treatment with a multi-targeted tyrosine kinase inhibitor pazopanib hydrochlorideat with daily doses of 800 mg was initiated. Pancytopenia developed

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due to chemotherapy, and 48 MU filgrastim SC (Neupogen®) was administered. Nausea and vomiting required antiemetic therapy. Control thoracic and abdominal CTs were performed every 3 months to evaluate the treatment response. Pazopanib was used continuously for 8 months until progression was seen in the lung metastasis on the thorax CT. Pazopanib was stopped in October 2015. She was followed-up for 20 months without any treatment. Then she visited the clinic due to headaches. Magnetic resonance imaging (MRI) revealed a 17 mm contrast-enhancing metastatic lesion in the vermis (Figure 2). The lesion was inaccessible, thus, the patient underwent SRS with Cyberknife at a total dose of 22 Gy in single fraction instead of neurosurgery (Figure 3). Two weeks later she visited the emergency department with abdominal pain. Multiple liver metastases were detected on her abdominopelvic CT. She died 45 days after completion of radiation therapy because of progressive liver and lung lesions. Therefore, radiotherapy response could not be assessed with MRI.

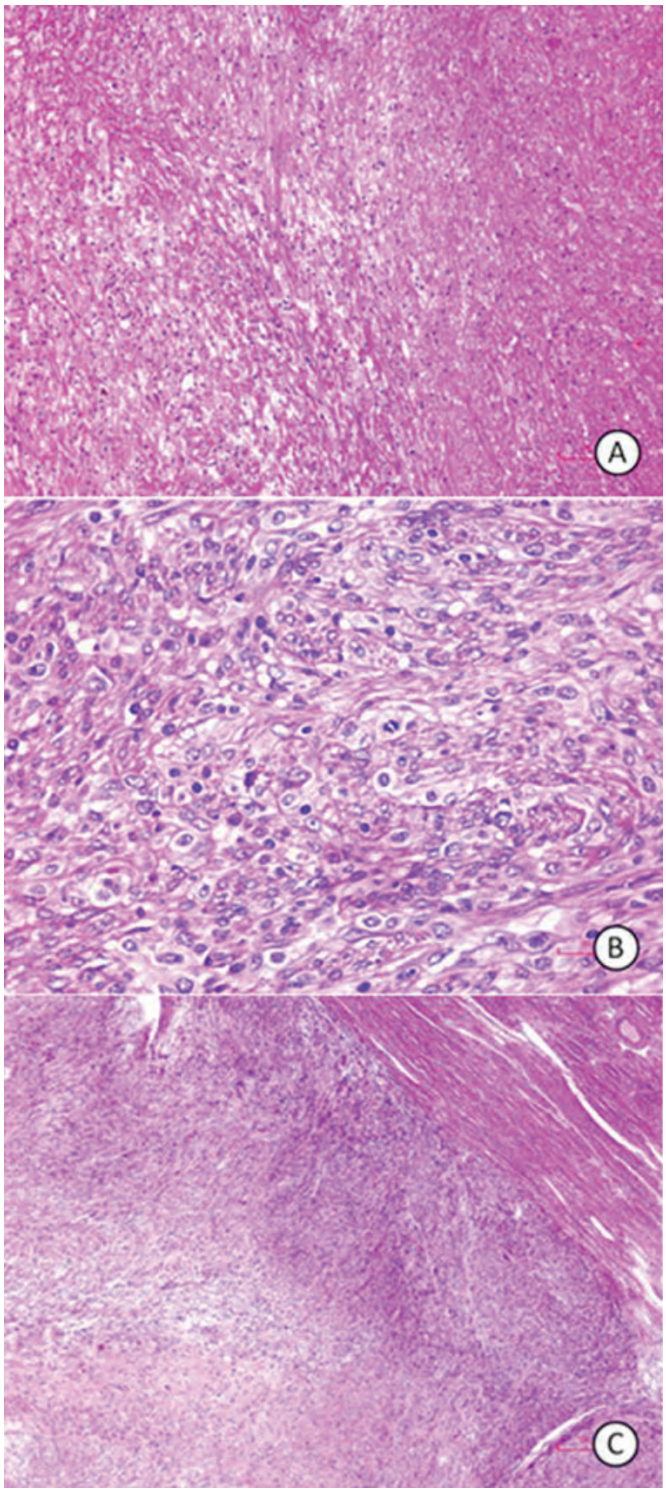

Figure 1. Histopathological examination of the uterus (H&E section). (A) Cellular smooth muscle tumor with nuclear pleomorphism and area of coagulative necrosis. (B) Atypical mitoses. (C) Atypical cells beneath the fascicles of smooth muscle cells
H&E: Hematoxylin and eosin

DISCUSSION

ULMS is an aggressive tumor and surgery is the first treatment option for the control of primary disease; however, higher rates of recurrence and metastasis are present. Hematogenous and lymphatic metastases are frequently seen (5). Concomitant brain metastases are more frequently seen in patients with lung metastasis (1,3).

In ULMS, where distant metastases are frequently seen, the effect of adjuvant chemotherapy on clinical outcomes is limited (6). Besides anthracycline and ifosfamide, novel agents such as gemcitabine, temozolamide, and taxanes are treatment options in locally advanced, recurrent, or metastatic disease. These cytostatic agents provide better systemic control and prolong overall survival (7). In a case study, pazopanib, a multi-targeted tyrosine kinase inhibitor with proven efficacy in soft tissue tumors, was used in a patient with pelvic lesions who had undergone resection of a cerebral metastatic lesion. Her pelvic lesions were kept under control for one year, without disease recurrence during this period (8). Brain metastases developing from gynecological malignancies, especially ULMS, are rarely seen; therefore, our literature information is limited to case series without robust guideline for optimal treatment for these patients (9).

The neurosurgical resection of the lesion is suggested as the mainstay treatment for brain metastasis of uterine sarcomas (1,10). Wroński et al. (1) detected a mean survival of 7 months following surgical resection, whereas Bindal et al. (10) reported a median survival of 11.8 months after surgical resection in 21 patients with brain metastasis of uterine sarcoma. The decision of surgical treatment should be based on the extent of primary

disease, location and number of brain metastases, time interval between initial diagnosis and development of brain metastasis, and expected life span of the patient.

In a prospective randomized study, Patchell et al. (11) reported that after surgical resection in the solitary brain metastases, postoperative whole brain radiotherapy (WBRT) achieved better disease control in the brain and decreased the number of deaths due to neurological etiologies, but did not contribute to survival.

No strong guideline was made for the management of brain metastasis of ULM; however, postoperative WBRT is frequently

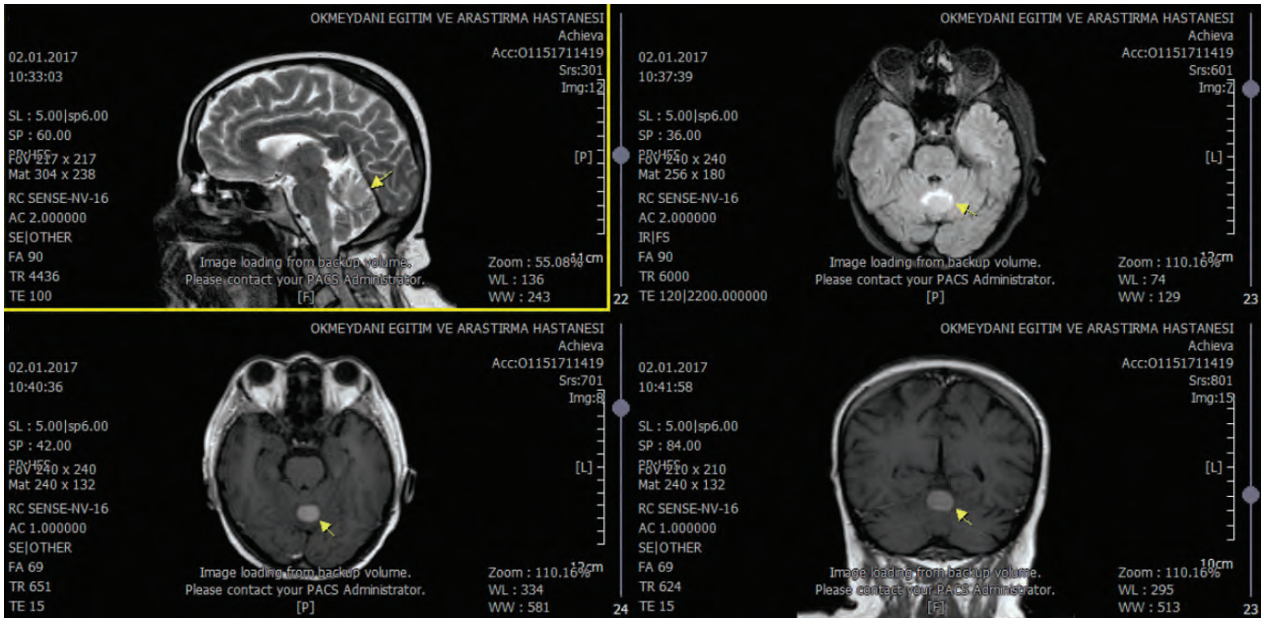

Figure 2. Initial MRI revealed a metastatic lesion in the vermis
MRI: Magnetic resonance imaging

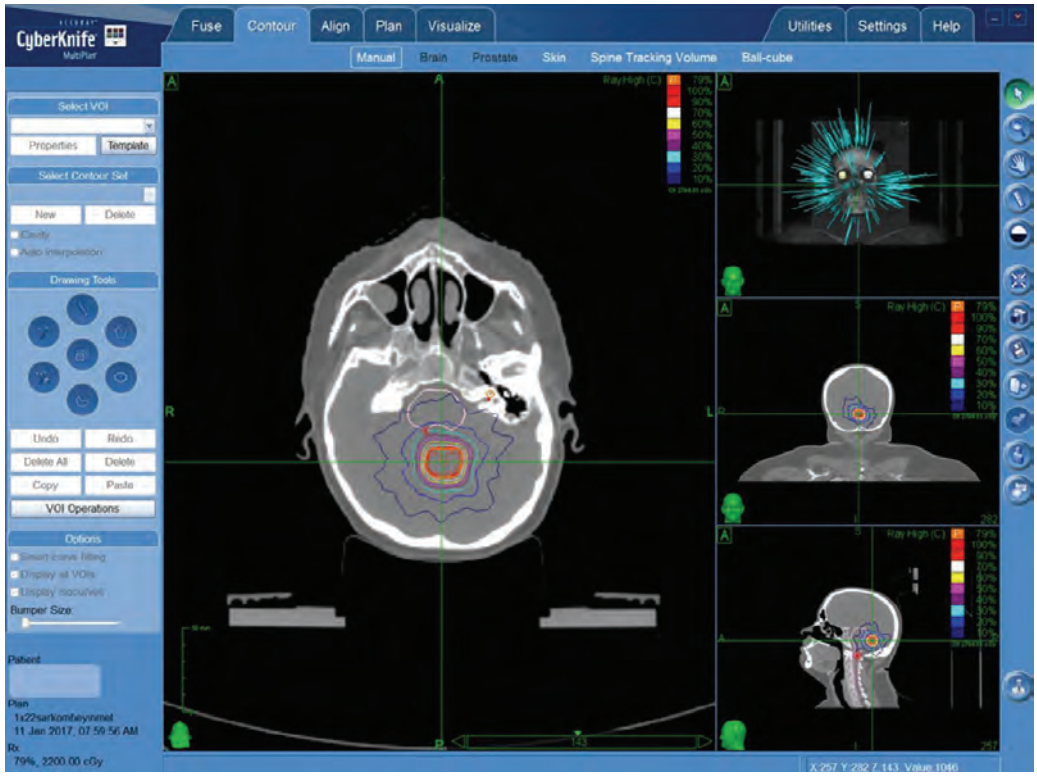

Figure 3. Representative of SRS treatment of metastasis in the vermis: Non-isocentric beam profile with dose distribution
SRS: Stereotactic radiosurgery

used as an adjuvant treatment. WBRT after neurosurgery can decrease the recurrence rates of brain metastasis, whereas long-term complications of radiotherapy increase. Therefore, neurocognitive decline should not be ignored in long-term survivals (12). However, WBRT can be preferred for widespread brain metastases and leptomeningeal invasion (13).

Nowadays, an increasing trend in the use of SRS for the management of oligometastatic brain tumors to avoid potential complications can be observed. Kasper et al. (13) performed SRS using Cyberknife for 20 brain metastases in 8 patients with gynecological malignancies and determined median distant brain progression-free survival and median overall survival times as 6 and 29 months, respectively. In retrospective studies of patients with gynecological malignancies who developed brain metastasis had undergone radiosurgery using Gamma Knife [(GKRS)-Elekta AB, Stockholm, Sweden], which is another radiotherapy method, excellent local control rates had been achieved without significant acute and long-term toxicities (14-16). In the study by Matsunaga et al. (14), median survival time was determined as 8 months, whereas more improved overall survival was detected in the group of patients with primary ovarian cancer and solitary brain metastasis whose extracranial metastases were under control. In addition, in the study by Shepard et al. (16), 16 patients were evaluated, brain metastases were detected in respective number of patients with ovarian cancer (n=1), endometrial cancer (n=6), cervical cancer (n=1), and leiomyosarcoma (n=1), and the median tumor dose of 20 Gy (range 10-22 Gy) had been delivered with GKRS. Local tumor control had been achieved in all patients. Median survival times following GKRS were 22.3 and 8.3 months in patients with primary ovarian cancer and endometrial cancer, respectively (p=0.02). The patient with leiomyosarcoma died due to primary disease progression within 1 month after the treatment (16). Our patient died 45 days after radiotherapy completion as a result of liver and lung metastases progression.

SRS provides local control rates equivalent to those obtained from surgical series, and is effective in treating patients with surgically inaccessible tumors (17). Patients with limited brain disease, controlled systemic disease, and good performance status appear to benefit from therapy. Especially in these selected solitary brain metastatic lesions, SRS can be applied without WBRT in such a group of patients (13,18).

The use of SRS alone was compared with SRS combined with WBRT in the group of patients with 1-3 brain metastases, and deterioration in neurocognitive functions was less frequently observed in the SRS arm at 3 months, which suggests that SRS is a preferred treatment approach for these patients (19). SRS was preferred for the case described here with solitary metastasis inaccessible for surgical resection located in the vermis.

CONCLUSION

In these patients, new systemic treatment options should be investigated in addition to radiosurgery to increase survival, as these patients are often lost due to extracranial tumor progression while maintaining local control of brain metastases.

Ethics

Informed Consent: Informed consent form was obtained before the patient was taken into treatment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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CASE REPORT

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COVID-19 Associated Miller Fisher Syndrome and Rhombencephalitis with Magnetic Resonance Imaging Findings

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Abstract

Coronaviruses, including severe acute respiratory syndrome-coronavirus 2, are responsible for upper respiratory tract infections. However, recent studies have reported that patients with coronavirus disease-2019 (COVID-19) may manifest neurological symptoms. The involvement of the neurological system causes different clinical situations, including meningitis, encephalitis, acute necrotizing hemorrhagic encephalopathies, acute cerebrovascular events, and Guillain-Barré syndrome. Miller Fisher syndrome and rhombencephalitis were separately reported in few cases of COVID-19. In this report, we present the neuroimaging findings of a patient with Miller Fisher syndrome and rhombencephalitis due to COVID-19.

Keywords: Encephalitis, encephalopathy, rhombencephalitis, COVID-19, SARS-CoV-2, Guillian Barré syndrome, Miller Fisher syndrome, neurological complications

INTRODUCTION

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)-associated coronavirus disease-2019 (COVID-19) was first documented in patients with unusual pneumonia in December 2019 at Wuhan, China (1). This novel infection was promptly spread throughout the world, thus becoming a serious global health problem. In March 2020, COVID-19 was declared a pandemic by World Health Organization. Coronaviruses, including SARS-CoV-2, are responsible for upper respiratory tract infections. However, recent studies have reported that patients may manifest neurological symptoms, such as headache, dizziness, myalgia, hyposmia/anosmia, and hypogeusia/ageusia (2).

The involvement of the neurological system causes different clinical situations, including meningitis, encephalitis, acute necrotizing hemorrhagic encephalopathies, acute cerebrovascular events, and Guillain-Barré syndrome (GBS). Miller Fisher syndrome, a GBS variant, is characterized by acute ophthalmoplegia, gait ataxia, and areflexia. Rhombencephalitis refers to inflammatory disorders that affect the hindbrain (brainstem and cerebellum) (3). Miller Fisher syndrome and rhombencephalitis were separately reported in few cases of COVID-19. In this report, we present the neuroimaging findings of a patient with Miller Fisher syndrome and rhombencephalitis due to COVID-19.

CASE PRESENTATION

A 35-year-old male patient was admitted in our emergency department with complaints of fever and shortness of breath.

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He was hospitalized due to worsening respiratory symptoms and poor general condition. Nasopharyngeal swab test for COVID-19 was positive. He has an unremarkable medical history. He rapidly developed speech disturbance, verbal clumsiness, blurred vision, gait disorder, and loss of balance. Two days later, the patient suffered from swallowing difficulty. On neurologic examination, the patient was conscious and well-oriented to time, place, and person. His pupils were equal size in both eyes. The direct and indirect light reflexes were normal. He had an adduction deficit in his right eye. The abduction deficit was remarkable in both eyes without double vision. The muscle strengths were normal in all extremities. There was no sensorial deficit. All deep tendon reflexes were absent. Plantar responses were flexor. He had an ataxic gait and a positive Romberg sign. Meningeal irritation signs were absent. Cerebrospinal fluid examination showed high protein (792.6 mg/L) and normal glucose levels with leukocyte counts (2/mm^3). Cerebrospinal polymerase chain reaction (PCR) for 2019-nCoV RNA and ganglioside GQ1b-IgG antibody was negative. Diffusion-weighted magnetic resonance imaging (MRI) showed a hyperintense signal in the brainstem surrounding the fourth ventricle, without hypointensity on apparent diffusion coefficient map (Figure 1) and cerebral T2-weighted sequence revealed symmetric hyperintense lesions in the pons, bulbus, mesencephalon, and cerebellum, without contrast enhancement (Figure 2).

On the fifth day of hospitalization, the patient was intubated due to respiratory failure. Distal muscle weakness simultaneously developed in all extremities. His ophthalmoparesis progressed to ophthalmoplegia. Due to the patient's poor general condition, electromyographic examination was not performed. He was treated with 400 mg/kg of intravenous immune globulin (IVIG) for 5 days. Afterward, the patient developed myocarditis and kidney failure. Follow-up MRI showed novel contrast-enhancing lesions on medulla oblongata, cervical medulla, thalamus, and left basal ganglia, as well as a dramatic increase in the size of previous lesions (Figure 3). Treatment was re-planned with

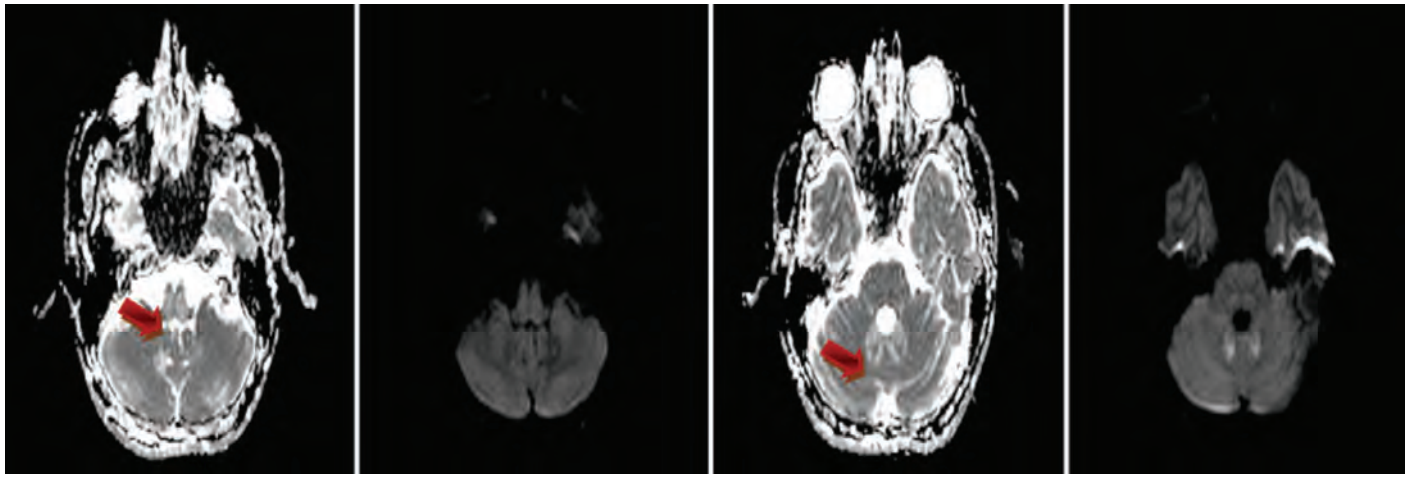

Figure 1. Diffusion-weighted imaging; showed hyperintense signal in the brainstem surrounding the fourth ventricle, without hypointensity on apparent diffusion coefficient map

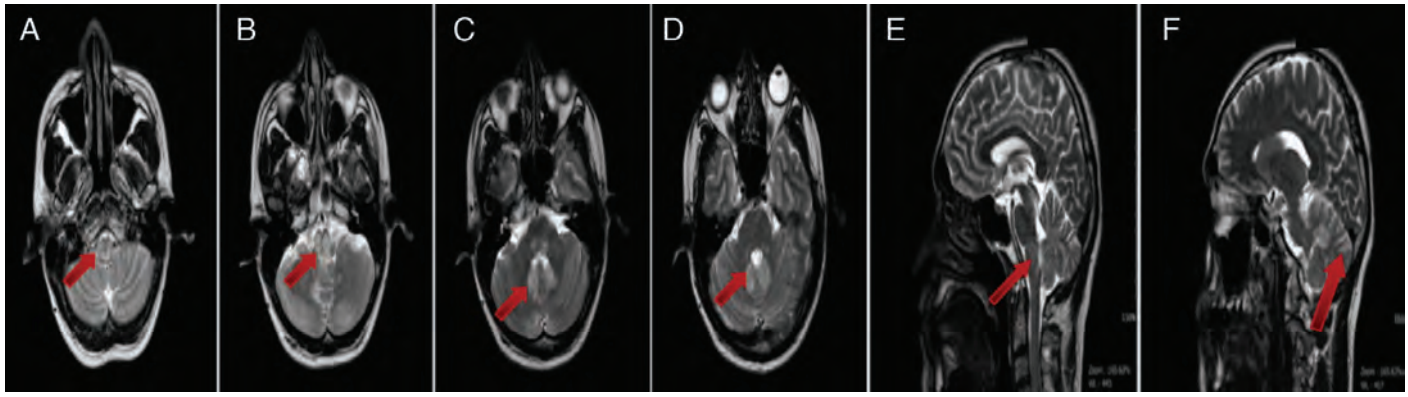

Figure 2. Axial (A-D) and sagittal (E, F) T2-weighted MRI sequences showed symmetric hyperintense lesions in the pons, bulbus, mesencephalon, and cerebellum

MRI: Magnetic resonance imaging

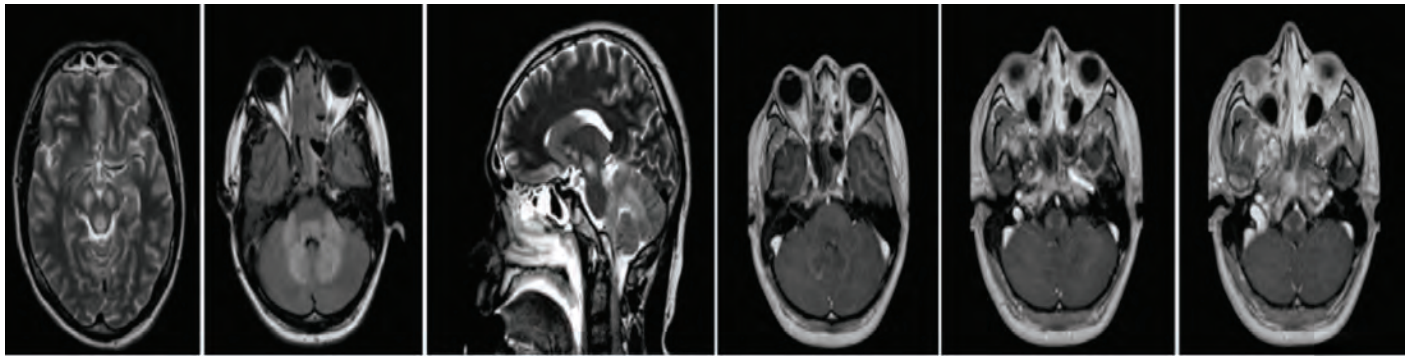

Figure 3. Increase in size of previous lesions with new contrast-enhancing lesions on medulla oblongata, cervical medulla, thalamus, and left basal ganglia

intravenous prednisolone infusion at a dosage of 1000 mg for 5 days. No apparent response was observed from IVIG and pulse prednisolone therapies, thus plasmapheresis was initiated. After the fifth session of plasmapheresis, the patient died due to cardiorespiratory failure.

DISCUSSION

The mechanisms underlying the neurological damage caused by SARS-CoV-2 are tempting research topics. The presumptive pathophysiological theories are direct viral invasion, postviral triggered immune response (postviral autoimmune process), or hypoxic-metabolic complications due to severe illness itself.

The spike proteins of SARS-CoV-2 use angiotensin-converting enzyme receptor type 2 (ACE-2), which is expressed in lung epithelial cells, heart, arteries, oral and nasal mucosa, and the central nervous system (predominantly in thalamic nuclei, cerebellum, and inferior olivary nuclei) (4). Alveolar type 2 cells, brain endothelial cells, neurons, and glial cells all possess ACE-2 receptors (5,6). Moreover, SARS-CoV-2 uses sialic acid-containing glycoproteins and gangliosides on cell surfaces to bind to cells (7). Endothelial cells of the blood-brain barrier express ACE-2 receptors, which facilitate viral entry into the central nervous system via hematogenous route (3). As a transneuronal route, SARS-CoV-2 infects the nasal epithelium and olfactory receptor neurons in the neuroepithelium, causing neuroinvasion of the olfactory bulb, which explains anosmia, the common and early symptom of SARS-CoV-2 infection (7). Infection with SARS-CoV-2 produces increased levels of tumor necrosis factor-alpha, interferon-gamma, as well as interleukin 6, 12, and 15, which is a phenomenon referred to as cytokine storm (8). A combination of this pro-inflammatory process and localized lung injury with severe hypoxia may be the reason for the cerebral vasodilation that leads to cerebral edema and ischemia (3). Acute lung injury and neurotoxicity may be caused by cytokine storms. Cytokine-driven injury and immune-mediated toxicity may disrupt the blood-brain barrier without direct viral invasion. Acute necrotizing encephalopathy may be caused by cytokine toxicity (8). A hypercoagulable state evidenced by increased D-dimer, prolonged prothrombin time, and disseminated intravascular coagulation may complicate COVID-19 by causing acute cerebrovascular disease (4).

Cerebrovascular disease, encephalopathy, and encephalitis, including Bickerstaff encephalitis, impaired level of consciousness, and GBS, are neurologic complications of SARS-CoV-2 (3,9). Encephalitis is an acute inflammatory condition of the brain, which is characterized by seizure, focal neurologic deficits, acute onset of fever, vomiting, and altered consciousness. Apart from direct viral invasion of SARS-CoV-2, encephalitis may be implicated in inflammatory and hypoxic-metabolic processes (3). It may be associated with autoimmune and paraneoplastic syndromes.

Miller Fisher, a variant of GBS, is an acute peripheral neuropathy. Miller Fisher syndrome can develop after various viral, bacterial, or fungal pathogens. The syndrome is characterized by a triad of ophthalmoplegia, ataxia, and areflexia and might be associated with anti-GQ1b antibody. Lantos et al. (9) reported a presumptive case of COVID-19 associated with Miller Fisher syndrome. Although the test was negative for anti-GQ1b antibody, the clinical picture was observed to be consistent with Miller Fisher syndrome. A review of 123 patients with Miller Fisher syndrome revealed that 15% were negative for anti-GQ1b (10). Given these findings, Lantos et al. (9) assumed that when antibody testing is negative, symptoms may be related to viral neurotropism rather than immune-mediated injury. On the other hand, their MRI demonstrated T2-hyperintensity and enhancement of the affected cranial nerve III from the cavernous sinus through

the orbit. Our patient exhibited multiple cerebral findings due to COVID-19. In our patient, we found not only Miller Fisher syndrome, but rhombencephalitis. The case in Lantos et al.'s (9) report improved after IVIG treatment. However, IVIG, pulse steroid, and plasmapheresis options all failed as a result of the severe clinical and neurological status of our patient. The present case was similar to an example of both central and peripheral involvement of the neurological system due to COVID-19.

Symmetric hyperintense lesions in the pons, bulbus, mesencephalon, and cerebellum were the remarkable MRI findings in our patient. These inflammatory changes in the brainstem and cerebellum prompted us to diagnose rhombencephalitis. On differential diagnosis, we considered Behçet disease, paraneoplastic syndrome, metronidazole intoxication, thiamine abstinence, Wernicke's encephalopathy, and infectious causes, such as listeria monocytogenes, Epstein-Barr virus, herpes, and tuberculosis. Multiple sclerosis, cerebral venous thrombosis, and brain abscess were not initially considered and excluded. Although cerebrospinal fluid PCR was negative for SARS-CoV-2 RNA, nasopharyngeal PCR test was positive. The combination of ophthalmoplegia, areflexia, ataxia, motor deficits/polyneuropathy, and negative cerebrospinal fluid results is considered to be associated with virus-mediated immune response rather than direct viral invasion.

Wong and colleagues reported a 40-year-old man who developed acute brainstem dysfunction 3 days after hospitalization, with symptoms of the novel SARS-CoV-2 infection (COVID-19). MRI showed changes consistent with inflammation of the brainstem and upper cervical cord. The patient had an unsteady gait, diplopia, oscillopsia, and limb ataxia. Unlike our patient, peripheral reflexes were intact. They considered Miller Fisher, a variant of GBS, in their clinical differential diagnosis; however, MRI of the brain and cervical spine suggested an inflammatory rhombencephalitis/myelitis (11).

Zhao et al. (12) reported the first case of COVID-19 that initially occurs with an acute GBS. A 61-year-old woman showed acute weakness and severe fatigue in both legs, which progressed within 1 day. She was diagnosed with GBS and was administered intravenous immunoglobulin treatment. It was reported that the patient's clinical condition gradually improved (12).

GBS has recently been associated with SARS-CoV-2 infection, with five cases reported in Italy and two additional cases from Wuhan, China (3,12-14). All patients experienced a varying prodrome of upper respiratory tract infection 5 to 14 days before the development of symmetrical weakness and 3 patients developed respiratory failure (12-14). All patients had a positive nasopharyngeal PCR and chest imaging of SARS-CoV-2, whereas all cerebrospinal fluid samples had a negative SARS-CoV-2 PCR. While all patients received IVIG, those who developed respiratory failure showed poor results (13). Interestingly, MRI of the brain and spine did not show abnormalities in half of the patients. In published cases, demyelinating-type involvement findings were found in 7 out of 13 patients who were examined by electromyography (3,10,12-15). IVIG was administered to 15 patients, in addition to the antiviral treatment they were receiving. Two cases of Miller Fisher variant and one case of demyelinating-type GBS fully recovered. Other GBS cases improved to varying degrees. However, the exact prognosis is not clear, since the follow-up periods of most patients were short.

This is the first case report indicating the coexistence of Miller Fisher syndrome and rhombencephalitis due to COVID-19. As demonstrated in our unusual case, care should be taken against the development of multisystem inflammatory response and neurological symptoms in COVID-19 over time.

CONCLUSION

COVID-19 may affect the central and peripheral nervous systems. Further studies are needed to elucidate whether the neurological manifestations might occur as result of an aberrant immune response to COVID-19.

Ethics

Informed Consent: Informed written consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: O.A., B.Y., Design: O.A., B.Y., Data Collection or Processing: O.A., B.Y., Analysis or Interpretation: O.A., B.Y., Literature Search: O.A., B.Y., Writing: O.A., B.Y., S.K., F.Ş., Ş.V., K.H., S.Ü.

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