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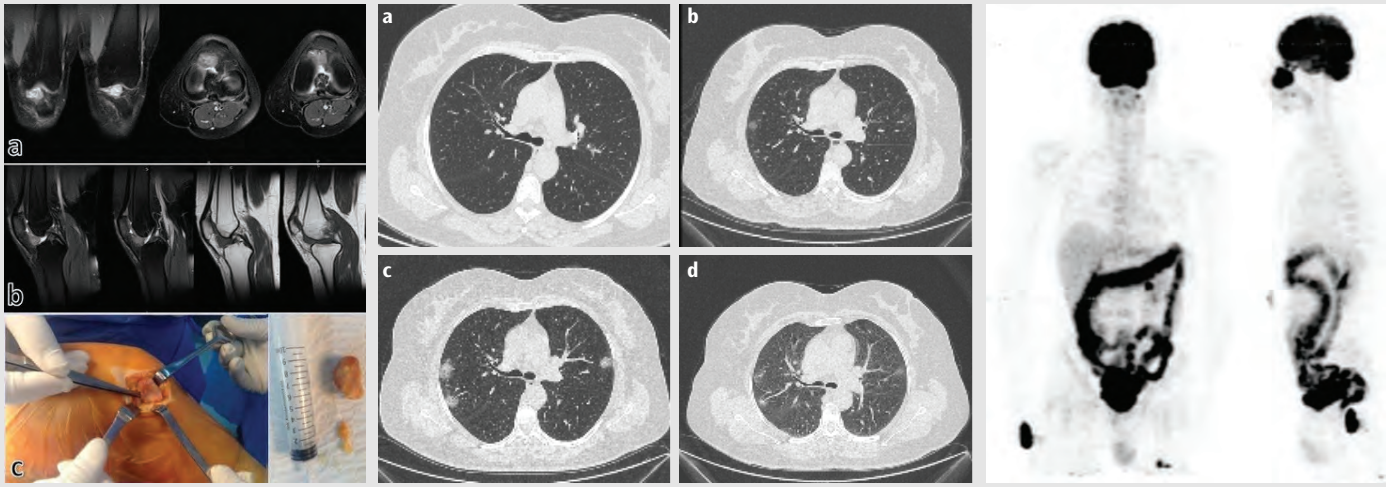

Highlights

galenos yayınevi

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- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

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Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

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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.

Case Series: The Case Series section reports a series of 2-6 similar cases. The cases should address a challenging diagnostic and/or therapeutic problem with possible solutions to help clinicians in managing these cases. Case series must be accompanied with a comprehensive review of literature. It should include six authors maximum. Structure of manuscript should include Introduction, Case Series, Discussion, Conclusion. It should have 3-5 keywords maximum. Please check Table 1 for the entire limitations for Case Series.

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Image(s): The number of images is left to the discretion of the author. (See Original article section)

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).

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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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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
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

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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.

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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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The Place of Urology in Aerospace Medicine; A New Horizon

Caner Baran, Mustafa Erkoç, Alper Ötünçtemur

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Abstract

In space, the special conditions of microgravity and exposure to cosmic radiation make substantial alterations compared to terrestrial circumstances to the human body and organ functions. This review will try summarizing the recent development in the urological aspect of the microgravitational environment and aerospace medicine despite the limited data as the topic. Aerospace has effects on kidney physiology, body fluid, urination, and fertility. The overall renal response to microgravity can be summarized as is the retention of sodium, edema, decreased blood volume, and an increase in the sympathetic tonus. Also, microgravitational environments facilitate urinary tract infections. Changes in urine volume, urinary pH, and urinary citrate, calcium, and oxalate levels during a flight may predispose to urolithiasis. The urological conditions necessitate special expertise in the field of space medicine. New technologies are also needed to develop providing better service in the field of urological space medicine.

Keywords: Urology, microgravity, space

INTRODUCTION

It has been almost half a century since Neil Armstrong, the NASA astronaut, walked on the moon's surface and spoke the phenomenal words "That's one small step for a man. One giant leap for human beings" (1). Nowadays, the steps of human beings are approaching Mars. Because of this effort, our species will eventually be an interplanetary species. This great success brings many different problems that need to be solved. There are two major parts of an aerospace mission. One is the vehicle and engineering problems, and the other is the crew and the physiological problems.

Homo sapiens evolved under gravitational forces. The physiology of the body faces the gravitational force in every aspect of life. The bones, blood pressure, muscle strength, the vertical position of the body, lungs, almost up to cell diffusion pressures, the gravitational forces must be in the equation.

As healthcare professionals, we must think, read, research and at least develop some hypotheses about the upcoming health issues in aerospace. This effort has started by Dr. Abraham T.K. Cockett et al. (2) who firstly published the urologic implications in zero gravity. This review will try summarizing the recent development in the urological aspect of the microgravitational environment and aerospace medicine despite the limited data as the topic.

Kidney Physiology, Body Fluid, and Microgravity

Renal adaptation in space has been studied during various space missions since the early 70s. Different hypotheses are suggested explaining water and electrolyte homeostasis. Alternative simulation models have also been suggested such as head-out water immersion, head-down bed rest, supine lying, and parabolic flights for human and tail-suspended rats for animals. However, the physiology of humans showed differently in the earth, in the lab, and in space (3,4).

The recent hypothesis about the adaptation of the human body to the non-gravity environment splits the process into acute and chronic phases. In the acute phase, the body fluids move up to the cephalad locations of the body in the early period of the flight (5).

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The overall result of the redistribution of the fluids to the head, neck, and thorax area is the dilatation of the small veins and astronauts have puffy faces. This alteration causes such symptoms as nasal congestion, headache, the elevation of intraocular pressure, and photophobia (6). Despite these alterations, because of the disappearance of the gravitational forces, central venous pressure is decreased and the left atrium capacity and central blood volume are increased (5).

During the chronic phase of the adaptation, the body weight remains the same while the effective blood volume decreases markedly and the activity of the renin-angiotensin-aldosterone system also increases. The overall renal response in the chronic phase to microgravity can be summarized as is the retention of sodium, edema, decreased blood volume, and an increase in the sympathetic tonus (7).

Voiding in Space

On a normal day on earth regular person void 6-8 times per day. However, voiding in space is fundamentally different from the earth in terms of physiology, collecting, recycling, or eliminating urine. It is an obligation to produce reliable solutions for urination, which is a physiological requirement repeated 6 to 8 times a day, suitable for extraterrestrial conditions.

In space, the lack of gravity influence the urine in the bladder. Normally on earth, urine collects at the bladder neck, while in space it adheres to the bladder wall. The surface tension is the major force for the urine. Thus, the sensation for urination triggers only when the bladder is completely full. In the continuation, negative pressure helps capillary action for the urine transport from the bladder to the outward (8,9).

The difference in the environment may cause urinary retention occasionally. There was a considerable number of acute urinary retention (AUR) events reported during space flights. The importance of AUR in space is an emergency that should be intervened immediately and may also cause a mission cancelation. The pathophysiology of the AUR was attributed to different mechanisms. The altered sensation of the urination, anticholinergic effects of the antiemetic drugs such as scopolamine and promethazine taken for space motion sickness, and possible unidentified voiding dysfunction were the major reported causes of AUR There was one prolonged AUR (more than 24 h) reported in astronauts who visited the orbit and required catheterization (10,11).

Despite there being no mission cancelation reported due to AUR, percutaneous bladder catheterization had been tested in microgravity. Jones et al. (12) had conducted the study and tested the feasibility of suprapubic catheterization on the anesthetized porcine model, in a scenario of a urethral catheterization is impossible. They also had used ultrasonography to facilitate the puncture. According to their reported result, suprapubic bladder drainage is a safe and effective method in microgravity in case of an emergency (12).

Another problem with the voiding in space is collecting the urine. In the first American space flight on the 5th of May, 1961, there was no urine collection system in the pressurized space suit. The mission duration was planned for only 15 min. However, unplanned delays caused the astronaut Alan Shepard to had to wait for 4 h on the launch pad and his body, naturally, continued to function. As a result, the land crew told the astronaut to do it in the space suit without any idea about the consequences of the electronics of the suit (13).

In early versions of space suits, there was no urine collecting system. Consequently, developers have planned to use urethral catheters for continuous drainage of the urine. However, this solution was harmful to astronauts due to being uncomfortable, non-hygienic, and could result in infection. Different urine collecting devices were developed in the logic of a condom shape cap, a connector, and a collecting bag. However, all designs were incapable of collecting the urine properly in the absence of gravity. Leakage, the flow of urine in one way in a pressurized suit, positioning the collecting bag, and cleaning the system were the major tackles. Recently, female astronauts were added to the crew and the developed systems were not suitable for female anatomy (8,13). Despite some efforts to develop a female version of a urine collecting device, it was not used widespread (14).

In the research to develop a gender-neutral urine collection method, the point is to use maximum absorbency garments with additional moisture wicking capability which is also called “space diapers”. These garments look like bike shorts and collect up to 2 liters of liquid and, worn by both male and female astronauts during launch, reentry, spacewalks, and emergencies (8).

Urinary Tract Infections

One of the important points in a long-term space flight is to maintain the health of the astronauts. It has been shown that space flights cause a state of immunosuppression (15). Also, virulence and antibiotic resistance of microorganisms is increased in a microgravitational environment (16-18). These factors facilitate a urinary tract infection during a space mission. Consequently, there were different types of genitourinary infections reported during space flights such as pyelonephritis

or prostatitis. However, none of them caused early termination of the mission and were treated successfully with antibiotics (9). The resources of a space shuttle are limited to diagnosing a urinary tract infection whereas the international space station has resources that allow through biochemical analysis of the blood or urine. Also, basic ultrasound can be performed with the guidance of ground control to diagnose a complicated factor such as urinary tract calculi. Different antibiotic options including broad-spectrum intravenous antibiotics exist in the international space station (19,20).

Urolithiasis in Space

Urolithiasis is an important medical condition that should be considered not only to impact the astronaut's health but also to affect the continuation of the mission. Various studies and reports showed that total urine volume, urinary pH, and urinary citrate decreased and urinary calcium and oxalate increased during a space flight (21). These alterations could depend on the limited intake of water, lack of fruit, and fresh vegetables (as a source of citrate), decreased vitamin D levels (decreased ultraviolet light exposure), limited mobilization (bone demineralization) (22,23).

Most of the space flight crew members developed stone after the mission. There were 12 NASA astronauts and 1 Russian cosmonaut who developed renal stone (21). None of the renal stone events have caused the cancelation of the mission. However, efforts remained to prevent the development of urolithiasis in astronauts during space missions. Whitson et al. (24) showed the efficacy of potassium citrate intake to prevent the development of renal stone in astronauts in their double-blind, placebo-controlled study. Besides the preventive efforts, a compact system to diagnose, burst, and reposition the stone has been developing (25). The goal is to redefine the kidney stone from an uncontrolled factor to a controlled component of space flight.

Fertility in Space

The magnetosphere layer of our planet protects all creatures living on earth from the radioactive effect of highly ionized heavy particles coming from space. However, during a space flight, radiation exposure is increased which has potential consequences such as nuclear damage (26). It has been shown that 150 mSv and 650 mSv radiation in men and women, respectively, to the gonadal tissues are sufficient to cause temporary infertility (27). Experiments on animals showed that short-term space flight does not influence the cytoskeletal of sperm-specific proteins while there are changes at the gene expression level (28). However, a different experimental animal study in mice claimed that long-term space flight causes degenerative changes in the seminiferous tubules and the reduction of the number of epididymal sperms (26).

These data suggest that the reliable solution for reproduction in space is to protect both male and female gametes from exposure to space radiation. Another experimental study demonstrated that the freeze-dried spermatozoa which are protected from space radiation in a special vehicle could be used to generate offspring (29). The future of human beings in space seems to be related to the improvements in assisted reproductive technologies.

CONCLUSION

Human beings are closer than ever to becoming an interplanetary species. Advances in space travel are pushing the boundaries of medicine in this regard. The urological conditions necessitate special expertise in the field of space medicine. New technologies are also needed to develop providing better service in the field of urological space medicine. This field, which is still in its infancy, can become popular in close future.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: C.B., Design: C.B., M.E., A.Ö., Literature Search: C.B., M.E., A.Ö., Writing: C.B., M.E., A.Ö.

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

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REFERENCES

1. Loff S. The Apollo missions. NASA. 2015 (cited 2021 November 13). Available from: http://www.nasa.gov/mission_pages/apollo/missions/index.html
2. Cockett AT, Beehler CC, Roberts JE. Astronautic urolithiasis: a potential hazard during prolonged weight-lessness in space travel. J Urol 1962;88:542-4.
3. Drummer C, Norsk P, Heer M. Water and sodium balance in space. Am J Kidney Dis 2001;38:684-90.
4. Regnard J, Heer M, Drummer C, Norsk P. Validity of microgravity simulation models on earth. Am J Kidney Dis 2001;38:668-74.
5. Kirsch KA, Röcker L, Gauer OH, Krause R, Leach C, Wicke HJ, et al. Venous pressure in man during weightlessness. Science 1984;225:218-9.
6. Noskov VB. Redistribution of bodily fluids under conditions of microgravity and in microgravity models. Hum Physiol 2013;39:698-706.

7. Liakopoulos V, Leivaditis K, Eleftheriadis T, Dombros N. The kidney in space. Int Urol Nephrol 2012;44:1893-901.
8. Maciolek KA, Best SL. How do astronauts urinate? The history of innovations enabling voiding in the void. Urology 2019;128:8-13.
9. Kahlenberg ZB, Carroll DJ, Cristea O, Urquieta E, Bissada NK, Jones JA. Urologic innovation in the spaceflight environment: challenges, opportunities, and future directions. Medical Research Archives. 2021 Sep 26 (cited 2022 Jan 1). Available from: https://esmed.org/MRA/mra/article/view/2542
10. Stepaniak PC, Ramchandani SR, Jones JA. Acute urinary retention among astronauts. Aviat Space Environ Med 2007;78(Suppl 4):A5-8.
11. Jones JA, Jennings R, Pietryzk R, Ciftcioglu N, Stepaniak P. Genitourinary issues during spaceflight: a review. Int J Impot Res 2005;17(Suppl 1):S64-7.
12. Jones JA, Kirkpatrick AW, Hamilton DR, Sargsyan AE, Campbell M, Melton S, et al. Percutaneous bladder catheterization in microgravity. Can J Urol 2007;14:3493-8.
13. Hollins H. Forgotten hardware: how to urinate in a spacesuit. Adv Physiol Educ 2013;37:123-8.
14. Bisson RU, Delger KL. A Prototype urine collection device for female aircrew. Armstrong Lab Brooks AFB TX; 1991. Available from: https://apps.dtic.mil/sti/citations/ADA327026
15. Spatz JM, Fulford MH, Tsai A, Gaudilliere D, Hedou J, Ganio E, et al. Human immune system adaptations to simulated microgravity revealed by single-cell mass cytometry. Sci Rep 2021;11:11872.
16. Aunins TR, Erickson KE, Prasad N, Levy SE, Jones A, Shrestha S, et al. Spaceflight modifies Escherichia coli gene expression in response to antibiotic exposure and reveals role of oxidative stress response. Front Microbiol 2018;9:310.
17. Juergensmeyer MA, Juergensmeyer EA, Guikema JA. Long-term exposure to spaceflight conditions affects bacterial response to antibiotics. Microgravity Sci Technol 1999;12:41-7.
18. Taylor PW. Impact of space flight on bacterial virulence and antibiotic susceptibility. Infect Drug Resist 2015;8:249-62.
19. Jones JA, Pietrzyk RA, Cristea O, Whitson PA. Renal and Genitourinary Concerns. In: Barratt M, Baker E, Pool S (eds) Principles of Clinical Medicine for Space Flight. New York, NY. Springer; 2019.
20. Jones JA, Sargsyan AE, Barr YR, Melton S, Hamilton DR, Dulchavsky SA, et al. Diagnostic ultrasound at MACH 20: retroperitoneal and pelvic imaging in space. Ultrasound Med Biol 2009;35:1059-67.
21. Patel SR, Witthaus MW, Erturk ES, Rabinowitz R, Nakada SY. A history of urolithiasis risk in space. Can J Urol 2020;27:10233-7.
22. Zerwekh JE. Nutrition and renal stone disease in space. Nutrition 2002;18:857-63.
23. Smith SM, Rice BL, Dlouhy H, Zwart SR. Assessment of nutritional intake during space flight and space flight analogs. Procedia Food Science 2013;2:27-34.
24. Whitson PA, Pietrzyk RA, Jones JA, Nelman-Gonzalez M, Hudson EK, Sams CF. Effect of potassium citrate therapy on the risk of renal stone formation during spaceflight. J Urol 2009;182:2490-6.
25. Simon JC, Dunmire B, Bailey MR, Sorensen MD. DEVELOPING complete ultrasonic management of kidney stones for spacefligHT. J Space Saf Eng 2016;3:50-7.
26. Masini MA, Albi E, Barmo C, Bonfiglio T, Bruni L, Canesi L, et al. The impact of long-term exposure to space environment on adult mammalian organisms: a study on mouse thyroid and testis. PLoS One 2012;7:e35418.
27. Ronca AE, Baker ES, Bavendam TG, Beck KD, Miller VM, Tash JS, et al. Effects of sex and gender on adaptations to space: reproductive health. J Womens Health (Larchmt) 2014;23:967-74.
28. Ogneva IV, Usik MA, Loktev SS, Zhdankina YS, Biryukov NS, Orlov OI, et al. Testes and duct deferens of mice during space flight: cytoskeleton structure, sperm-specific proteins and epigenetic events. Sci Rep 2019;9:9730.
29. Wakayama S, Kamada Y, Yamanaka K, Kohda T, Suzuki H, Shimazu T, et al. Healthy offspring from freeze-dried mouse spermatozoa held on the International Space Station for 9 months. Proc Natl Acad Sci U S A 2017;114:5988-93.

ORIGINAL ARTICLE

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Clinicopathological Features and Surgical Outcomes in Patients Undergoing Radical Resection for Gastric Cancer with Undifferentiated Carcinoma, Neuroendocrine Tumor, and Gastrointestinal Stromal Tumor Histology

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Abstract

Objective: Gastric cancer consists of many histological subtypes. The prognostic value of histological types in stomach cancer is not well defined. In this study, we investigated the effects of different histological types on surgical and oncological outcomes in stomach cancer.

Methods: Patients with a histology of undifferentiated carcinoma, neuroendocrine tumors, and gastrointestinal stromal tumors were included in the study of 1,060 patients who underwent gastrectomy for gastric cancer between 2010 and 2019. They were divided into three groups as group 1 (undifferentiated tumor), group 2 (neuroendocrine tumor), and group 3 (gastrointestinal stromal tumor). Demographic and clinical features, operative and oncological outcomes, and survival were compared between the groups.

Results: Of a sample group that included 1,060 diseases, 53 patients (5%) were included in the study. Group 1 consisted of 24 patients, group 2 consisted of 10 patients, and group 3 consisted of 19 patients. Average age (p=0.591), was similar across all groups. Tumors were most frequently located in the corpus (41.7% vs. 80% vs. 42%, respectively) (p=0.283). Patients in group 1 and group 2 underwent total gastrectomy at a higher rate, with 79.2% and 60%, respectively, whereas in group 3, subtotal gastrectomy was performed on 63.2% of the patients. The number of lymph nodes dissected was highest in group 1 (24.25 vs. 13.70 vs. 9.52, p=0.00). The anastomosis leak (p=0.285) and post-operative 90-day mortality (p=0.285) were similar in each group. Local recurrence was most frequent in group 1 (50% vs. 40% vs. 10.5%, p=0.023). Total survival time was shortest in group 1 (31 months vs. 78 months vs. 99 months, p=0.005).

Conclusion: While demographic characteristics, clinical features, and surgical results were not affected by tumor histology, oncological results (overall survey and local recurrence) were associated with tumor histology. Undifferentiated carcinoma showed an oncologically aggressive course compared to other histological types.

Keywords: Gastric cancer, operative therapy histopathology, survival, post-operative complications

INTRODUCTION

Gastric cancer, with 989,600 new cases and 738,000 deaths per year worldwide, constitutes around eight percent of all cancers, making it one of the most common forms of the disease (1). In 2015 statistics from Turkey, the incidence of gastric cancer in men was reported to be 14.2/100,000, while in women it was reported to be 6.3/100000. It was also reported as the second most common cause of cancer-related death in men and the fourth most common in women (2).

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There are various histopathological classification systems for the diagnosis of stomach cancer. The most detailed classification system is the histopathological classification system made by the World Health Organization (WHO) in 2010 and updated in 2019. Unlike other systems, the WHO classification includes all other types of low-frequency gastric tumors other than gastric adenocarcinoma (3,4).

Undifferentiated gastric carcinoma is a rare neoplasm that does not show any differentiation from adenocarcinoma or squamous cell carcinoma (5). Various immunohistochemical stains are needed to exclude any differentiation. It should be distinguished from other neoplasms. As it is rare, the clinical behavior of undifferentiated gastric carcinoma has not been fully characterized yet, but it is thought to exhibit poor prognostic properties (6). Undifferentiated carcinoma is included in WHO classifications 4 and 5, but details are not offered (2,3).

Gastric neuroendocrine tumors are commonly referred to as carcinoids. They are tumors that arise from neuroendocrine cells within the enterochromaffin-like cells of the gastric mucosa (7).

Gastrointestinal stromal tumors are the most common mesenchymal tumors of the gastrointestinal tract and develop from interstitial Cajal cells in the intestinal wall (8).

Many variables on the outcome and prognosis of surgical treatment in stomach cancer have been discussed in the literature. It was determined that results were affected depending on numerous variables, such as tumor stage, tumor differentiation, applied surgical approach, hospital volume, surgeon volume, patient-related factors, age, immune status, and nutritional status (9-13).

Many studies have investigated the relationship between histopathological features and patient characteristics, disease-specific criteria, and overall outcomes in gastric cancer (14-16). In the literature, however, there are limited comparative studies were limited on how surgical results will be affected, and how the different histological types will affect oncological results due to different tumor histology.

In this study, we discussed the surgical results and prognoses of undifferentiated carcinoma, neuroendocrine carcinoma, and stromal tumor, in our clinic. These are the less common histological types of gastric cancer, according to the literature.

METHODS

Materials/Patients and Methods

After the approval of the Ethics Committee of Erciyes University Faculty of Medicine dated 10.06.2020 and numbered 2020/270 fifty-three patients, out of the 1,060 patients who underwent curative surgery in our clinic between 2010 and 2019, who were diagnosed with undifferentiated carcinomas, neuroendocrine tumors, and gastrointestinal stromal tumors were included in the study. Mix tumors accompanied by this histological type, other histological subtypes, and patients undergoing palliative surgery were excluded from the study. The study was conducted in accordance with the ethical rules based on the principles of the Declaration of Helsinki.

Patient files, electronic records, pathology reports, surgery reports, anesthesia follow-up forms, and nurse observation forms were examined, and a common database was created prospectively. Patients were analyzed retrospectively using this database. The population registration system was used for survival analysis.

Patients were divided into three groups: Group 1 (undifferentiated tumor), group 2 (neuroendocrine tumor) and group 3 (gastrointestinal stromal tumor). The demographic and clinical features of the patients, body mass index (BMI), American Society of Anesthesiologists (ASA) score, blood parameters during hospitalization, tumor marker levels, tumor localizations, surgical procedure applied, additional organ resection, intraoperative complication status, duration of surgery, total number of lymph nodes dissected, number of metastatic lymph nodes, tumor size, presence of post-operative complications, anastomosis leak, oral-food onset time, hospital stay duration, post-operative 90-day mortality, 90-day unplanned hospital re-admission, 90-day reoperation, local recurrence and systemic metastasis in the follow-up, and mean survival times were compared.

In all patients, distant metastases were scanned by thorax and abdominal computed tomography, and the diagnosis of malignancy was made because of pathological examination of the part taken by endoscopic biopsy. Histological subtypes were classified using WHO classifications (Figure 1-3) (3,4,17).

Standard D2 lymph node dissection was performed in patients with undifferentiated carcinoma. The extent of lymph node dissection was determined according to the degree of neuroendocrine tumors. In stromal tumors, lymph node dissection was performed when lymph node positivity was shown. The patients were operated on using conventional techniques. Total gastrectomy, subtotal gastrectomy, and wedge resection were performed using the previously recognized and accepted techniques. The location and size of the tumor were effective in choosing the type of resection.

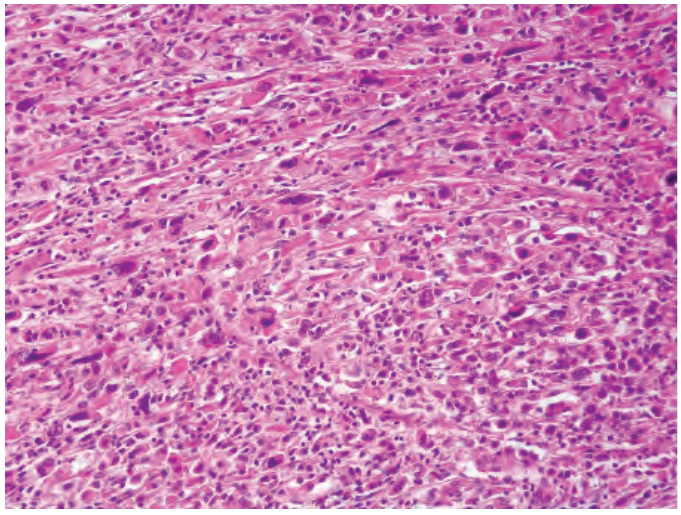


Figure 1. Undifferentiated carcinoma H&E, X100 carcinoma cell infiltration with a high degree of atypia
H&E: Hematoxylin and eosin

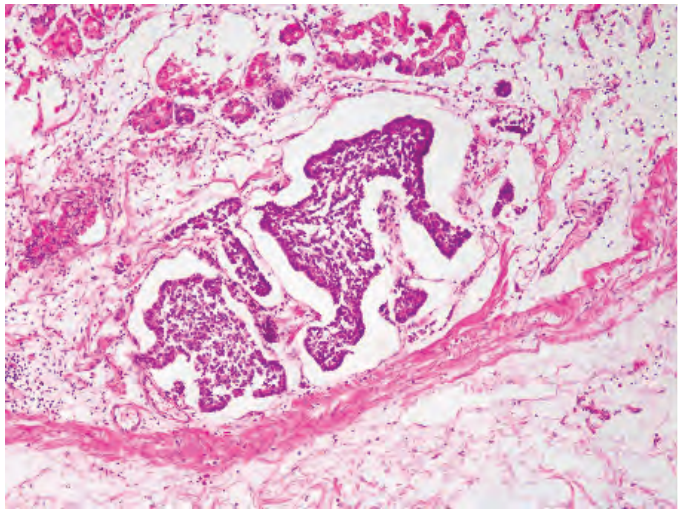


Figure 2. Neuroendocrine tumor H&E, X40 neuroendocrine tumor of the stomach, consisting of uniform cells within the mucosa
H&E: Hematoxylin and eosin

Anastomosis leak was defined as a disruption in the integrity of anastomosis, documented by a combination of clinical, radiological, and operative tools. Wound infection was defined as a superficial or deep incisional surgical-site infection occurring in the surgical wound, according to the definition of the centers for disease control (18).

Surgical quality was evaluated with markers post-operative 90-day mortality such as 90-day re-admission and re-operation. Unplanned hospitalization within the first 90 days after discharge was considered an unplanned re-admission. We considered unplanned re-operation as a surgical procedure under general, spinal, or epidural anesthesia within 90 days of the index operative procedure, for any reason other than follow-up procedures based on pathology results.

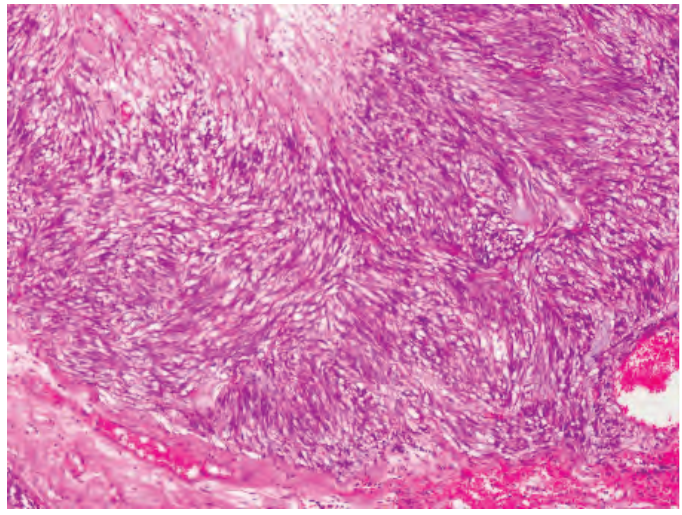


Figure 3. Gastrointestinal stromal tumor H&E, X40 stomach gastro intestinal stromal tumor showing proliferation of spindle cells
H&E: Hematoxylin and eosin

Oncological results were evaluated with parameters such as overall survival systematic metastasis and local recurrence.

The discharge criteria were similar in both groups, including meal tolerance without nausea or vomiting, adequate analgesia and pain control, and independent mobilization.

Total blood count was measured by an automated hematology analyzer

Roche Hitachi Cobas® 8000 Roche Diagnostics, Indianapolis, IN, USA.

Since the study was retrospective, patient consent could not be obtained.

Statistical Analysis

The Statistical Package for the Social Sciences 23.0 program was used for the statistical analysis of data. Categorical measurements were summarized as numbers and percentages, while continuous measurements were summarized as mean and standard deviation (median and minimum-maximum, where necessary). Pearson's chi-square test statistics were used to compare categorical variables. The Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. In comparing the continuous measurements between the groups, the distributions were checked and One-Way ANOVA was used for the parameters with normal distribution, and the Kruskal-Wallis test was used for parameters without normal distribution. Post-hoc analysis was used to determine the differences between the groups. Kaplan-

Meier analysis and log rank tests were used in survival analyses. Statistical significance level was taken as 0.05 in all tests.

RESULTS

Fifty-three patients (5%) from the 1,060 diseases were included in the study. Mean age of the patients (p=0.591), BMI (p=0.723), and ASA scores (p=0.559) were similar in the groups. Tumors were most frequently located in the corpus (41.7% vs. 80% vs. 42%, p=0.283). Demographic and clinical features were similar when the groups were compared in pairs. Demographic data of the patients are shown in Table 1.

There was no significant difference between the groups in terms of white blood cell counts (p=0.355), neutrophil counts (p=0.445), lymphocyte counts (p=0.491), or albumin level (p=0.112) parameters. Hemoglobin levels (12.90 vs. 12.84 vs. 10.84, p=0.018), carcinoembryonic antigen (CEA) levels (2.53 vs. 2.51 vs. 1.41) and CA 19.9 levels (44.90 vs. 8.92 vs. 10.2) (p=0.001) were significantly different between the groups. The laboratory parameters of the patients are shown in Table 2.

Patients in groups 1 and 2 underwent total gastrectomy at a higher rate, with 79.2% and 60%, respectively, whereas in group 3, subtotal gastrectomy was performed on 63.2% of the patients. All groups (p=0.002) exhibited differences in terms of operation type. There was no statistical difference in terms of operation duration (215 min vs. 216 min vs. 208 min, p=0.0448). Additional organ resection was similar between the groups and was frequently performed (20.8% vs. 30% vs. 31.6%, p=0.701). No patient had intraoperative complications. The number of lymph nodes dissected was high in group 1 (24.25 vs. 13.70 vs. 9.52, p=0.00). Between the groups it was seen as group 1-2 (p=0.001) and group 1-3 (p=0.000). The number of metastatic lymph nodes was highest in group 1 (11.50 vs. 70 vs. 0.36, p=0.000). Between the groups it was seen as group 1-2 (p=0.002) and group 1-3 (p=0.000). Average tumor size was highest in group 3 (5.57 cm vs. 4.26 cm vs 7.39 cm, p=0.048). Groups 3-1 (p=0.050) exhibited this difference. These results are displayed in Table 3.

The onset of oral intake was latest in group 1 (5.04 days vs. 4.60 days vs. 4.15 days, p=0.043) (group 1-3, p=0.033). Anastomosis leak was seen only in two patients in group 1. Post-operative 90-day mortality was seen only in two patients in group 1. Ninety-day re-admission rates were similar (12.5% vs. 20% vs. 5.3%, p=0.478). In the post-operative period, one patient in group 1 underwent surgical intervention due to intra-abdominal hemorrhage. Local recurrence was more common in group 1 during follow-up (50% vs. 40% vs. 10.5%, p=0.0023) (group 1-3, p=0.007). Systemic metastasis was most common in group 2, with the most common location being the liver (40%), and peritoneal carcinomatosis was most common in group 1 (20.8%) (group 1-2 p=0.006, group 2-3 p=0.040). In the evaluation of current clinical status, the number of patients who died was highest in group 1 (79.2% vs. 20% vs. 21.2%, p=0.00). Between the groups, the relationships were seen to be group 1-2 (p=0.002) and group 1-3 (p=0.00). This is shown in Table 4. Five-year overall survival was found as X% in group 1, Y% in group 2, and Z% in group 3.

Overall survival duration was significantly shorter in group 1 (31 vs. 78 vs. 99 months, p=0.005). This is shown in both Table 5 and Graphic 1.

Table 1. Demographic and clinical characteristics

n (%)		Group 1 (n=24)	Group 2 (n=10)	Group 3 (n=19)	p	Source of difference between groups
		n (%)	n (%)			
Sex+	Male	16 (66.7)	5 (50.0)	12 (63.2)	0.656	No significant difference
	Female	8 (33.3)	5 (50.0)	7 (36.8)		
Age (F)		58.5±13.28	56.3±13.03	61.15±11.25	0.591	No significant difference
BMI (x^2)		24.90±4.07	24.13±4.96	23.93±3.58	0.723	No significant difference
ASA+	1	16 (66.7)	4 (40.0)	12 (63.2)	0.559	No significant difference
	2	5 (20.8)	3 (30.0)	5 (26.3)		
	3	3 (12.5)	3 (30.0)	2 (10.5)		
Location+	Antrum	7 (29.2)	0 (0.0)	3 (15.8)	0.283	No significant difference
	Large curvature	1 (4.2)	1 (10.0)	0 (0.0)		
	GEJ	0 (0.0)	0 (0.0)	1 (5.3)		
	Cardia	3 (12.5)	0 (0.0)	2 (10.5)		
	Corpus	10 (41.7)	8 (80.0)	8 (42.)		
	Small curvature	3 (12.5)	1 (10.0)	5 (26.3)		

p<0.05, BMI: Body mass index, ASA: American Society of Anesthesiologists, GEJ: Gastroesophageal junction, +: Pearson chi-square, x^2: Kruskall-Wallis test, F: One-Way ANOVA

Table 2. Laboratory parameters					
	Group 1 (n=24)	Group 2 (n=10)	Group 3 (n=19)	p	Source of difference between groups
	Mean ± SD	Mean ± SD	Mean ± SD		
WBC (F)	8.42±2.57	7.78±2.12	9.22±2.94	0.355	No significant difference
Neutrophil mm^3 (x^2)	6.57±4.34	5.04±1.70	6.68±2.97	0.445	No significant difference
Lymphocyte mm^3 (F)	1.68±0.65	1.97±0.60	1.72±0.70	0.491	No significant difference
Hgb gr/dL (F)	12.90±2.71	12.84±1.57	10.84±2.36	**0.018**	1-3: p=0.021
Albumin gr/dL (x^2)	3.76±0.75	4.20±0.34	3.67±0.64	0.112	No significant difference
Pre-op CEA (x^2)	2.53±1.80	2.51±1.00	1.41±1.08	**0.036**	1-3: p=0.041
Pre-op CA19-9 (x^2)	44.04±9.10	8.92±5.75	10.2±7.30	**0.001**	1-2: p=0.010 1-3: p=0.002
p<0.05, x^2: Kruskall-Wallis test, WBC: White blood cell, F: One-Way ANOVA, SD: Standard deviation, CEA: Carcinoembryonic antigen					

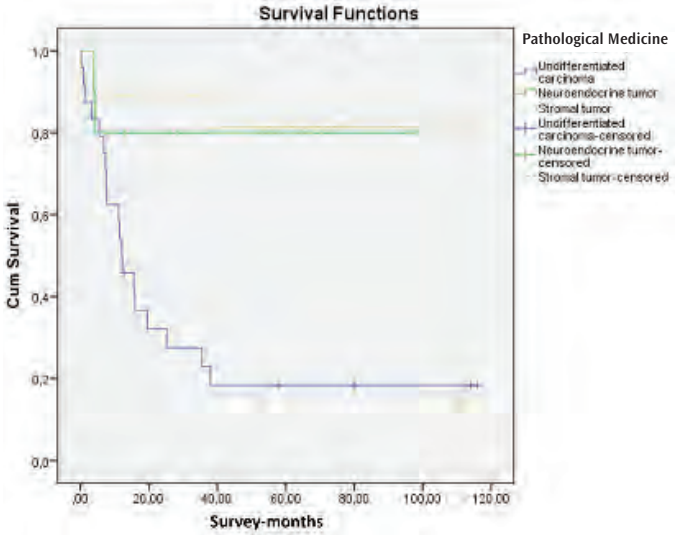
Table 3. Operation details						
n (%)		Group 1 (n=24)	Group 2 (n=10)	Group 3 (n=19)	p	Source of difference between groups
		n (%)	n (%)			
Type of operation$^+$	Subtotal	5 (20.8)	4 (40.0)	12 (63.2)	**0.009**	1-3: p=0.002
	Total	19 (79.2)	6 (60.0)	5 (26.3)		
	Wedge	0 (0.0)	0 (0.0)	2 (10.5)		
Operation duration (minutes) (x^2)		215.83±17.54	216.0±24.47	208.42±21.47	0.448	No significant difference
Additional organ resection$^+$	No	19 (79.2)	7 (70.0)	13 (68.4)	0.701	No significant difference
	Yes	5 (20.8)	3 (30.0)	6 (31.6)		
Additional organ resection$^+$	Spleen	2 (8.3)	0 (0.0)	1 (5.3)	0.247	No significant difference
	Distal esophagus	0 (0.0)	0 (0.0)	2 (10.5)		
	Duodenum	1 (4.2)	0 (0.0)	0 (0.0)		
	Small intestine	0 (0.0)	0 (0.0)	1 (5.3)		
	Colon and liver	0 (0.0)	2 (20.0)	0 (0.0)		
	Gallbladder	1 (4.2)	0 (0.0)	1 (5.3)		
	Gallbladder and spleen	1 (4.2)	1 (10.0)	1 (5.3)		
	No	19 (79.2)	7 (70.0)	13 (68,4)		
Intraoperative complication$^+$	None	24 (100.0)	10 (100.0)	19 (100.0)	1.000	No significant difference
	Present	0 (0.0)	0 (0.0)	0 (0.0)		
Total lymph node (F)		24.25±8.14	13.70±8.42	9.52±6.06	**0.000**	1-2: p=0.001 1-3: p=0.000
Metastatic lymph node (x^2)		11.50±10.11	1.70±2.83	0.36±1.60	**0.000**	1-2: p=0.002 1-3: p=0.000
Mean tumor size (cm) (x^2)		5.57±2.44	4.26±3.75	7.39±4.00	**0.048**	3-1: p=0.050
p<0.05, +: Pearson chi-square, x^2: Kruskall-Wallis test, F: One-Way ANOVA						

DISCUSSION

Historically, gastric carcinomas have been classified into two histological types through standard hematoxylin and eosin staining. Lauren classified them as "intestinal" type and "diffuse" type, while "differentiated" type and "undifferentiated" type where the classifications presented by Nakamura et al. (19,20). In the WHO histological classifications, gastric cancers are divided into many histological subtypes and subtypes within these subtypes (3,4).

Although the prognosis of resectable gastric cancer clearly depends on the pathological stage of the disease, controversy still surrounds the prognostic value of the histological type. The

Table 4. Post-operative and oncologic outcomes						
n (%)		Group 1 (n=24)	Group 2 (n=10)	Group 3 (n=19)	p	Source of difference between groups
		n (%)	n (%)			
Onset of oral intake (day) (x^2)		5.04±1.36	4.60±1.07	4.15±0.68	**0.043***	**1-3: p=0.033**
Hospitalization duration (day) (x^2)		11.66±4.92	12.20±3.61	11.78±5.10	0.957	No significant difference
Anastomosis leakage+	No	22 (91.7)	10 (100.0)	19 (100.0)	0.285	No significant difference
	Yes	2 (8.3)	0 (0.0)	0 (0.0)		
Post-op 90-day mortality+	No	22 (91.7)	10 (100.0)	19 (100.0)	0.285	No significant difference
	Yes	2 (8.3)	0 (0.0)	0 (0.0)		
90-day readmission+	No	21 (87.5)	8 (80.0)	18 (94.7)	0.478	No significant difference
	Yes	3 (12.5)	2 (20.0)	1 (5.3)		
90-day readmission+	Ileus	0 (0.0)	1 (10.0)	0 (0.0)	0.352	No significant difference
	Oral intake disorder	2 (8.3)	1 (10.0)	0 (0.0)		
	Wound site infection	1 (4.2)	0 (0.0)	1 (5.3)		
	No	21 (87.5)	8 (80.0)	18 (94.7)		
90-day reoperation+	No	23 (95.8)	10 (100.0)	19 (100.0)	0.540	No significant difference
	Yes	1 (4.2)	0 (0.0)	0 (0.0)		
Local recurrence+	No	12 (50.0)	6 (60.0)	17 (89.5)	**0.023**	**1-3: p=0.007**
	Yes	12 (50.0)	4 (40.0)	2 (10.5)		
Systematic metastasis+	No	18 (75.0)	6 (60.0)	15 (78.9)	0.534	No significant difference
	Yes	6 (25.0)	4 (40.0)	4 (21.1)		
Systematic metastasis+	Brain	1 (4.2)	0 (0.0)	1 (5.3)	**0.004**	**1-2: p=0.006** **2-3: p=0.040**
	Liver	0 (0.0)	4 (40.0)	0 (0.0)		
	Esophagus	0 (0.0)	0 (0.0)	1 (5.3)		
	Peritoneum	5 (20.8)	0 (0.0)	2 (10.5)		
	No	18 (75.0)	6 (60.0)	15 (78.9)		
Current status+	Ex	19 (79.2)	2 (20.0)	4 (21.1)	**0.000**	**1-2: p=0.002** **1-3: p=0.000**
	Alive	5 (20.8)	8 (80.0)	15 (78.9)		
*p<0.05, +: Pearson chi-square, x^2: Kruskall-Wallis test						



Graphic 1. Overall survival in terms of the histologic type

Table 5. Mean survival duration by groups		
Group	Average [mean + SD (minimum-maximum)]	p
1	31.79±8.61 (14.91-48.68)	**0.005***
2	78.05±11.70 (55.11-100.99)	
3	99.86±9.90 (80.44-119.28)	
*p<0.05, SD: Standard deviation		

histological type appears to be an important clinical parameter for tumors. Additionally, histological type has been proposed as an important factor in evaluating the prognosis of the patient (21). Research on the prognosis of the WHO histological classification is increasingly prevalent. Zu et al. (22) highlighted significant differences in clinical and tumor characteristics of different histological subtypes of advanced gastric cancer.

Tumor markers are often used to determine the prognosis of cancer patients after radical surgery, but the role of tumor markers in stomach cancer is still controversial. Since high-serum tumor markers are often associated with tumor progression, most of the previous reports have found pre-operative high serum markers to be significantly associated with long-term poor patient survival (23,24). The relationship between serum tumor marker levels and tumor histology is also controversial. In a study by Mattar et al. (25) no correlation was found between serum tumor marker levels and the histology of the tumor. The study of Ishigami et al. (26) displayed the lowest positivity rate of tumor markers in patients with undifferentiated tumors, when they grouped patients as "differentiated" and "undifferentiated". In our series, CEA levels were higher in undifferentiated carcinoma, and oncological results were worse in this group.

Stromal tumors are slow-progressing tumors by nature and may not cause symptoms until they reach large sizes. Large tumors can often cause gastrointestinal bleeding (8). Neuroendocrine tumors are tumors that show the hormonal activity and show these activities even with a small tumor diameter. Considering the increasing rates of endoscopy, they can be detected even in small tumor sizes (8). We linked the difference in tumor diameters in our study to these tumors. With stromal tumors, low hemoglobin was noted due to the frequent gastrointestinal bleeding they cause.

The lymphatic metastasis rates of stromal tumors are low. They spread hematogenously and through adjacency. Therefore, lymphadenectomy is not routinely recommended (8). In contrast, differentiated tumors frequently exhibit lymph node metastasis and are aggressive by nature (6). Regarding lymphadenectomy for neuroendocrine tumors, it is recommended if there is extra gastric involvement or poor prognostic factors (as with type 3 gastric neuroendocrine tumors) (7). In our series, we decided on the width of lymphadenectomy by considering recommendations from the literature. Similar to findings in the literature, lymph node positivity was low in stromal tumors. In contrast, undifferentiated tumors showed a high rate of lymph node involvement.

Despite the recent decrease in the incidence of anastomosis leakage due to the increased awareness of surgical techniques, risk factors, and treatment options, it remains the most feared complication and is reported in the literature to range from 2.1% to 14.6% (27). Risk factors previously reported include the patient's tumor characteristics and intraoperative factors (28,29). In our series, anastomosis leakage developed in two patients in the undifferentiated group, and tumor types were not associated with this.

Following surgery, reoperation is associated with morbidity, mortality, and increased health-care system costs, and is a potentially sensitive surgical quality marker (30,31). The patient's re-admission after discharge from the hospital disrupts the predicted course of post-operative recovery and is a concern for the patient and their family. Additionally, it increases costs, causes labor loss and hinders the effective usage of hospital beds. Unplanned re-applications and re-operations may lead to delays in chemotherapy programs and oncological outcomes. Therefore, it is important to uncover the related factors. The need for unplanned re-operation after surgery generally manages some rare, serious, or life-threatening post-operative complications, following gastrectomy, and has rarely been reported. In the literature, many parameters related to the patient, surgical method, and tumor have been evaluated for post-operative mortality, re-operation, and re-admission (23-34). Yalav and Topal (34) found the adenocarcinoma histology as a risk factor for post-operative mortality in their study investigating the relationship between tumor histology and post-operative mortality.

In our series, tumor histology was not directly related to surgical quality. As expected, our most common reasons for application after discharge were wound problems and impaired oral food intake. There were two patients who developed post-operative mortality. The cause of mortality had cardiac origin in one patient and sepsis, due to anastomosis leak, in the other.

In the literature, studies on undifferentiated gastric carcinoma are in the form of case series, and there are no broad-based studies. In the series of Endo et al. (6) tumors were detected at an advanced stage and followed an aggressive course. Average survival were between three and seven months. Similar to other cases in the literature, these cases were associated with lower survival and an increased risk of metastasis (35,36). In our series, local recurrence was detected in half of the patients in undifferentiated carcinoma. Peritoneal carcinomatosis developed in five of our patients, and 80% of these patients died during their follow-up. Mean survival was very low in this group compared with other groups. Undifferentiated tumors were more aggressive than other histological subtypes.

Study Limitations

The most significant limitation of our study was that it was retrospective and the number of patients was low. Considering the low incidence of these tumors, and the limited number of studies in the literature on the comparison of results relating to them, we believe that our study contributes to the body of research.

CONCLUSION

While demographic and clinical features and operation results were not affected by tumor type, oncological results (overall survival, systematic metastasis, and local recurrence) were generally closely related to tumor type. A multidisciplinary approach that includes endoscopist, pathologist, radiologist, medical oncologist, and surgical team is required for optimal management of stomach cancer. The prognosis of patients cannot be considered independent of the histological type of tumor. Identification of tumors with aggressive biological characteristics will guide us in the management of patients. Even if the demographic, clinical, and surgical quality results of the cases were similar, the tumor histological type directly related to patient prognosis.

Ethics

Ethics Committee Approval: Approval was obtained with the decision of Erciyes University Faculty of Medicine Ethics Committee dated 10.06.2020 and numbered 2020/270.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90. Erratum in: CA Cancer J Clin 2011;61:134.
2. 2-Türkiye'de Kanser istatistikleri. Available at: https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/Turkiye_Kanser_Istatistikleri_2015.pdf acces date 15.04.2020
3. Lauwers GY, Carneiro F, Graham DY, Curado MP. Gastric Carcinoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. WHO Classification of Tumours of the Digestive System. IARC, Lyon; 2010.p.48-58.
4. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182-8.
5. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101-12.
6. Endo S, Nishikawa K, Yamada T, Nakagawa T, Fushimi H, Chihara T, et al. Our experience of treating undifferentiated gastric carcinoma: report of four cases. Surg Today 2015;45:235-40.
7. Corey B, Chen H. Neuroendocrine tumors of the stomach. Surg Clin North Am 2017;97:333-43.
8. Gupta SK, Rateria N. Gastrointestinal stromal tumors (GIST): an overview. Indian J Surg 2020;83:647-53.
9. Yalav O, Topal U, Unal AG. Clinical value of neutrophil/lymphocyte ratio in predicting postoperative complications, lymph node positivity and prognosis in gastric cancer patients who underwent curative surgical resection. Ann Med Res 2019;26:2513-9.
10. Iwatsuki M, Yamamoto H, Miyata H, Kakeji Y, Yoshida K, Konno H, et al. Effect of hospital and surgeon volume on postoperative outcomes after distal gastrectomy for gastric cancer based on data from 145,523 Japanese patients collected from a nationwide web-based data entry system. Gastric Cancer 2019;22:190-201.
11. Claassen YHM, van Amelsfoort RM, Hartgrink HH, Dikken JL, de Steur WO, van Sandick JW, et al. Effect of hospital volume with respect to performing gastric cancer resection on recurrence and survival: results from the CRITICS trial. Ann Surg 2019;270:1096-102.
12. Orman S, Cayci HM. Gastric cancer: factors affecting survival. Acta Chir Belg 2019;119:24-30.
13. Lee HJ, Hyung WJ, Yang HK, Han SU, Park YK, An JY, et al. Short-term outcomes of a multicenter randomized controlled trial comparing laparoscopic distal gastrectomy with D2 lymphadenectomy to open distal gastrectomy for locally advanced gastric cancer (KLASS-02-RCT). Ann Surg 2019;270:983-91.
14. Zheng HC, Zheng YS, Xia P, Xu XY, Xing YN, Takahashi H, et al. The pathobiological behaviors and prognosis associated with Japanese gastric adenocarcinomas of pure WHO histological subtypes. Histol Histopathol 2010;25:445-52.
15. Su JS, Chen YT, Wang RC, Wu CY, Lee SW, Lee TY. Clinicopathological characteristics in the differential diagnosis of hepatoid adenocarcinoma: a literature review. World J Gastroenterol 2013;19:321-7.
16. Berlth F, Bollschweiler E, Drebber U, Hoelscher AH, Moenig S. Pathohistological classification systems in gastric cancer: diagnostic relevance and prognostic value. World J Gastroenterol 2014;20:5679-84.
17. Hamilton SR, Aaltonen LA. Pathology and genetics of tumours of the digestive system b2000 (volume 2). Lyon: IARC press.
18. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 1992;13:606-8.
19. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. Acta Pathol Microbiol Scand 1965;64:31-49.
20. Nakamura K, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. Gan 1968;59:251-8.
21. Park JM, Jang YJ, Kim JH, Park SS, Park SH, Kim SJ, et al. Gastric cancer histology: clinicopathologic characteristics and prognostic value. J Surg Oncol 2008;98:520-5.
22. Zu H, Wang H, Li C, Xue Y. Clinicopathologic characteristics and prognostic value of various histological types in advanced gastric cancer. Int J Clin Exp Pathol 2014;7:5692-700.
23. Huang ZB, Zhou X, Xu J, Du YP, Zhu W, Wang J, et al. Prognostic value of preoperative serum tumor markers in gastric cancer. World J Clin Oncol 2014;5:170-6.

24. Shimada H, Noie T, Ohashi M, Oba K, Takahashi Y. Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the Task Force of the Japanese Gastric Cancer Association. Gastric Cancer 2014;17:26-33.

25. Mattar R, Alves de Andrade CR, DiFavero GM, Gama-Rodrigues JJ, Laudanna AA. Preoperative serum levels of CA 72-4, CEA, CA 19-9, and alpha-fetoprotein in patients with gastric cancer. Rev Hosp Clin Fac Med Sao Paulo 2002;57:89-92.

26. Ishigami S, Natsugoe S, Hokita S, Che X, Tokuda K, Nakajo A, et al. Clinical importance of preoperative carcinoembryonic antigen and carbohydrate antigen 19-9 levels in gastric cancer. J Clin Gastroenterol 2001;32:41-4.

27. Makuuchi R, Irino T, Tanizawa Y, Bando E, Kawamura T, Terashima M. Esophagojejunal anastomotic leakage following gastrectomy for gastric cancer. Surg Today 2019;49:187-96.

28. Russell MC, Mansfield PF. Surgical approaches to gastric cancer. J Surg Oncol 2013;107:250-8.

29. Yalav O, Topal U. Risk factors for leakage after total gastrectomy. Ann Med Res 2020;27:174-80.

30. Tsai TC, Joynt KE, Orav EJ, Gawande AA, Jha AK. Variation in surgical-readmission rates and quality of hospital care. N Engl J Med 2013;369:1134-42.

31. Merkow RP, Bilimoria KY, Cohen ME, Richards K, Ko CY, Hall BL. Variability in reoperation rates at 182 hospitals: a potential target for quality improvement. J Am Coll Surg 2009;209:557-64.

32. Li SS, Costantino CL, Mullen JT. Morbidity and mortality of total gastrectomy: a comprehensive analysis of 90-day outcomes. J Gastrointest Surg 2019;23:1340-8.

33. Xiao H, Wang Y, Quan H, Ouyang Y. Incidence, causes and risk factors for 30-day unplanned reoperation after gastrectomy for gastric cancer: experience of a high-volume center. Gastroenterology Res 2018;11:213-20.

34. Yalav O, Topal U. Predictive factors associated mortality after gastrectomy. Ann Med Res 2020;27:326-33.

35. Ueda K, Yamazoe S, Kawazoe Y, Iwasaki Y, Naka T, Yamaue H, et al. Perforated undifferentiated gastric cancer with metastaticsmall intestinal tumors: a case report (in Japanese with English abstract). J Abdom Emerg Med 2010;30:937-40.

36. Yamamoto M, Kobayashi Y, Ochiai M, Terasawa H, MizumotoY, Tsubota Y. A rapidly progressed case of undifferentiated gastric cancer (in Japanese with English abstract). J Jpn Surg Assoc 2012;73:2841-46. https://www.jstage.jst.go.jp/article/jjsa/73/11/73_2841/_pdf/-char/en

ORIGINAL ARTICLE

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The Giant Cell Tumor of Tendon Sheath: Risk Factors for Recurrence

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Abstract

Objective: Giant cell tumors of tendon sheath (GCTTS) are the most common soft tissue tumors of the hand after ganglion cysts. Some other areas such as the foot, ankle, knee and thigh can also be involved. The recurrence rates up to 44% have been reported. This study evaluated the clinical results of GCTTS patients who underwent marginal resection and investigate any clinical or histopathological features that might be associated with recurrence.

Methods: Thirty patients who underwent surgical excision between 2011 and 2015 were analyzed retrospectively. Clinical, pathological and radiological examination results were collected from the patient files. The variables including tumor localization, tumor subtype, bone erosion and the presence of mitotic figures were analyzed for a possible association with recurrence.

Results: Amongst 30 patients who were treated surgically due to GCTTS, twenty-one patients were female (70%) and 9 were male (30%). The mean age was 40 [standard deviation (SD): ±14.4, range: 18-68 years]. The average follow-up period was 51 months (SD: ±29.2, range: 16-177 months). Histopathologically, 23 cases were identified as nodular type, 7 as diffuse type. In 8 patients, postoperative recurrence was observed. The recurrence rate was significantly higher in patients with preoperative bone erosion (p=0.015), while other variables including histopathological type, presence of mitotic figures and tumor localization did not significantly affect the recurrence rate. None of the patients experienced a malignant transformation.

Conclusion: Bone erosion at the time of presentation was found to be a risk factor for recurrence in GCTTSs. The presence of mitotic figures, histopathological type and tumor localization was not associated with recurrence.

Keywords: Giant cell tumor of tendon sheath, recurrence, risk factor, histopathology

INTRODUCTION

The giant cell tumor of tendon sheath (GCTTS) is a benign synovial tissue tumor, which is most commonly seen in hands, while they can also be encountered in other parts of the body such as foot, ankle, elbow, knee, hip and occasionally in spine. GCTTS is the most common solid soft tissue mass of the hand, and the second most common benign lesion of the hand after ganglion cyst (1). Total excision of the lesion is the generally preferred approach (2).

GCTTS is morphologically classified as nodular and diffuse types. The nodular type is usually located in hands while the diffuse type is usually located around large joints. In contrast to more localized and encapsulated nodular type, the diffuse type has multicentric lesions without encapsulation. The recurrence is more common in diffuse type (3).

Long-term stress on the bone may cause bone erosion and tumor recurrence has been reported at rates ranging from 7% to 44% (4-7). Recurrences usually occur within the first two years after surgery. This study aimed to analyze GCTTS case series operated in our clinic and investigate any clinical or pathological features that might be associated with increased recurrence.

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METHODS

After obtaining the approval of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Local Ethical Committee (year: 2016, no: 83045809), all GCTTS patients who were treated surgically by marginal excision between 2011 and 2015 were included and investigated retrospectively. A total of 31 patients were available and the patient files were reviewed for clinical, radiological [direct radiography and magnetic resonance imaging (MRI) and pathological examinations]. The patients with missing file information or lost to follow-up were excluded. Only one patient was excluded due to loss of follow-up. The tumors were removed with marginal excision which was also confirmed by pathological examination. The patients were followed up by clinical examination and direct radiography during routine follow-ups. Direct radiographs were obtained per 3 months during the first year and per 6 months during the second year. After that, the clinical follow up and direct radiography evaluation was performed with one-year intervals. The patients were examined with MRI if any recurrence was suspected clinically (swelling, pain, warmth, erythema, deformity, etc.) or radiologically (soft tissue mass, cortical erosion, etc.) during follow-ups.

Bone erosion, tumor localization (only for lesions of the hand, as proximal and distal according to proximal interphalangeal joint), histopathological type and the presence of mitotic figures were investigated for any possible association with the recurrence. The size of the lesions was measured during pathological examination macroscopically.

Statistical Analysis

Descriptive statistics were employed using measures of the mean and standard deviation (SD). Categorical variables were analyzed using Fisher's Exact test. Bonferroni correction was used to calculate the actual p-value. The difference was considered significant when the p-value was less than 0.016. The analysis was performed using SPSS version 20 (SPSS, Chicago, IL).

RESULTS

In 30 patients who were treated surgically due to GCTTS, twenty-one patients were female (70%) and 9 were male (30%). The mean age was 40 (SD: ±14.4, range: 18-68 years) (Figure 1). The mean follow-up period was 51 months (SD: ±29.2, range: 16-177 months). Twenty-one lesions were seen in the upper extremity (70%) and 9 in the lower extremity (30%). (Table 1) The lesions in the hand were mostly located on the volar side (n=16, 84.2%) rather than the dorsal side (n=3, 15.8%).

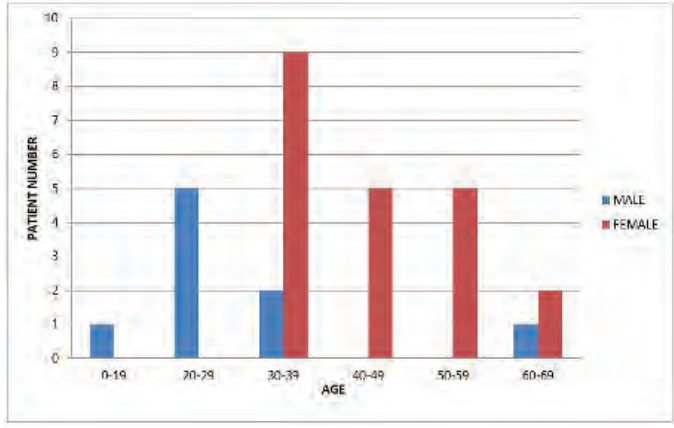

Figure 1. Distribution of the lesions according to age and gender

Table 1. Localization of the lesions		
Localization	**Number**	**Percent**
Hand	19	63.3
Foot	5	16.6
Ankle	3	10
Wrist	1	3.3
Knee	1	3.3
Elbow	1	3.3
Total	30	100

The histopathological type of tumor was 23 (76.6%) nodular (type 1) and 3 (23.3%) diffuse (type 2) GCTTS. In 19 hand cases, 18 were nodular type and one case was diffuse type GCTTS. The average lesion size (largest diameter) was 1.6 cm (SD: ±0.8, range; 0.6-4). The largest lesion was approximately 4x2.5x1.5 cm located on the left knee and was nodular type lesion (Figure 2). The average lesion size for recurrent lesions was 1.8 cm (SD: ±0.9, range; 0.8-3.4) and 1.5 cm (SD: ±0.7, range; 0.6-4) for non-recurrent lesions (p=0.35). None of the patients had an invasion of the neurovascular structures and no neurovascular damage was encountered. The pathological examination verified that all lesions were removed as marginal resection.

Recurrence was developed in 8 of the patients (26.6%). Four of the patients with recurrence were re-operated. The other 4 patients were not re-operated since they did not give their consent. Four of the recurrences were seen in the upper extremity (all of them in the fingers) and 4 in the lower extremity (3 in toes, one in the dorsum of the foot). Seven of the patients with recurrence were female (87.5%) and one patient was male (12.5%). Six of recurrent lesions were pathologically diagnosed as nodular type GCTTS and the other 2 were diffuse type GCTTS. The histopathological type of tumor was not found as a risk factor for recurrence (p=0.33) (Table 2). The number of mitotic figures was investigated to

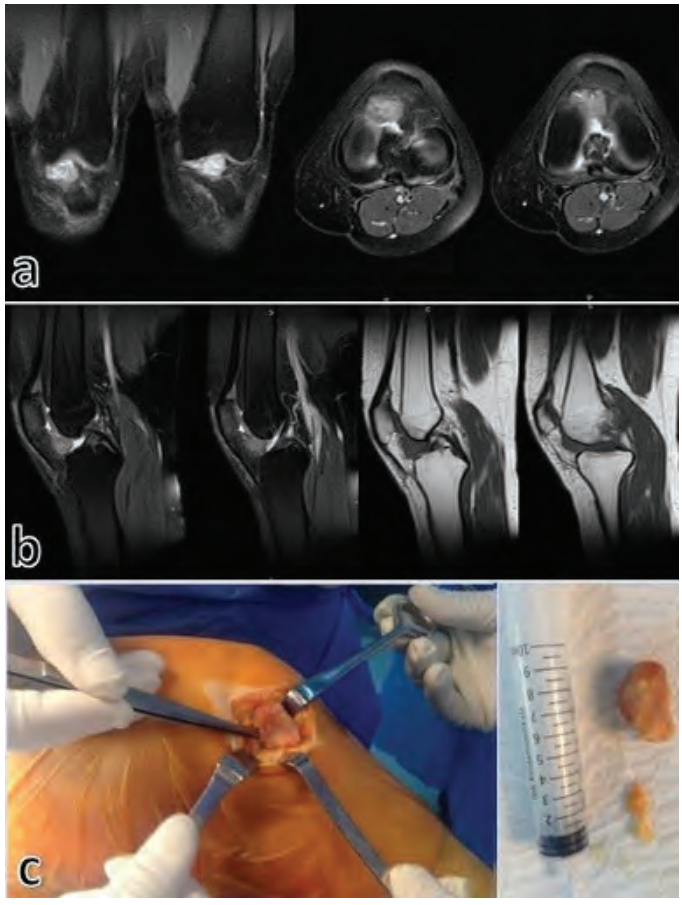

Figure 2. GCTTS of the left knee. (a) View on the coronal and axial sections of the MRI T2-weighted sequences, heterogeneous slightly high signal intensity of the tumor. (b) View on the sagittal sections of the MRI T2 fat-suppressed (moderate signal) &T1-weighted (low signal) sequences. (c) Perioperative image of excisional biopsy of the lesion and macroscopic views of the mass and it's pedicle (size: 4x2.5x1.5 cm) (the patient provided written informed consent for print and electronic publication of the figures)
GCTTS: Giant cell tumors of tendon sheath, MRI: Magnetic resonance imaging

evaluate their possible effect on recurrence development. Mitotic figures were detected in 7 of 8 patients who developed recurrence. Eleven of 22 patients without recurrence also had mitotic figures and the difference was not statistically significant (p=0.06) (Table 2). There was also no significant correlation between the localization of the hand lesions and recurrence rates (1 recurrence in the distal region (distal interphalangeal region and distal phalanx) and 3 recurrences in the proximal region) (p=0.82) (Table 2).

Bone erosion was detected in 3 of the cases (10%) preoperatively. Two of these cases were in the foot and one was in the hand. All patients with bone erosion developed recurrence. Bone erosion was found as a risk factor for recurrence (p=0.015) (Table 2). When a post hoc power analysis was performed using alpha 0.05, the power of the study was found to be 0.67. None of the patients had malignant transformation. No other complication was seen in the patients.

Table 2. Results of statistical analysis for possible risk factor variables

Variables	Patients without recurrence (%)	Patients with recurrence (%)	Risk ratio	p value
Bone erosion				
Yes	0 (0)	3 (100)	5.4	0.015*
No	22 (81)	5 (19)		
Mitotic figures				
Yes	11 (61)	7 (39)	4.66	0.06
No	11 (91.7)	1 (8.3)		
Tumor type				
Type 1 (nodular)	17 (74)	6 (26)	0.91	0.89
Type 2 (diffuse)	5 (71)	2 (29)		
Tumor localization (hand)				
Distal	3 (75)	1 (25)	0.75	0.82
Proximal	12 (80)	3 (20)		
*p<0.016 (Bonferroni correction)				

DISCUSSION

The treatment of GCTTS can represent a challenge for orthopedic surgeons due to the possibility of bone erosion and recurrent lesions. We analyzed the recurrence rate in our patient series and investigated the possible risk factors for recurrence. The overall recurrence rate was found as 26.6%. GCTTS with the presence of bone erosion was found related to increased risk of recurrence, while the presence of mitotic figures, histopathological type and tumor localization was not associated with recurrence.

GCTTSs are most frequently encountered in hands but they can also be seen in wrist, foot, ankle, elbow, knee, hip and rarely in spine. In a study of Ushijima et al. (8) which was published in 1986, out of 207 GCTTS patients; 158 lesions were on the fingers of the hand (76.3%), 25 lesions were on the toes (12%), 8 lesions were in the knee joint (3.8%), 4 lesions were in the wrist (1.9%) and 1 lesion was in the elbow. There were 30 patients in our series and the lesions of 19 patients were in hand (63,3%), 4 lesions in the toe (13,3%), 4 lesions in the foot and ankle (13,3%), 1 lesion in knee (3.3%) and 1 lesion in elbow (3.3%).

GCTTSs are more common in the volar face of the hand compared to the dorsal face and can interfere with grab and grip functions of the hand. In a study of 84 patients, published by Lautenbach et al. (9) 60 lesions were detected on the volar face (71%) and 24 lesions were detected on the dorsal surface of the hand (29%). In

our study, among 19 patients with lesions on their hand, 16 were volar (84.2%) and 3 were dorsal sided (15.8%) consistent with the literature.

There are two histopathological types of GCTTSs; type 1 (nodular) and type 2 (diffuse) (10). Nodular type is more common than diffuse type. Diffuse type is usually seen in the lower extremities, while nodular type GCTTS is usually seen on the hand (2). In Al-Qattan's (10) series of 43 cases, only 2 cases of diffuse type GCTTS were detected. In a study with 18 GCTTS cases published by Ikeda et al. (11); 10 cases were reported as nodular type and 8 as diffuse type GCTTS. In our study, 23 cases were identified as nodular type (76.66%) and 7 as diffuse type (23.33%). Among 19 cases with GCTTS in hand, 18 were classified as nodular type and one as diffuse type GCTTS.

Although GCTTSs are benign, they have high recurrence potentials. Recurrence rates has been reported in the literature from 7% to 44% (6). In our study, recurrence was detected in 8 patients (26.6%). In a study by Reilly et al. (12), 70 patients with GCTTS were followed and recurrence was detected in 19 (27%) of the patients and tumor localization was found to be a probable factor affecting recurrence. Most of the recurrences (57.6%) were seen in patients with lesions on the distal interphalangeal joint (12). They claimed that adequate excision is more difficult distally due to the limited space, the proximity to neurovascular structures, and limited soft tissue envelope leading to higher recurrence rates. In our study, 4 cases of recurrence were seen in the hand. There was no significant correlation between the localization of the hand lesions (proximal vs. distal) and recurrence rates (p=0.82). The recurrence rate of hand lesions in our study (21%) was slightly higher to current studies by Koutserimpas et al. (7) who found 11.1% recurrence rate among 36 patients, Jalgaonkar et al. (6) who found 9% recurrence rate among 46 patients and Williams et al. (13) who found 12.6% recurrence rate among 213 patients.

In a study with 43 cases by Al-Qattan (10), recurrence rates were higher in diffuse type GCTTS than in nodular type. Recurrence was observed in 5 patients out of 13 patients with diffuse type lesions (38%). It has been reported that no recurrence has been detected in any of the 30 cases with the nodular type lesions (10). In a recent study by Shi et al. (14), diffuse form was found related with recurrence. However, Reilly et al. (12) couldn't show a relation with the histopathology of the tumor and recurrence rate. In our study, recurrence was detected in 6 of 23 patients with nodular lesions (26%) and in 2 (28.5%) of the 7 cases with diffuse type. According to these findings, no significant relation was found between histopathological type and recurrence rates (p=0.33).

Although there are some publications in the literature reported that the increased number of mitotic figures is related to recurrence (15), there is not enough evidence. Rao and Vigorita (16) found a higher recurrence rate for tumors with increased cellularity and mitotic activity on histological examination. A high mitotic rate was thought to be indicative of local recurrence. Kotwal et al. (17) recommended radiotherapy in the presence of mitotic figures to overcome recurrences. However, Al-Qattan (10) reported that neither cellularity nor mitoses could be considered significant prognostic histological factors for recurrence. In their 71 patient series, Monaghan et al. (18) concluded that mitotic figures do not predict the clinical behavior of the tumor. In our study, no significant association was found between the presence of mitotic figures and recurrence (p=0.06). However, p value was close to significance, so the difference can become significant in patient series with a higher number of patients.

In GCTTSs, bone erosion can be observed because of long-term pressure by the lesion and these erosion can be detected in direct radiographs. In a study by Moore et al. (19), bone erosion was detected in 9% of 115 patients. Fyfe and MacFarlane (20) reported 36% bone erosion in their patient series of 51 cases. In our study, bone erosion was detected in 3 of 30 cases (10%) with a similar rate to the literature. Jalgaonkar et al. (6) reported that recurrence was detected more frequently in cases with bone erosion. In our study, recurrence was detected in all 3 patients with bone erosion and it was found as a risk factor similar to the literature. GCTTSs are benign tumors but rarely, they can also represent malignant transformation (21). In our study, the malignant transformation was not observed in any case.

Study Limitations

The most important limitation of this study was the small number of patients. However, even most recent studies on GCTTS include similar patient numbers since it is a relatively rare lesion (6,7,22,23). Larger multicenter studies will give more reliable results. The retrospective design of this study was another limiting factor.

CONCLUSION

Preoperative bone erosion is an important risk factor for recurrence in GCTTS and patients with preoperative bone erosion should be followed closely. The presence of mitotic figures, histopathological type and tumor localization didn't significantly increased the recurrence rate.

Ethics

Ethics Committee Approval: Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Local Ethical Committee (year: 2016, no: 83045809).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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REFERENCES

1. Ozalp T, Yercan H, Kurt C, Ozdemir O, Coşkunol E. Giant-cell tumors of the tendon sheath involving the hand or the wrist: an analysis of 141 patients. Acta Orthop Traumatol Turc 2004;38:120-4.
2. Gouin F, Noailles T. Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented villonodular synovitis). Orthop Traumatol Surg Res 2017;103:S91-7.
3. Lanzinger WD, Bindra R. Giant cell tumor of the tendon sheath. J Hand Surg Am 2013;38:154-7; quiz 157.
4. Çevik HB, Kayahan S, Eceviz E, Gümüştaş SA. Tenosynovial giant cell tumor in the hand: experience with 173 cases. J Hand Surg Asian Pac Vol 2020;25:158-63.
5. Ozben H, Coskun T. Giant cell tumor of tendon sheath in the hand: analysis of risk factors for recurrence in 50 cases. BMC Musculoskelet Disord 2019;20:457.
6. Jalgaonkar A, Dhinsa B, Cottam H, Mani G. Giant cell tumours of tendon sheath of hand: causes and strategies to prevent recurrence. Hand Surg 2011;16:149-54.
7. Koutserimpas C, Kastanis G, Ioannidis A, Filippou D, Balalis K. Giant cell tumors of the tendon sheath of the hand: an 11-year retrospective study. J BUON 2018;23:1546-51.
8. Ushijima M, Hashimoto H, Tsuneyoshi M, Enjoji M. Giant cell tumor of the tendon sheath (nodular tenosynovitis). A study of 207 cases to compare the large joint group with the common digit group. Cancer 1986;57:875-84.
9. Lautenbach M, Kim S, Millrose M, Eisenschenk A. Nodular giant cell tumour of the tendon sheath of the hand: analysis of eighty-four cases: diagnostic decisions and outcome. Int Orthop 2013;37:2211-5.
10. Al-Qattan MM. Giant cell tumours of tendon sheath: classification and recurrence rate. J Hand Surg Br 2001;26:72-5.
11. Ikeda K, Osamura N, Tomita K. Giant cell tumour in the tendon sheath of the hand: importance of the type of lesion. Scand J Plast Reconstr Surg Hand Surg 2007;41:138-42.
12. Reilly KE, Stern PJ, Dale JA. Recurrent giant cell tumors of the tendon sheath. J Hand Surg Am 1999;24:1298-302.
13. Williams J, Hodari A, Janevski P, Siddiqui A. Recurrence of giant cell tumors in the hand: a prospective study. J Hand Surg Am 2010;35:451-6.
14. Shi J, Zheng J, Zhou X, Li Z, Chen X, Gao W, et al. Risk factors associated with postoperative recurrence in patients with tenosynovial giant cell tumor of the hand: a retrospective cohort study. Ann Plast Surg 2019;83:523-8.
15. Wright CJE. Benign giant-cell synovioma: an investigation of 85 cases. Br J Surg 1951;38:257-71.
16. Rao AS, Vigorita VJ. Pigmented villonodular synovitis (giant-cell tumor of the tendon sheath and synovial membrane). A review of eighty-one cases. J Bone Joint Surg Am 1984;66:76-94.
17. Kotwal PP, Gupta V, Malhotra R. Giant-cell tumour of the tendon sheath. Is radiotherapy indicated to prevent recurrence after surgery? J Bone Joint Surg Br 2000;82:571-3.
18. Monaghan H, Salter DM, Al-Nafussi A. Giant cell tumour of tendon sheath (localised nodular tenosynovitis): clinicopathological features of 71 cases. J Clin Pathol 2001;54:404-7.
19. Moore JR, Weiland AJ, Curtis RM. Localized nodular tenosynovitis: experience with 115 cases. J Hand Surg Am 1984;9:412-7.
20. Fyfe IS, MacFarlane AU. Pigmented villonodular synovitis of the hand. Hand 1980;12:179-88.
21. Bertoni F, Unni KK, Beabout JW, Sim FH. Malignant giant cell tumor of the tendon sheaths and joints (malignant pigmented villonodular synovitis). Am J Surg Pathol 1997;21:153-63.
22. Galbiatti JA, Milhomens GRDS, Silva LFHFE, Santiago DDS, Silva Neto JCD, Belluci SOB. Retrospective study of the results of surgical treatment of 31 giant cell tumors of the tendon sheath in the hand. Rev Bras Ortop (Sao Paulo) 2019;54:26-32.
23. Kumar R, Bharani V, Gupta N, Gupta K, Dey P, Srinivasan R, et al. Giant cell tumour of tendon sheath: a 10-year study from a tertiary care centre. Cytopathology 2018;29:288-93.

ORIGINAL ARTICLE

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Relationship Between Overactive Bladder and Anxiety in Young Men Population in Turkey

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Abstract

Objective: Overactive bladder (OAB) symptoms affect quality of life. The current study evaluates the relationship between anxiety and OAB in young male patients in Turkish society.

Methods: Male patients aged 18-35 years, diagnosed with OAB between 2015 and 2020, were included in the study. OAB query form (OAB-V8) was filled by participants. Hamilton anxiety scale (HAM-A) was used to evaluate the anxiety levels of OAB patients. OAB-V8 scores were compared statistically before and after anxiolytic treatment of anxious patients.

Results: The mean age of 87 patients was 26.28±4.53 (95% confidence interval: 25.5-27.2) and the mean OAB-V8 symptom score was 24.96±5.7 (14-36). The OAB-V8 symptom score in the group without anxiety (group 1) and the group with moderate anxiety (group 2) improved significantly at 1 month compared to the pre-treatment period ($p<0.001$). When the OAB-V8 symptom scores in the third month were analyzed, the 1st group who didn't receive anxiolytic treatment and the 2nd and 3rd group scores receiving anxiolytic treatment were 9.6±1.8, 11.2±3.2, 10.6±2.8, and significant change in all three groups compared to the 1st month was observed ($p<0.001$).

Conclusion: In patients with anxiety, the problems caused by OAB are significantly higher than the normal population. In our study, HAM-A anxiety scores were found higher in patients with OAB. OAB is a common condition that can be seen in the young male population and may accompany anxiety. Treatments combined with multidisciplinary approaches are highly effective in these patients.

Keywords: Overactive bladder, anxiety, male, young

INTRODUCTION

Overactive bladder (OAB) is a condition characterized by a sudden feeling of urination, accompanied by urinary frequency and nocturia, with incontinence. The frequency of OAB in the USA is 16% for men and 17% for women (1). According to the EpiLUTS study conducted in the USA, 27% of men and 43% of women experienced symptoms of OAB at some point in their lives (2).

Studies indicate that many patients with OAB also have non-urological symptoms. It has been reported that symptoms of urination, storage and urine are significantly associated with arthritis, asthma, chronic anxiety, depression, heart disease, irritable bowel syndrome, neurological diseases and sleep disorders (3). OAB symptoms affect daily life, decrease the quality of life, affect work efficiency negatively, disrupt family life, social relationships and sleep patterns (4). Besides all these negativities exacerbate each other, these conditions also negatively affect the mental health of the patients. However, it is still a matter of debate whether anxiety is the cause or the result of OAB (5,6). Studies are generally directed at the fact that OAB impairs the psychosocial situation. However, the number of studies conducted in the literature that the mental state causes OAB is low. Also, most of the studies in the literature are related to female patients. The number of studies on male patients is low.

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The current study evaluates the relationship between anxiety and OAB in young male patients in Turkish society.

METHODS

Male patients between the ages of 18-35 who were diagnosed with OAB between 2015 and 2020 were included in this retrospective study. Inclusion criteria; according to the International Continence Association (ICS) 2002 criteria, it was determined that there was a diagnosis of OAB with or without urinary incontinence, infection that could make a feeling of urgent urination, pelvic radiotherapy history, no neurological diseases, and not diagnosed with anxiety and/or treatment in the last 6 months. Clinical evaluation was made according to the AUA guideline with a history, physical examination, urinalysis, post-voiding residual volume. Written consent was obtained from all patients who participated in the study. This study was approved by the University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital Ethics Committee; 2020/52, and conducted in accordance with the provisions of the Helsinki Declaration.

Evaluation

The clinical diagnosis of OAB was made using the 2002 ICS diagnostic criteria and published AUA guidelines were followed. All study participants filled the OAB query form (OAB-V8), the Turkish version of which was validated to evaluate lower urinary tract symptoms (7). For the score, 11 was accepted as the threshold value and 2 additional points were added to the score for the male gender.

The patients were consulted to the psychiatry clinic for the diagnosis of anxiety. Hamilton anxiety rating scale (HAM-A) was used to evaluate the anxiety of OAB patients. HAM-A was one of the first grading scales developed to measure the severity of anxiety symptoms and is still widely used in both clinical and research fields today. The scale consists of 14 items, each defined by a series of symptoms and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical anxiety-related complaints). Each item is scored on a scale of 0 (unavailable) to 4 (severe), and the total score range is 0-56. Patients diagnosed with OAB and included in the study were divided into 3 groups according to Hamilton anxiety scores. Those with a score below 17 had no anxiety, 18-24 were moderate anxious and greater than 25 were considered severe anxious. The group without anxiety was called group 1 (mild), the group with moderate anxiety (group 2) (group) and the group with severe anxiety group 3 (severe).

Patients diagnosed with OAB according to the OAB-V8 symptom score were filled with the HAM-A scale before starting anticholinergic treatment. Solifenacin was started at a dose of 5 mg/day for OAB treatment. OAB-V8 symptom scores were again filled in the patients who were called for control one month later. The 1 month OAB-V8 scores of the patients who were divided into groups according to anxiety severity were compared statistically. Patients who had no improvement in symptom score and had moderate and severe anxiety according to the HAM-A scale before anticholinergic treatment was consulted to the psychiatry department. OAB-V8 symptom scores were reassessed in the 3rd month of patients who were started on anxiolytic treatment appropriate to the patient and continued concomitant anticholinergic treatment by psychiatry. OAB-V8 symptom scores were compared statistically before and after the anxiolytic treatment of anxious patients.

Statistical Analysis

Statistical Package 23.0 (Social SPSS Statistics; New York, USA) was used for statistical analysis. Data for continuous variables are expressed as mean and standard deviation. Data for categorical variables were expressed as percentage and frequency. For continuous variables, the differences between the three groups analyzed using the Kruskal-Wallis test, and meaningful two groups were analyzed using the Dunnet test. In the OAB score analysis, it was analyzed using Freidman test and Dunn test. Statistical significance level was set at $p<0.05$.

RESULTS

Ninety-five patients who applied to the outpatient clinic and whose OAB-V8 symptom score was above 11 participated in the study. Three of the patients who participated in the study were excluded from the study because they did not come for control and 5 of them left the drug due to anticholinergic side effects. The mean age of 87 patients participating in the study was 26.28±4.53 (95% confidence interval: 25.5-27.2) years, and the patients' OAB-V8 symptom score was 24.96±5.7 (14-36). Before anticholinergic treatment, HAM-A scale was completed. Mild anxiety was detected in 49 patients, moderate in 22 patients, severe anxiety in 16 patients and patients were divided into 3 groups accordingly. The median OAB-V8 symptom score before treatment was found as 20 [interquartile range (IQR): 18.0-26.0], 28 (IQR: 26.0-30.0), 31 (IQR: 28.0-33.0) in groups 1, 2, and 3 respectively. OAB-V8 score before treatment was significantly lower in group 1 ($p<0.001$), but there was no significant difference between groups 2 and 3 ($p=0.22$). A significant improvement was achieved in the OAB-V8 symptom score at 1

month compared to the pre-treatment period in the group of patients without anxiety (group 1) and group with moderate anxiety (group 2) ($p<0.001$) (Figure 1). However, in the group with severe anxiety (group 3), it was observed that there was a statistically insignificant decrease in the OAB score at 1 month ($p=0.64$) (Table 1).

When the OAB-V8 symptom scores in the third month were analyzed, the 1st group who did not receive anxiolytic treatment and the 2nd and 3rd group scores receiving anxiolytic treatment was 10 (IQR: 9.0-10.0), 10 (IQR: 9.0-13.0), 10.5 (IQR: 9.0-11.5), and the significant change was observed in all three groups at 3rd month compared to the pretreatment ($p<0.001$). There was no statically considerable change found between 1st month and 3rd months scores ($p=0.10$). Additionally, there was no statistically significant found between 1st month and pretreatment scores in group 3 ($p=0.64$).

DISCUSSION

In a study conducted by the world health organization, anxiety was reported to be the most common psychiatric disorder globally (8). The prevalence of lifelong anxiety disorder in the USA is around 18%. Some researchers thought that psychosomatic disorders such as anxiety may affect the pathogenesis of OAB (9), and this has been shown in clinical-based and epidemiological studies (10). In our study, a relationship was found between OAB and anxiety. The relationship between affective disorders and lower urinary tract symptoms was first described by Engel in 1964. The link between the brain and bladder has not been clarified today, but it has been reported that it may be using the same neuropharmacological pathways according to the hypotheses (10,11). It is unclear which OAB and anxiety that are thought to be related trigger the other.

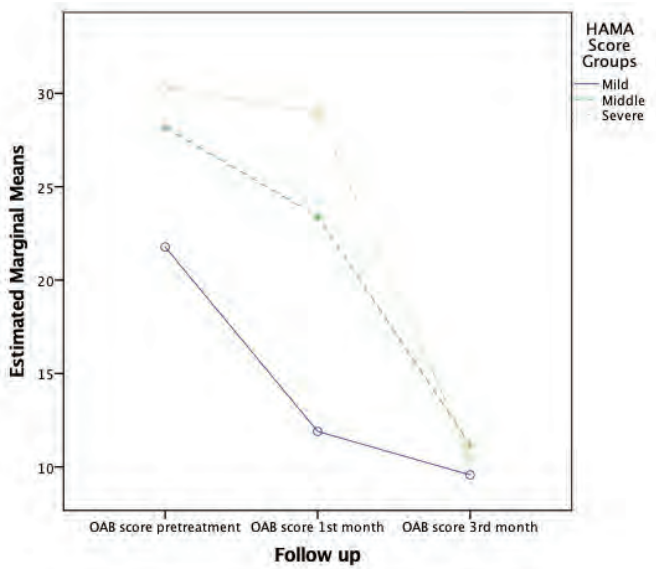

Figure 1. OAB-V8 score changes of groups after treatment
OAB: Over active bladder, HAM-A: Hamilton anxiety scale

In a study by Milsom et al. (12), OAB, and OAB in participants with hospital anxiety and depression scale (HADS) -anxiety and HADS-depression (HADS-D) scores and who showed clinically significant anxiety and depression levels. The problems caused by the patients were found to be significantly higher than those with low anxiety and depression scores ($p<0.001$). In logistic regression analysis, the strongest ailment markers associated with OAB for both men and women were determined as urine urgency, urinary incontinence, urinary frequency and nocturia, respectively. A significant increase in OAB -related disorders were observed in male participants as the level of education, HADS-anxiety (HADS-A) score and general health problems increased. In our study, as the level of anxiety increases in male patients, the OAB-V8 symptom score increases and the treatment of OAB becomes difficult. With anxiolytic treatment given in addition to anticholinergic treatment, a significant improvement in OAB-V8 symptom score is observed in the 3rd month. In the EpiLUTS study, in the interviews with patients with OAB symptoms, the reason for the anxiety of the patients was stated as the concern of finding a toilet in time and the urinary incontinence. Simultaneously, constant anxiety of going to the toilet in some participants led to a feeling of hopelessness and depression in patients (12).

In the literature, Lai et al. (13) in a study he conducted and compared the psychological scales, OAB patients with common systemic symptoms had worse HADS-D, HADS-A,

Table 1. OAB-V8 scores of anxiety groups

	HAM-A score groups			
	Mild	Moderate	Severe	p
OAB score pretreatment	20 (18.0-26.0)	28 (26.0-30.0)	31 (28.0-33.0)	p<0.001
OAB score 1st month	11 (9.0-15.0)	23 (21.0-26.0)	30 (27.0-30.5)	p<0.001
OAB score 3st month	10 (9.0-10.0)	10 (9.0-13.0)	10.5 (9.0-11.5)	p=0.16

All data was expressed as median + interquartile range. OAB: Over active bladder, HAM-A: Hamilton anxiety scale

fatigue symptoms (PROMIS-Fatigue) and higher than OAB patients without common systemic symptoms. They detected psychological stress (13). Results were statistically significant for all comparisons adjusted for age and gender ($p<0.05$). Similar to the literature, HAM-A scores were higher in patients with OAB with urinary incontinence in our study.

In a study of Alves et al. (14), Hopkins investigated the relationship of OAB with anxiety symptoms using three items of the symptom checklist, and although the cause-effect relationship could not be established, the authors concluded that individuals with OAB are more prone to anxiety symptoms. Similar to these results, although we showed the relationship between anxiety and OAB in our study, we could not show the cause-effect relationship between the two disorders.

CONCLUSION

OAB is a common condition that can also be seen in the young male population and may accompany anxiety. Questioning the psychosomatic complaints of patients and treating them with a multidisciplinary approach may provide better results.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital Ethics Committee; 2020/52, and conducted in accordance with the provisions of the Helsinki Declaration.

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: O.K., B.V., Design: O.K., B.V., Data Collection or Processing: O.K., M.Ü., Analysis or Interpretation: F.G., Literature Search: A.Ö.H., Writing: O.K., Ö.M.

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REFERENCES

1. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003;20:327-36.
2. Coyne KS, Sexton CC, Vats V, Thompson C, Kopp ZS, Milsom I. National community prevalence of overactive bladder in the United States stratified by sex and age. Urology 2011;77:1081-7.
3. Coyne KS, Kaplan SA, Chapple CR, Sexton CC, Kopp ZS, Bush EN, et al. Risk factors and comorbid conditions associated with lower urinary tract symptoms: EpiLUTS. BJU Int 2009;103(Suppl 3):24-32.
4. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int 2008;101:1388-95.
5. Bogner HR, Gallo JJ, Swartz KL, Ford DE. Anxiety disorders and disability secondary to urinary incontinence among adults over age 50. Int J Psychiatry Med 2002;32:141-54.
6. Felde G, Bjelland I, Hunskaar S. Anxiety and depression associated with incontinence in middle-aged women: a large Norwegian cross-sectional study. Int Urogynecol J 2012;23:299-306.
7. Tarcan T, Mangır N, Özgür MÖ, Akbal C. OAB-V8 Overactive bladder questionnaire validation study. Üroloji Bülteni 2012;21:113-6.
8. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:629-40.
9. Freeman RM, McPherson FM, Baxby K. Psychological features of women with idiopathic detrusor instability. Urol Int 1985;40:257-9.
10. Zorn BH, Montgomery H, Pieper K, Gray M, Steers WD. Urinary incontinence and depression. J Urol 1999;162:82-4.
11. Klausner AP, Steers WD. Corticotropin releasing factor: a mediator of emotional influences on bladder function. J Urol 2004;172:2570-3.
12. Milsom I, Kaplan SA, Coyne KS, Sexton CC, Kopp ZS. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. Urology 2012;80:90-6.
13. Lai HH, Vetter J, Jain S, Andriole GL. Systemic nonurological symptoms in patients with overactive bladder. J Urol 2016;196:467-72.
14. Alves AT, Jácomo RH, Gomide LB, Garcia PA, Bontempo AP, Karnikoskwi MG. Relationship between anxiety and overactive bladder syndrome in older women. Rev Bras Ginecol Obstet 2014;36:310-4.

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Evaluation of Quality of Life, Anxiety and Depression in Patients with Recurrent Aphthous Stomatitis

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Abstract

Objective: Recurrent aphthous stomatitis (RAS) is one of the most common diseases of the oral mucosa characterized by recurrent painful oral ulcers. We evaluated the effect of RAS on quality of life and the relationship between RAS and anxiety and depression.

Methods: The study involved 70 patients (35 female, 35 male) with RAS and 70 healthy volunteers (32 females, 38 males) who matched the patients with age and gender. Demographic features and medical histories of individuals were recorded. Patients and controls filled out the dermatology quality of life index (DLQI) and the hospital anxiety and depression scale (HADS). The results were compared statistically.

Results: The DLQI score of RAS patients was significantly higher than the control group [$p<0.001$, interquartile range (IQR): 6.0-15.0 vs. 2.0-9.0]. DLQI score for the patients during the active phase was significantly higher than that for the patients during the remission period ($p=0.039$, IQR: 6.5-16.0 vs. 2.0-10.0). There was no significant difference in HAD score between the groups ($p>0.05$).

Conclusion: The results of our study show that there is no relationship between RAS and anxiety and depression. However, RAS significantly decreases the quality of life, particularly during the active phase.

Keywords: Anxiety, aphthous stomatitis, depression, oral ulcer, quality of life

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most common disease of oral mucosa characterized with recurrent painful ulcerations. The prevalence of the disease ranges from 5% to 60% with an average of 20% (1,2). RAS can affect people at any age; oral ulcerative episodes first appear before the age of 30 years in about 80% of cases and generally, the severity and frequency decreases as age advances (3,4). Approximately 40% of the patients with RAS have a family history (5). Three main types include minor, major and herpetiform aphthae which change in size, number, duration, place and potential for scarring of ulcerations. The lesions are identified by a single or multiple round or oval-shaped, inflamed ulcers, with a grayish or yellowish background, surrounded by an erythematous halo. RAS is a multifactorial condition with various predisposing factors. Investigations have proposed genetics, malnutrition, hematological deficiencies, microbial factors, immunodeficiency disorders, trauma, endocrinological, gastroenterological disorders, drugs and stress (6,7). There are many studies in the literature regarding the impact of stress, anxiety, and depression in the etiology of RAS, but the results are controversial. Some authors suggest that stress and anxiety are involved in the etiology of RAS (8-10). They suggest that anxiety and severe stress trigger the immune system activity by increasing the number of leukocytes in the inflammation sites consequently, leading to onset and progression of RAS (11-13). However, some authors report that there is no association

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between the psychological status of patients and RAS (14-16). In this study, we evaluated the association between quality of life, anxiety, and depression with RAS.

METHODS

Patients and Study Design

A prospective and controlled clinical trial was planned to assess dermatology quality of life index (DLQI) and hospital anxiety and depression scale (HADS) in patients with RAS. The study was administered with the cooperation of Ataturk University Faculty of Medicine, Departments of Dermatology and Venereal Diseases. Atatürk University Faculty of Medicine Ethics Committee approved the study (number of meetings: 6, decision no: 10, date: 30.11.2017). Seventy patients with RAS and 70 healthy controls were included between November 2017 and November 2018 after giving their informed consent.

All cases with oral aphthous ulcerations that occur more than three episodes per year were included in the RAS group after anamnesis, physical examination and laboratory evaluation. Exclusion criteria were:

1. Cases with a history of systemic condition, in particular, Behcet's syndrome, systemic lupus erythematosus or any other diseases presenting with oral mucosal findings,

2. Patients with a history of psychiatric diseases,

3. Those with a history of antimicrobial, anti-inflammatory medication, immunomodulatory agents and vitamin or antioxidant drug usage through the four weeks before the study.

The control group consisted of age and sex-matched healthy 70 people. They were selected from hospital staff, students and relatives without any systemic and psychiatric diseases.

Personal data and anamnesis of patients were documented and the patients completed DLQI and HADS on the day of clinical examination. Personal data of controls were documented and controls completed DLQI and HADS.

DLQI is the most frequently used method because it is simple and clear. Patients' direction to affect social and physical activations in the last week has been tried to be understood. It is designed on the basis of symptoms, feelings of the patient, daily activity, leisure time, school/work life, personal relationships and treatment. DLQI, consists of 10 items, each item is scored: "Very much" - score 3, "a lot" - score 2, "a little" - score 1, "not at all" and "irrelevant" - score 0. Based on their scores, five score ranges can be classified as follows: No effect at all on patient's life (0-1), a small effect on patient's life (2-5), a moderate effect on patient's life (6-10), and very large effect on patient's life (11-20), extremely large effect on patient's life (21-30).

The HADS detect mood disorders in non-psychiatric hospital clinics, evaluate anxiety and depression separately and exclude symptoms to prevent physical illnesses' effects on the scores. It is quick, short and easy to answer and consists of seven anxiety items and seven depression items (14 items). Each item is responded on a four-point measure. The total score ranges from 0 to 21 points for anxiety and similarly 0 to 21 points for depression. Based on their scores, three score ranges can be categorized as follows: Normal (0-7), borderline abnormal (8-10), and abnormal (11-21).

Statistical Analysis

Statistical analysis was performed using SPSS software, version 22. Descriptive data were shown as n, percent in categorical data, and as median, interquartile range (25-75 percentile values) in scale data. Chi-square test was used to compare categorical data. The normality of data was tested using a Kolmogorov-Smirnov test. Mann-Whitney U test and Kruskal-Wallis test was used for not having a normal distribution. A p value of less than 0.05 was considered statistically significant.

RESULTS

This study encompassed 70 RAS cases (35 males and 35 females) with a mean age of 29.6±10.8 years and 70 controls (38 males and 32 females) with a mean age of 29.3±10.6 years. There were no differences in terms of age, gender, marital status, and educational level (Table 1).

Table 1. Demographic characteristics of groups

		Patients		Controls		p[a]
Parameter	**Category**	**n**	**%**	**n**	**%**	
Age	≤30 years	42	60.0	44	63.8	0.647
	>30 years	28	40.0	25	36.2	
Gender	Female	35	50.0	38	54.3	0.612
	Male	35	50.0	32	45.7	
Marital status	Single	32	45.7	41	58.6	0.128
	Married	38	54.3	29	41.4	
Educational level	Primary school	21	30.0	11	15.7	0.094
	High school	21	30.0	30	42.9	
	University	28	40.0	29	41.4	
Occupation	Student	22	31.4	19	27.1	0.593
	Housewife	16	22.9	13	18.6	
	Other	32	45.7	38	54.3	

[a]Chi square test

Sixty (85.7%) of patients were in the active phase and 10 (14.3%) of patients were in remission period during examination. 36 (51.4%) of the patients had disease for five years and more (Table 2). Most of the patients had 2 to 3 attacks per month.

DLQI scores of RAS patients ranged from 0 to 30 [interquartile range (IQR): 6.0-15.0]; DLQI scores of controls ranged from 0 to 30 (IQR: 2.0-9.0). DLQI score was significantly higher in the patient group than the control group (p<0.001, Table 3, Figure 1).

HADS of patients ranged from 1 to 20 (IOR 4.0-11.0) for anxiety, 0 to 15 (IQR: 2.0-7.0) for depression. Similarly, the control group's HAD scores ranged from 1 to 18 (IQR: 5.0-10.0) for anxiety, 0 to 14 (IQR: 2.0-8.0) for depression. There was no statistically significant difference between two groups with respect to both anxiety and depression scores (p=0.912, p=0.978) (Table 3).

Anxiety HADS of female patients was higher than that of male patients (IQR: 5.0-12.0 vs. 4.0-9.0, p=0.019). There was no relationship between gender and DLQI and depression scores as well as age, marital status, education status, family history and DLQI and HADS (Table 4).

DLQI score of the patients with RAS during the active phase was higher than that for those with RAS during the remission period (IQR: 6.5-16.0 vs. 2.0-10.0, p=0.039, Figure 2). There was no difference between the patients during the active phase and the patients during the remission period in terms of scores of anxiety and depression. No difference was found between the duration of disease and frequency of attacks, and scale scores (Table 4).

Table 2. Detailed characteristics of patients

Parameter	Category	n	%
Family history	Positive (+)	42	60.0
	Negative (-)	28	40.0
Mean duration of disease (year)	<5	34	48.6
	≥5	36	51.4
Frequency of attacks (per year)	≤12	14	20.0
	13-36	34	48.6
	>36	22	31.4
Presence of oral ulcer	Active phase	60	85.7
	Remission period	10	14.3

Table 3. The statistical analysis of scale scores in RAS patients and controls

	Patients		Controls		p[a]
Parameter	**Median**	**IQR**	**Median**	**IQR**	
DLQI	10.0	6.0-15.0	5.0	2.0-9.0	**<0.001**
HADS-A	7.0	4.0-11.0	7.0	5.0-10.0	0.912
HADS-D	5.0	2.0-7.0	5.0	2.0-8.0	0.978

[a]Mann-Whitney U test, IQR: Interquartile range, DLQI: Dermatology life quality index, HADS-A: Hospital anxiety and depression scale anxiety, HADS-D: Hospital anxiety and depression scale depression, RAS: Recurrent aphthous stomatitis

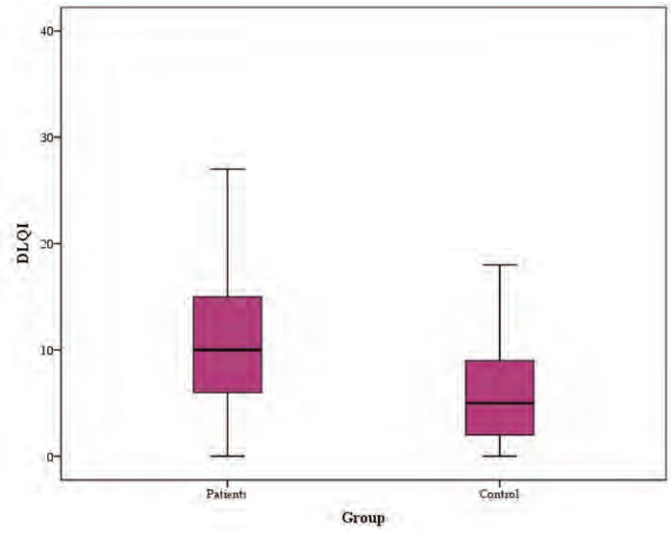

Figure 1. DLQI scores of RAS patients and controls
DLQI: Dermatology life quality index, RAS: Recurrent aphthous stomatitis

DISCUSSION

Our study is a prospective and comparative evaluation of the quality of life, anxiety and depression status of RAS patients in Turkey by using DLQI and HADS. There are many studies in the literature about the relationship between quality of life, anxiety and depression and RAS. Most of the studies assessed quality of life by using the oral health impact profile (OHIP-14) (17-19). DLQI is the most frequently used method worldwide in dermatology clinics. HADS, the social readjustment rating scale, structured clinical interview for DSM-IV clinical version, self-rating anxiety scale, general health questionnaire scale, Spielberger state-trait anxiety inventory (STAI), Hamilton's anxiety rating scale (HARS) and Hamilton's depression rating scale (HDRS), Lipp's inventory of stress symptoms (LSSI), Beck anxiety inventory and Beck depression inventory-II are used for the evaluation of the anxiety and depression in patients with oral disease, particularly RAS (8,14,20,21). We assessed the state of anxiety and depression in RAS patients by using HADS because it excludes somatic symptoms, which prevent the effects of physical illnesses on the scores (14,22).

Yang et al. (18), analyzed psychological problems of the patients with RAS, oral lichen planus (OLP) and burning mouth syndrome (BMS) using OHIP-14 and HADS. They reported that patients with RAS, OLP, and BMS had lower quality of life and higher levels of

Table 4. The statistical analysis of scale scores in RAS patients

		DLQI		HADS-A		HADS-D	
Parameter	**Category**	**Median (IQR)**	**p**	**Median (IQR)**	**p**	**Median (IQR)**	**p**
Age[a] (year)	≤30	9.5 (6.0-14.0)	0.986	7.0 (4.0-11.0)	0.750	5.0 (2.0-7.0)	0.157
	>30	10.5 (5.0-16.5)		6.5 (5.0-10.5)		6.0 (3.0-9.5)	
Gender[a]	Female	11.0 (8.0-16.0)	0.070	8.0 (5.0-12.0)	**0.019**	6.0 (3.0-8.0)	0.306
	Male	8.0 (4.0-15.0)		6.0 (4.0-9.0)		5.0 (2.0-7.0)	
Marital status[a]	Single	10.5 (7.5-14.0)	0.493	8.0 (3.5-11.0)	0.335	5.0 (2.5-7.5)	0.817
	Married	9.0 (5.0-17.0)		6.0 (4.0-9.0)		5.5 (2.0-7.0)	
Educational level[b]	Primary school	11.0 (6.0-17.0)	0.232	8.0 (5.0-11.0)	0.655	7.0 (4.0-12.0)	0.168
	High school	9.0 (5.0-11.0)		6.0 (4.0-10.0)		5.0 (2.0-7.0)	
	University	10.5 (6.0-19.5)		6.5 (5.0-9.0)		5.0 (2.0-7.0)	
Family history[a]	Positive	10.5 (5.0-16.0)	0.666	6.5 (4.0-10.0)	0.904	5.5 (2.0-7.0)	0.837
	Negative	9.0 (6.0-13.5)		7.0 (4.0-11.0)		5.0 (2.0-8.0)	
Duration of disease (year)[a]	<5	10.0 (6.0-14.0)	0.906	6.5 (4.0-11.0)	0.710	5.0 (3.0-7.0)	0.976
	≥5	9.5 (5.0-18.0)		7.0 (5.0-10.0)		5.5 (2.0-7.5)	
Frequency of attacks[b] (per year)	≤12	8.0 (5.0-14.0)	0.315	5.5 (4.0-9.0)	0.419	5.0 (2.0-7.0)	0.263
	13-36	10.5 (5.0-13.0)		6.5 (4.0-11.0)		5.0 (2.0-7.0)	
	>36	11.0 (8.0-18.0)		8.5 (4.0-11.0)		7.0 (4.0-10.0)	
Oral ulcer[a]	Active phase	11.0 (6.5-16.0)	**0.039**	7.0 (4.5-11.0)	0.084	5.0 (2.5-8.0)	0.467
	Remission period	5.0 (2.0-10.0)		5.0 (2.0-6.0)		5.5 (2.0-6.0)	

[a]Mann-Whitney U test, [b]Kruskal-Wallis test, IQR: Interquartile range, DLQI: Dermatology life quality index, HADS-A: Hospital anxiety and depression scale anxiety, HADS-D: Hospital anxiety and depression scale depression, RAS: Recurrent aphthous stomatitis

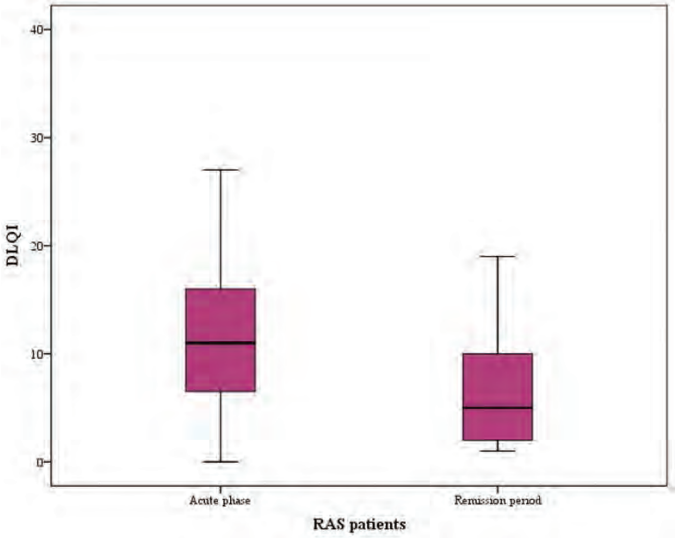

Figure 2. DLQI scores of the patients during active phase and the patients during remission period
DLQI: Dermatology life quality index

anxiety and depression. Suresh et al. (23), estimated the validity of other oral mucosal diseases in anxiety and depression patients. In the study, there was a statistically significant difference in oral diseases in patients with anxiety and depression compared to the control group. They detected RAS with a rate of 12% in the patient group and 2.2% in the control group and suggested that anxiety and depression is a risk factor for RAS. Nadendla et al. (13), compared RAS patients with controls by using HARS and reported that the mean anxiety scores of the RAS group were significantly higher. They suggested anxiety may be involved in the etiopathogenesis of RAS and psychological support is beneficial for patients with RAS. Similarly, Cardoso et al. (24), assessed anxiety levels of RAS patients by using LSSI and BAI and they reported that higher levels of anxiety were associated with RAS. Gallo et al. (25), proposed that psychological conditions might play a role as a trigger or a modifying factor in RAS rather than being a cause of the disease.

The authors who reported that stress was related to the etiopathogenesis of RAS have suggested some mechanisms whereby stress might result in RAS. Increasing the number of leukocytes in the sites of inflammation due to immune system activity, increased production of inflammatory cytokines due to oxidative stress, increased salivary cortisol levels and trauma associated with biting the oral mucosa in stressful times are the proposed mechanisms (11,12,26,27).

Polat et al. (20), evaluated the state of anxiety and depression by using HARS and HDRS and found no difference between the

patients and controls for anxiety, but there was a significant difference between the groups in terms of depression. Zwiri (14), evaluated the quality of life, anxiety, and depression by using OHIP-14 and HADS in patients and controls. The patients had inferior quality of life compared to controls, and there was no difference between scores of HADs among both groups, as in our study. The author suggested that RAS affects quality of life negatively. However, stressful conditions such as anxiety and depression were not related to quality of life in patients with RAS. Sherman et al. (15), examined the relationships between physical characteristics and psychologic symptoms in RAS patients and reported that the pain intensity was not affected by psychological characteristics. Picek et al. (16), reported similar results with our study by using STAI and BDI-II, and they found no difference in the level of depression and anxiety between the groups. They concluded that psychological disturbance is irrelevant with the occurrence of RAS.

Study Limitations

The limitation of our study was being performed in a single center. Psychological conditions may vary with the cultural structure and socioeconomic status of societies. Therefore, multicenter studies involving wider populations are needed to clarify whether anxiety and depression play a definitive role in the etiopathogenesis of RAS.

CONCLUSION

The results of our study showed that patients with RAS had impaired quality of life and were particularly more affected negatively in the acute phase because of pain during normal life activities such as eating and speaking. Because of the absence of relationship between RAS and psychological conditions, we suggest that both anxiety and depression may not be associated with the etiopathogenesis of RAS. Hence, studies on larger patient groups should be conducted.

Ethics

Ethics Committee Approval: Ataturk University Faculty of Medicine Ethics Committee approved the study (number of meetings: 6, decision no: 10, date: 30.11.2017).

Informed Consent: Consent was received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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REFERENCES

1. Hu X, Pan H, He W, Hua H, Yan Z. Evaluation of the content quality of websites for recurrent aphthous ulcers and oral lichen planus. BMC Oral Health 2017;17:170.
2. Chiang CP, Yu-Fong Chang J, Wang YP, Wu YH, Wu YC, Sun A. Recurrent aphthous stomatitis - Etiology, serum autoantibodies, anemia, hematinic deficiencies, and management. J Formos Med Assoc 2019;118:1279-89.
3. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. J Am Dent Assoc 2003;134:200-7.
4. McCullough MJ, Abdel-Hafeth S, Scully C. Recurrent aphthous stomatitis revisited; clinical features, associations, and new association with infant feeding practices? J Oral Pathol Med 2007;36:615-20.
5. Marakoğlu K, Sezer RE, Toker HC, Marakoğlu I. The recurrent aphthous stomatitis frequency in the smoking cessation people. Clin Oral Investig 2007;11:149-53.
6. Zhang Z, Li S, Fang H. Enzymatic antioxidants status in patients with recurrent aphthous stomatitis. J Oral Pathol Med 2017;46:817-20.
7. Bankvall M, Sjöberg F, Gale G, Wold A, Jontell M, Östman S. The oral microbiota of patients with recurrent aphthous stomatitis. J Oral Microbiol 2014;6:25739.
8. Dhopte A, Naidu G, Singh-Makkad R, Nagi R, Bagde H, Jain S. Psychometric analysis of stress, anxiety and depression in patients with recurrent aphthous stomatitis-A cross-sectional survey based study. J Clin Exp Dent 2018;10:e1109-14.
9. Al-Omiri MK, Karasneh J, Lynch E. Psychological profiles in patients with recurrent aphthous ulcers. Int J Oral Maxillofac Surg 2012;41:384-8.
10. Soto Araya M, Rojas Alcayaga G, Esguep A. Association between psychological disorders and the presence of oral lichen planus, Burning mouth syndrome and recurrent aphthous stomatitis. Med Oral 2004;9:1-7.
11. Huling LB, Baccaglini L, Choquette L, Feinn RS, Lalla RV. Effect of stressful life events on the onset and duration of recurrent aphthous stomatitis. J Oral Pathol Med 2012;41:149-52.
12. Redwine L, Snow S, Mills P, Irwin M. Acute psychological stress: effects on chemotaxis and cellular adhesion molecule expression. Psychosom Med 2003;65:598-603.
13. Nadendla LK, Meduri V, Paramkusam G, Pachava KR. Relationship of salivary cortisol and anxiety in recurrent aphthous stomatitis. Indian J Endocrinol Metab 2015;19:56-9.
14. Zwiri AM. Anxiety, depression and quality of life among patients with recurrent aphthous ulcers. J Contemp Dent Pract 2015;16:112-7.
15. Sherman JJ, Barach R, Whitcomb KK, Haley J, Martin MD. Pain and pain-related interference associated with recurrent aphthous ulcers. J Orofac Pain 2007;21:99-106.

16. Picek P, Buljan D, Rogulj AA, Stipetić-Ovcarićek J, Catić A, Plestina S, et al. Psychological status and recurrent aphthous ulceration. Coll Antropol 2012;36:157-9.

17. Hapa A, Aksoy B, Polat M, Aslan U, Atakan N. Does recurrent aphthous stomatitis affect quality of life? A prospective study with 128 patients evaluating different treatment modalities. J Dermatolog Treat 2011;22:215-20.

18. Yang C, Liu L, Shi H, Zhang Y. Psychological problems and quality of life of patients with oral mucosal diseases: a preliminary study in Chinese population. BMC Oral Health 2018;18:226.

19. Kürklü-Gürleyen E, Öğüt-Erişen M, Çakır O, Uysal Ö, Ak G. Quality of life in patients with recurrent aphthous stomatitis treated with a mucoadhesive patch containing citrus essential oil. Patient Prefer Adherence 2016;10:967-73.

20. Polat C, Düzer S, Ayyıldız H, Seç S, Aksoy N, Sakallıoğlu Ö, et al. Association between anxiety, depression, and salivary cortisol levels in patients with recurrent aphthous stomatitis. Turk Arch Otorhinolaryngol. 2018;56:166-9.

21. Maina G, Albert U, Gandolfo S, Vitalucci A, Bogetto F. Personality disorders in patients with burning mouth syndrome. J Pers Disord 2005;19:84-93.

22. Aylard PR, Gooding JH, McKenna PJ, Snaith RP. A validation study of three anxiety and depression self-assessment scales. J Psychosom Res 1987;31:261-8.

23. Suresh KV, Shenai P, Chatra L, Ronad YA, Bilahari N, Pramod RC, et al. Oral mucosal diseases in anxiety and depression patients: Hospital based observational study from south India. J Clin Exp Dent 2015;7:e95-9.

24. Cardoso JA, Dos Santos Junior AA, Nunes ML, de Figueiredo MA, Cherubini K, Salum FG. Salivary alpha-amylase enzyme, psychological disorders, and life quality in patients with recurrent aphthous stomatitis. Int J Dent 2017;2017:5269856.

25. Gallo Cde B, Mimura MA, Sugaya NN. Psychological stress and recurrent aphthous stomatitis. Clinics (Sao Paulo) 2009;64:645-8.

26. Albanidou-Farmaki E, Poulopoulos AK, Epivatianos A, Farmakis K, Karamouzis M, Antoniades D. Increased anxiety level and high salivary and serum cortisol concentrations in patients with recurrent aphthous stomatitis. Tohoku J Exp Med 2008;214:291-6.

27. Cağlayan F, Miloglu O, Altun O, Erel O, Yilmaz AB. Oxidative stress and myeloperoxidase levels in saliva of patients with recurrent aphthous stomatitis. Oral Dis 2008;14:700-4.

ORIGINAL ARTICLE

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Determination of Maternal Anxiety Levels During COVID-19 Pandemic Quarantine Period. A Cross-sectional Study

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Abstract

Objective: The novel coronavirus, named as severe acute respiratory syndrome-coronavirus-2 Coronavirus disease-2019 (COVID-19), spreads primarily through humans to human transmission and for this reason governments across the globe have enforced social isolation rules. Isolation and the fear of getting infected affected the entire population, but it is felt more in pregnant women.The aim of this study is to examine the anxiety and behavioral changes in pregnant women caused by COVID-19 pandemic and antenatal care quality during the quarantine period.

Methods: A cross-sectional study was initiated at outpatient clinic of Obstetrics and Gynecology Department in University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey, between 07 May and May 31, 2020 during the COVID-19 outbreak curfew quarantine period. A total of 291 patients (174 pregnant and 102 non-pregnant) were included. The data were obtained from both qualitative and quantitative methods using face-to-face survey, using the state-trait anxiety inventory (STAI) and personal information form with lifestyle change questionnaire. Anxiety levels, behavioral changes were compared and antenatal care quality assessed.

Results: Pregnant participants had higher anxiety STAI state (STAI-S) scores than the non-pregnant participants (43.67±10.77 vs. 39.62±9.45, p=0.02). The STAI trait (STAI-T) anxiety scores were similar between the two groups (43.57±8.07 vs. 43.33±9.56, p=0.82. 60 of pregnant participants were in first trimester, 53 were in second and 61 were in third trimester. The education level of the pregnant participants and whether they received psychosocial support or in which trimester they were, did not make any difference between the STAI-S and STAI-T scores. 67.8% of pregnant participants stated about the fear of going to the hospital and 46.6% canceled their appointments of prenatal care. Appointment canceling was highest in third trimester (p=<0.001).

Conclusion: During the quarantine period, increased maternal anxiety and decreased antenatal care quality determined, that may lead to increase in perinatal morbidity and mortality.

Keywords: Maternal anxiety, antenatal care quality, COVID-19, lifestyle changes, STAI

INTRODUCTION

Coronavirus disease-2019 (COVID-19) which was initially perceived as a regional "epidemic" affecting China and its surroundings, began crossing the Asian borders and then threatened public health globally in the following days (1). Thereafter, the World Health Organization declared COVID-19 as a pandemic, most of the countries closed their borders, and people were quarantined (2). The novel coronavirus, named as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), spreads primarily through a human being to human transmission when people are in close contact (3,4), for this reason, businesses, schools, places of worship, restaurants closed, and many social events canceled. Isolation and inadequate information about the

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outbreak caused fear. Psychological distress and symptoms of mental disorders have increased during the pandemic such as COVID-19 (5,6). Although the fear of getting infected affected the entire population, it was felt more in pregnant women who are especially sensitive because of the anxiety of contamination of the fetus and due to physiological immunosuppression (7).

There are limited studies on psychological wellness in pregnancy during an outbreak. During the 2003 SARS outbreak in Hong Kong, it was reported that pregnant individuals had exaggerated fear of encountering infection and higher anxiety than before SARS (8).

Maternal anxiety is associated with poor perinatal outcomes as preterm birth, low birth weight, small for gestational age (9).

Although it is important to get adequate psychosocial support during pregnancy, pregnant women feel lonely because of the quarantine process in a pandemic. Furthermore, they also avoid visits to their physicians in fear of encountering infection in public transports or at the hospital.

When the COVID-19 pandemic reached Istanbul-Turkey, our research team used the opportunity to research the psychological impact of COVID-19 on pregnant women during their visit to our maternity ward and outpatient clinic with face-to-face surveys.

METHODS

The study was designed as a cross-sectional study at the Outpatient Clinic of Obstetrics and Gynecology Department in University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey, between 07 May (after the start of restrictions) and 31 May (the date restrictions eased) during the COVID-19 outbreak curfew. This study was approved by the Medical Ethical Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (no: 48670771-514.10; date: 05.05.2020) and informed consent was obtained from all patients. A total of 276 participants were included who applied for routine antenatal control or gynecologic complaints. They had no clinical symptoms of COVID-19 and had no suspicion of disease. One hundred seventy four of the participants were pregnant, and 102 were non-pregnant. The data were obtained from both qualitative and quantitative methods between 05 May (after the start of restrictions) and 31 May (the date restrictions eased) during the COVID-19 outbreak.

Participants were excluded if they had a history of psychiatric disorders, could not read, or write in Turkish, did not agree to participate in the study, had COVID-19 symptoms and COVID-19 PCR positivity.

Survey Method

After descriptive information (age, education, working status) and obstetric history (gravida, parity number, last menstrual period) was recorded, we asked the following questions to determine behavioral changes and concerns about pregnancy follow up during COVID-19 outbreak: “During the COVID-19 pandemic, are you getting adequate psychosocial support?”, “Are you afraid of visiting the hospital for prenatal checks?”, “If you are afraid of visiting the hospital, what is the reason?”, “Are you afraid of you or your baby, or both of you being infected with COVID-19?”, “Have you missed any pregnancy visit?”, “How often do you wash your hands?”, “Are you wearing a mask?”, “Are you wearing gloves?”.

Upon completing the above, the participants were asked to complete the Spielberger state-trait anxiety inventory (STAI) form to determine the level of anxiety. The STAI is a 40-item self-report rating scale. Each statement has four scales of feelings, participants were asked to select the best matching feeling, the state anxiety scales include “not at all, somewhat, moderately so, or very much so”. Whereas the responses to the items related to trait anxiety include “almost never, sometimes, often, and almost always”. The scale has internal consistency coefficients ranged from 0.86 to 0.95 (10). It can vary with changes in support systems, health, and other individual characteristics (11). Validity and reliability study of the Turkish form of the scale was conducted by Öner and LeCompte (12). Since the STAI is used to measure the intensity of anxiety (instead of identifying possible clinical cases), no cut-off score is recommended.

Statistical Analysis

In this study, all information obtained was entered into a statistical package for the social sciences, version 25.0, SPSS Inc, Chicago, Illinois, USA (SPSS). Descriptive statistics were used to calculate the frequency (n), percentage (%), central tendency (mean, median & mode), and dispersion (range, variance, standard deviation, maximum & minimum) for each variable when appropriate. The consistency of the data with the normal dispersion has been evaluated by the Kolmogorov-Smirnov test. Student’s t-test, Mann-Whitney U test, One-Way ANOVA test or chi-square test was used when appropriate.

RESULTS

Characteristics, Anxiety Level, and Behavioral Changes of All Participants

In this study, we approached 174 pregnant and 102 non-pregnant participants, none of them were healthcare workers and diagnosed with COVID-19. The sociodemographic and clinical

characteristics (age, educational, and employment status) of the participants were similar and summarized in Table 1. Elderly people in non-pregnant participants were excluded from the study because age-related anxiety may change the result.

Pregnant participants had significantly higher anxiety STAI state (STAI-S) scores than the non-pregnant participants (43.67±10.77 vs. 39.62±9.45, p=0.02). The STAI trait (STAI-T) anxiety scores were not different between the two groups (43.57±8.07 vs. 43.33±9.56, p=0.82).

58.7% of all participants and 62.0% of all pregnant participants mentioned that they get enough psychosocial support, but did not affect anxiety scores (p=0.137).

Behavioral changes due to the pandemic (wearing masks, washing hands, and using gloves) in both groups were highly observed. To reduce the risk of infection, 97.9% of total participants wear a mask, 56.1% wear gloves. While all pregnant participants washed their hands more frequently than usual, just 2 non-pregnant participants said they wash their hands as usual. A higher number of pregnant participants responded "never" to the question "Are you going out from your house" than non-pregnant participants (26.8% vs. 9.8%; p=<0.001) (Table 1).

Table 1. Demographics and characteristics of all participants

	Pregnant (n=174)	Non-pregnant (n=102)	p value
Age (years; mean ± 50)	28.48±5.73	29.44±42	0.26
Educational level			
Less than 8 years	20 (7.2%)	22 (8.0%)	0.78
8 years	100 (36.2%)	51 (10.5%)	
More than 13 years	54 (19.6%)	29 (10.5%)	
Employment status			
Employed	43 (15.6%)	36 (13.0%)	0.6
Unemployed	131 (47.5%)	66 (23.9%)	
STAI[a] state (mean)	43.67±10.77	39.62±9.45	
STAI[a] trait (mean)	43.57±8.07	43.33±9.56	
Psychosocial support			
Adequate	108 (39.1%)	54 (19.6%)	0.137
Inadequate	66 (23.9%)	48 (17.4%)	
Going out from home			
Never	74 (26.8%)	27 (9.8%)	<0.001*
If necessary	90 (32.6%)	54 (19.6%)	
Yes	10 (3.6%)	21 (7.6%)	
Washing hand			
More than usual	174 (63.0%)	100 (36.2%)	0.136
As usual	0 (0%)	2 (0.7%)	
Wearing gloves			
Yes	95 (34.4%)	60 (21.7%)	0.495
No	79 (28.6%)	42 (15.2%)	
Wearing mask			
Yes	171 (61.3%)	101 (36.6%)	1
No	3 (1.1%)	1 (0.4%)	

*Statistical significance, [a]STAI: State-trait anxiety inventory

Characteristics, Anxiety Level, and Behavioral Changes in Pregnant Participants

The mean of gravida and parity of 174 pregnant participants were 2.3 (min: 1, max: 7) and 0.97 (min: 0, max: 5). Sixty (34.48%) of pregnant participants were in the first trimester, 53 (30.45%) were in the second and 61 (35.05%) were in the third trimester. STAI-S and STAI-T scores were not statistically different amongst the trimester groups. Furthermore, the education level of the pregnant participants and whether they received psychosocial support or in which trimester they were, did not make any difference between the STAI-S scores. STAI-S scores were significantly different in the different age groups (p=0.031) (Table 2). Post-hoc comparisons revealed that STAI-S scores for pregnant participants in age groups "over 20 years" were similar, whereas STAI-S scores of pregnant participants "under 20 years" showed a significant difference compared to pregnant participants in the older age groups of "20-30-year-old" (p=0.02) and "30-40-year-old" (p=0.03).

67.8% of total pregnant participants stated that they were afraid of going to the hospital, because of this 46.6% of total pregnant participants canceled or missed their appointments of prenatal care. Fear of going to the hospital and appointment canceling was high in the third trimester (p=0.002, p=<0.001) (Table 3). Pregnant participants, who did not go to antenatal visits, stated that they were afraid of contracting COVID-19 in the hospital themselves or their unborn baby or both, there was no difference between the trimester groups (Table 3).

DISCUSSION

After COVID-19 outbreak spread worldwide from Wuhan, China, it has resulted as an ongoing pandemic (13). The increasing number of death tolls caused global fear and panic. After the first case of COVID-19, detected in Turkey, the Turkish government rapidly carried out interventions and restrictions to prevent the spread of the virus (14). 05 May, the date of the beginning of our study, the Turkish Ministry of Health announced that total coronavirus cases in Turkey were 129,491 and total death tolls were 3,520. Our study was conducted after the start of restrictions in Turkey when the psychological and behavioral changes of the

Table 2. The factors affect STAI scores of pregnant women				
	STAI[a] state Mean ± SD	p value	STAI[a] trait Mean ± SD	p value
Age group (years)				
<20 years old	35.86±2.13	0.031*	38.80±2.04	0.077
20-30 years old	44.36±1.09		43.63±0.84	
30-40 years old	44.33±1.37		44.84±0.91	
>40 years old	46.40±6.47		42.20±5.85	
Educational level				
Less than 8 years	44.07±1.08	0.715	44.22±0.83	0.40
8 years	43.61±1.54		43.03±1.04	
more than 13 years	41.90±1.96		41.8±1.68	
Psychosocial support				
Adequate	42.66±0.94	0.096	42.77±0.77	0.114
Inadequate	45.33±1.48		44.87±0.98	
Employment status				
Employed	43.86±1.75	0.839	44.32±1.21	0.469
Unemployed	43.47±0.91		43.29±0.71	
Trimester				
First	43.46±1.41	0.366	43.63±0.89	0.638
Second	42.26±1.42		42.77±1.14	
Third	45.11±1.40		44.21±1.13	

*Statistical significance, [a]STAI: State-trait anxiety inventory, SD: Standard deviation

Table 3. COVID-19-specific factors that affect prenatal care according to trimester group				
	Trimester			
	First	Second	Third	p value
Fear of going to antenatal visit in the hospital				
Have fear	34 (28.8%)	35 (29.7%)	49 (41.5%)	0.002*
Do not have fear	26 (46.4%)	18 (32.1%)	12 (21.4%)	
Worried about contracting COVID-19 in the hospital				
To herself	4 (40%)	7 (20%)	14 (40%)	0.396
To unborn baby	17 (27.9%)	20 (32.8%)	24 (39.3%)	
Both	29 (37.2%)	26 (33.3%)	23 (29.5%)	
Canceling or missing prenatal care appointments				
Canceled or missed	16 (19.8%)	27 (33.3%)	38 (46.9%)	<0.001*
Not canceled or missed	44 (47.3%)	26 (28%)	23 (24.7%)	

*Statistical significance, COVID-19: Coronavirus disease-2019

subjects were fully settled. It is not an initial phase study, thus it was planned that psychosocial changes to pandemics could be followed up more clearly. A similar situation had been shown in a study, conducted in the 2003 SARS outbreak in Hong Kong; with the rising in the number of cases, the level of anxiety scores also increased. The anxiety scores were highest approximately 1 month after the first SARS case was announced. Participants between the 30-49 ages and less educated were more concerned. Anxiety scores of those who perceived that they were more likely to contract or die due to SARS were significantly higher (15).

Perinatal anxiety is quite common and deserves clinical attention. According to a meta-analyze published in 2017, which included 102 studies with a total of 221,974 participants, the overall prevalence for any anxiety disorder was 15.2% (16). Antenatal anxiety was associated increased risks for preterm birth, low birth

weight, earlier gestational age, and being small for gestational age, smaller head circumference. Also, the development of brain structure in children is associated with prenatal anxiety and depression (9,17). While we know widely about perinatal anxiety, there is limited knowledge about psychological responses caused by a pandemic. Wu et al. (18) initiated a multi-center cross-sectional study in China to compare the mental status of pregnant women before and after the announcement of the COVID-19 epidemic. A total of 4,124 pregnant women during their third trimester were examined in this cross-sectional study, using the Edinburgh postnatal depression scale (EPDS). They found that awareness of the COVID-19 epidemic significantly increased the prevalence of depressive symptoms (EPDS ≥10) ($p=0.01$) and the risk of self-harm thoughts ($p=0.005$) (18). Wu et al. (18) did not evaluate anxiety status, but Corbett et al. (19) questioned 71 patients in the second and third trimester of pregnancy and found that half of the women without anxiety before, worried about their health during the delay phase of the outbreak. This anxiety was related to the health of their older relatives, other children they had, and then their unborn baby (19).

The previous studies mostly compared pregnant women's anxiety levels before and after the pandemic, not with non-pregnant participants. From former studies (5,6) we know that the entire community had higher anxiety so we researched if there is a difference in pregnant individuals. Our cohort demonstrates that pregnant participants had significantly higher anxiety STAI-S scores than the non-pregnant participants, which means pregnant individuals are vulnerable, and they feel fear deeper. Interaction with their relatives (mother, father, friends), provides psychological support, but the necessity of social distancing did not allow this. However, Mirzadeh and Khedmat (20) also highlighted the need for psychological support for pregnant women during this pandemic, in our study 62% of pregnant participants reported that they get adequate support, but it did not make difference on their anxiety levels.

From an online survey, 92.9% of individuals reported feeling loneliness more than usual due to the COVID-19 pandemic in Calgary, Canada. 56.6% of participants had clinically elevated anxiety and 37.0% elevated symptoms of depression. Most of the participants expressed worries about their own life and their unborn baby due to the possibility of infection. Researchers recorded that depression and anxiety symptoms were reduced if participants could complete enough sleep time and had better social support (21). Furthermore, educational level and employment status are other factors that affect depression and anxiety levels. Despite previous literature (22), our cohort did not show any difference in educational level and employment status, it might be because of the increased basal anxiety level in the whole community due to the outbreak.

Due to the pandemic, there have been many lifestyle changes; for protection from the virus wearing masks, gloves, and washing hands have become daily life necessities. All our pregnant participants specified that they washed their hands more than usual, almost all claimed to wear a mask and half of them claimed to wear gloves when they were outside to mitigate the risk of contracting the virus. These attitudes were experienced before, in 2003, during the SARS outbreak, about 70% of women wore a mask all or most of the time, and 40% washed their hands much more frequently than before (8).

Self-isolation and "not leaving home" is another reaction to the COVID-19 pandemic in pregnant women. Furthermore, domestic transportation registrations and the intensity of COVID-19 patients in hospitals, caused pregnant women to avoid going to their prenatal visits. It was reported formerly in the SARS outbreak, the rate of canceling or post-ponement of antenatal visits was high and about half of the women decided to deliver in hospitals with fewer SARS cases (8). However meta-analyses revealed that visiting antenatal care clinics during pregnancy was significantly associated with lower rates of neonatal and maternal death (23,24), during pandemic time, it has been reported that canceling appointments, difficulties in accessing health units, or going to physicians without a supporter caused the poor quality of prenatal care (21). The fear of going to the hospital was high also in our study and half of the pregnant women stated that they canceled or missed their prenatal visits.

Maternal anxiety varies during the pregnancy, Haddad et al. (25), Teixeira et al. (26), and Bhagwanani et al. (27) reported that STAI-S levels were increased in the first and third trimester. Other studies have reported that STAI-S scores elevated significantly in the third trimester (28,29). The anxiety-level differences between trimesters had not been evaluated in an outbreak period, we found that there was no difference in STAI-S and STAI-T levels between trimesters.

Spielberger defined trait anxiety as, the propensity of individuals to respond and state anxiety as a temporary feeling of fear and tension (30). In our study, pregnant women showed a psychosocial reaction to a pandemic with a feeling of fear and anxiety

The Strength of the Study

There are limited studies about maternal anxiety in a pandemic and much less in the quarantine period. Previous surveys were mostly conducted using an online panel, but we conducted

face-to-face survey that enables more accurate information. Furthermore, as far as we know this is the first study that compares anxiety scores trimester groups in the COVID-19 pandemic.

Study Limitations

Questionnaire limitations: Gunning et al. (28) reported that the STAI state scale reflects situation-specific anxiety, but the location of the antenatal clinic in which it was completed, could change anxiety levels.

Single-center study: Our data may not be entirely representative of all pregnant individuals. Although our hospital is a training and research hospital with high patient capacity, the study is a single-center study.

CONCLUSION

Although there are many studies on the physiological effects of SARS-CoV-2 (COVID-19) so far, the psychosomatic effects of the quarantine period of a pandemic have not been emphasized extensively. With this study, we revealed that during COVID-19 pandemic, state anxiety levels were similar between pregnant and non-pregnant women but trait anxiety levels, which define a temporary sense of fear and tension were higher in pregnant women. These high levels of anxiety have more impact on pregnant participants and caused an interruption of antenatal care especially in the quarantine period. Future researches needed to examine the psychosocial and perinatal effects of the COVID-19 pandemic.

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Ethics

Ethics Committee Approval: This study was approved by the Medical Ethical Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (no: 48670771-514.10; date: 05.05.2020).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.C., E.A., F.Y.Ö., S.G., B.A., H.T.Ö., A.K., B.T., E.D.K., O.Ş., V.M., Concept: B.C., E.A., F.Y.Ö., S.G., H.T.Ö., A.K., B.T., E.D.K., O.Ş., V.M., Design: B.C., E.A., F.Y.Ö., S.G., B.A., H.T.Ö., A.K., B.T., O.Ş., V.M., Data Collection or Processing: B.C., E.A., F.Y.Ö., S.G., B.A., A.K., B.T., E.D.K., O.Ş., V.M., Analysis or Interpretation: B.C., E.A., F.Y.Ö., S.G., B.A., H.T.Ö., A.K., B.T., O.Ş., V.M., Literature Search: B.C., E.A., F.Y.Ö., B.A., H.T.Ö., B.T., E.D.K., O.Ş., V.M., Writing: B.C., E.A., F.Y.Ö., S.G., B.A., H.T.Ö., A.K., B.T., E.D.K., V.M.

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REFERENCES

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395:470-3.
2. WHO. Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: interim guidance. Accessed date: Jan 20, 2020. Available from: URL: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
3. Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395:514-23.
4. "Symptoms of Coronavirus"CDC - National Center for Health Statistics - Homepage. Accessed date: May 13, 2020. Available from: URL: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
5. Bao Y, Sun Y, Meng S, Shi J, Lu L. 2019-nCoV epidemic: address mental health care to empower society. Lancet 2020;395:e37-8.
6. Rajkumar RP. COVID-19 and mental health: a review of the existing literature. Asian J Psychiatr 2020;52:102066.
7. Armenti VT, Moritz MJ, Cardonick EH, Davison JM. Immunosuppression in pregnancy: choices for infant and maternal health. Drugs 2002;62:2361-75.
8. Lee DT, Sahota D, Leung TN, Yip AS, Lee FF, Chung TK. Psychological responses of pregnant women to an infectious outbreak: a case-control study of the 2003 SARS outbreak in Hong Kong. J Psychosom Res 2006;61:707-13.
9. Grigoriadis S, Graves L, Peer M, Mamisashvili L, Tomlinson G, Vigod SN, et al. Maternal anxiety during pregnancy and the association with adverse perinatal outcomes: systematic review and meta-analysis. J Clin Psychiatry 2018;79:17r12011.
10. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press;1983.
11. Elliott TR, Shewchuk RM, Richards JS. Family caregiver problem solving abilities and adjustment during the initial year of the caregiving role. J Couns Psychol 2001;48:223-32.
12. Öner N, LeCompte WA. State-Trait Anxiety Inventory Handbook. Boğaziçi Üniversitesi Yayınları, İstanbul;1985.
13. Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global

health - the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020;91:264-6.

14. Demirbilek Y, Pehlivantürk G, Özgüler ZÖ, Alp Meşe E. COVID-19 outbreak control, example of ministry of health of Turkey. Turk J Med Sci 2020;50(Suppl 1):489-94.
15. Leung GM, Ho LM, Chan SK, Ho SY, Bacon-Shone J, Choy RY, et al. Longitudinal assessment of community psychobehavioral responses during and after the 2003 outbreak of severe acute respiratory syndrome in Hong Kong. Clin Infect Dis 2005;40:1713-20.
16. Dennis CL, Falah-Hassani K, Shiri R. Prevalence of antenatal and postnatal anxiety: systematic review and meta-analysis. Br J Psychiatry 2017;210:315-23.
17. Adamson B, Letourneau N, Lebel C. Prenatal maternal anxiety and children's brain structure and function: a systematic review of neuroimaging studies. J Affect Disord 2018;241:117-26. Erratum in: J Affect Disord 2019;253.
18. Wu Y, Zhang C, Liu H, Duan C, Li C, Fan J, et al. Perinatal depressive and anxiety symptoms of pregnant women during the coronavirus disease 2019 outbreak in China. Am J Obstet Gynecol 2020;223:240.e1-240.e9.
19. Corbett GA, Milne SJ, Hehir MP, Lindow SW, O'connell MP. Health anxiety and behavioural changes of pregnant women during the COVID-19 pandemic. Eur J Obstet Gynecol Reprod Biol 2020;249:96-7.
20. Mirzadeh M, Khedmat L. Pregnant women in the exposure to COVID-19 infection outbreak: the unseen risk factors and preventive healthcare patterns. J Matern Fetal Neonatal Med 2020:1-2.
21. Lebel C, MacKinnon A, Bagshawe M, Tomfohr-Madsen L, Giesbrecht G. Elevated depression and anxiety symptoms among pregnant individuals during the COVID-19 pandemic. J Affect Disord 2020;277:5-13. Erratum in: J Affect Disord 2021;279:377-9.
22. Santric-Milicevic M, Jankovic J, Trajkovic G, Terzic-Supic Z, Babic U, Petrovic M. Socioeconomic Inequalities in Mental Health of Adult Population: Serbian National Health Survey. Balkan Med J 2016;33:36-44.
23. Wong PC, Kitsantas P. A review of maternal mortality and quality of care in the USA. J Matern Fetal Neonatal Med 2020;33:3355-67.
24. Wondemagegn AT, Alebel A, Tesema C, Abie W. The effect of antenatal care follow-up on neonatal health outcomes: a systematic review and meta-analysis. Public Health Rev 2018;39:33.
25. Haddad PF, Morris NF, Spielberger CD. Anxiety in pregnancy and its relation to use of oxytocin and analgesia in labor. J Obstet Gynaecol 1985;6:77-81.
26. Teixeira C, Figueiredo B, Conde A, Pacheco A, Costa R. Anxiety and depression during pregnancy in women and men. J Affect Disord 2009;119:142-8.
27. Bhagwanani SG, Seagraves K, Dierker LJ, Lax M. Relationship between prenatal anxiety and perinatal outcome in nulliparous women: a prospective study. J Natl Med Assoc 1997;89:93-8.
28. Gunning MD, Denison FC, Stockley CJ, Ho SP, Sandhu HK, Reynolds RM. Assessing maternal anxiety in pregnancy with the state-trait anxiety inventory (STAI): issues of validity, location and participation. J Reprod Infant Psychol 2010;28:266-73.
29. Da Costa D, Larouche J, Dritsa M, Brender W. Variations in stress levels over the course of pregnancy: factors associated with elevated hassles, state anxiety and pregnancy-specific stress. J Psychosom Res 1999;47:609-21.
30. Endler NS, Kocovski NL. State and trait anxiety revisited. J Anxiety Disord 2001;15:231-45.

ORIGINAL ARTICLE

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Contribution of Lower Extremity ^{68}Ga PSMA PET/CT Imaging to Diagnosis and Treatment in Prostate Cancer

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Abstract

Objective: The aim of this study is to evaluate the effectiveness of routine additional acquisitions for lower extremity in the diagnosis and treatment of patients undergoing ^{68}Ga prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT).

Methods: The files of 59 prostate cancer patients who underwent additional acquisition of the lower extremities in addition to the vertex-upper thigh in ^{68}Ga PSMA PET/CT studies were included in the study. In our study, patients with both lower limb acquisition on clinical suspicion and with routine lower limb acquisition were included. Along with the difference in the effectiveness of the lower limb acquisition between these two arms, the efficacy and clinical utility of the additional acquisiton were evaluated in the entire sample.

Results: The rate of metastasis detected in the group with lower limb acquisiton with clinical suspicion (31.1%) is higher than in the other group (7.6%). However, metastases detected in both groups do not cause changes in the treatment.

Conclusion: Considering the loss of time caused by additional acquisitons in the clinic, the radiation dose exposure of the patient and the outcomes in this study, it may be possible to say that the lower extremity acquisitons are not effective.

Keywords: Prostate cancer, ^{68}Ga PSMA, PET/CT, molecular imaging

INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide. It is the most frequently diagnosed cancer among men in many countries such as America, Northern and Western European countries, Sub-Saharan African countries, and Australia, with easier diagnosis in the last few decades especially with the widespread use of prostate-specific antigen (PSA). In 2018, 1.3 million new prostate cancer cases were seen worldwide, whereas 359 thousand prostate cancer-related deaths were reported in the same period (1). In a study evaluating the American cancer statistics, approximately 20% of cancers in men in 2019 are stated to be prostate cancer and 10% of cancer-related deaths are related to prostate cancer (2). In the Turkey Cancer Statistics published in 2018, incidence of prostate cancer in men according to the 2015 data is reported as 33.1/100,000 (3).

Besides the histopathological features, the existence of distant metastases is an important factor in determining the prognosis in prostate cancer. Skeletal system is the most common site of hematogenous metastasis in prostate cancer. In an autopsy series in which 1,589 prostate cancer cadavers were examined, hematogenous bone metastases were detected in 90% of cadavers (4). According to a study conducted by Shou et al. (5) among 265,900 cases of prostate cancer, at least one bone metastasis was observed in 59.43% of patients. Therefore, it is extremely important to focus on bone metastases when investigating distant organ metastasis. Bone scintigraphy has been used for many years to evaluate bone metastases in prostate cancer because of this basic information. Prostate-specific membrane antigen (PSMA), first described in 1987 and later revealed to be a transmembrane glycoprotein, is an important diagnostic

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alternative as it is expressed in prostate cancer cells, as well as being expressed more extensively in prostate cancer cells (6). PSMA-based positron emission tomography/computed tomography (PET/CT) imaging is becoming more and more important in the clinic because it provides significant tumor/background area ratio in the primary lesion as well as distant metastases and lymph nodes. Current literature shows that ^{68}Ga-PSMA PET/CT is a highly effective imaging method to detect bone metastases especially in cases of biochemical recurrence (7,8). Lower extremities can also be considered among the major areas of metastasis in cases with diffuse skeletal metastasis. Its effect on the treatment decision is controversial; however, it is a routine approach to include the lower limb in PET/CT acquisition according to both legal regulations and established clinical practices in our country.

This study aimed to understand the contribution of the lower limbs in diagnosis acquisition and provide any advantage over its drawback in prolonging the whole process duration.

METHODS

Patients

In our study, data from a total of 59 prostate cancer cases (mean age: 69 years, age range: 41-81 years) and their images in the picture archiving and communication system were retrospectively evaluated. In addition to routine vertex-upper thighs, lower extremities were also included in the acquisition of patients who underwent ^{68}Ga-PSMA PET/CT at the University of Health Sciences Turkey, Okmeydani Training and Research Hospital Nuclear Medicine Unit between June 9, 2017-September 19, 2018. A total of 36 patients were evaluated for staging, 23 for restaging, and none for secondary malignancy. Patients enrolled in the study were also grouped according to the indication of the lower-extremity acquisition. In 13 out of 59 patients, lower limbs were involved in the acquisition routinely. Meanwhile, the lower limbs were involved in the acquisition in the remaining 46 patients, only if there is high risk of illness, if the patient described symptoms, or in cases without recent scintigraphic imaging.

All patients signed a written informed consent form for evaluation purposes and data publication. This study was approved by the Ethics Committee of University of Health Sciences Turkey, Okmeydani Training and Research Hospital (04/10/2018-996).

Preparation of ^{68}Ga-PSMA

A fully automated Scintomics Good Radiopharmaceutical Practice (GRP) synthesis module with Scintomics Control Center and GRP-Interface software was used for the radiolabeling of ^{68}Ga-DOTAGA-PSMA (named as ^{68}Ga-PSMA I&T). The ^{68}Ge/^{68}Ga generator was purchased from iThemba LABS, South Africa. DOTAGA-PSMA was purchased from Scintomics GRP, Germany via a local distributor. The synthesis of the ^{68}Ga peptides was performed using a cationic purification method with 20 µg of peptide used for the reaction. The labeling efficiency and radiochemical purity were determined using radio thin-layer chromatography and radio-high-performance liquid chromatography. The radiochemical purities of ^{68}Ga-labeled PSMA conjugates were ≥95%.

Imaging

Patients were imaged using an integrated PET/CT scanner that consisted of a full-ring HI-REZ LSO PET and a six-slice CT scanner (Siemens Biograph 6, Chicago, IL, USA). Each patient was injected with a standardized weight-based dose of 2 MBq/kg (range 70-180 MBq), and images were obtained in a dual-phase mode. At 60 min post-injection, a whole-body PET/CT scan was conducted with an emission time of 3 min per bed position. Before emission images, a low-dose CT was performed for attenuation correction and anatomic localization with the following parameters: 50 mA, 140 kV, and 5 mm section thickness. All patients were positioned feet first, supine on the scanning pallet with imaging from toe to vertex, and arms up.

Images Evaluation

Images were visually evaluated by two nuclear medicine physicians with at least 10 years of experience. Areas with markedly increased focal ^{68}Ga-PSMA uptake compared to background activity were evaluated in favor of metastasis when they were outside the prostate tissue and did not coincide with physiological involvement sites or known benign lesions that may have ^{68}Ga-PSMA uptake. Metastases observed in the skeletal system were classified into two groups as seen in routine acquisition area and additional acquisition area.

Statistical Analysis

When evaluating the findings obtained in the study, International Business Machines Corporation Statistical Package for the Social Science Statistics 25 (SPSS IBM, Turkey) program was used for statistical analysis. Descriptive methods (Frequency, Percentage, Average, Standard deviation) were used to evaluate the study data.

RESULTS

Lesions were detected in the lower extremities in 19 of 59 patients, wherein 3 had lesions in the vertex-upper thigh acquisition that could be detected because lesions were located in the femoral

head and/or proximal femur Figure 1. Therefore, involvement of the lower extremity to the acquisition did not provide any additional benefit in these 3 patients. In 1 of 16 patients whose lesions were detected by lower-extremity acquisition, intense patella involvement was observed in the form of "hot patella" without widespread metastasis in the body Figure 2. In this study, findings were considered suspicious since it was not confirmed histopathologically. Excluding the suspected positive case, 15 out of 58 patients (25.86%) provided additional information by involvement of the lower extremities in the acquisition. All of these 15 patients had extensive metastasis in the body. Because of that they didn't provided additional benefit from the involvement of the lower extremities in the acquisition Figure 3.

High-risk disease group includes 25 of 36 patients who underwent ^{68}Ga-PSMA PET/CT imaging for staging purposes. Lower-extremity metastases were detected in 8 of 24 patients (33%) when the suspicious case with patellar involvement was not included.

Lower limb metastasis was not detected in 11 patients in the low and medium risk group. In all patients who were evaluated for staging purposes, lower limb metastasis was detected in 17% thanks to additional acquisition.

When all restaging patients were considered, 7 of 23 patients had lower limb lesions detected with additional acquisition (30.4%), whereas 18 of these patients were metastatic and 8 of them had extensive bone metastasis. This group consisted of a group of patients who were expected to have a high rate of bone metastases in general Table 1.

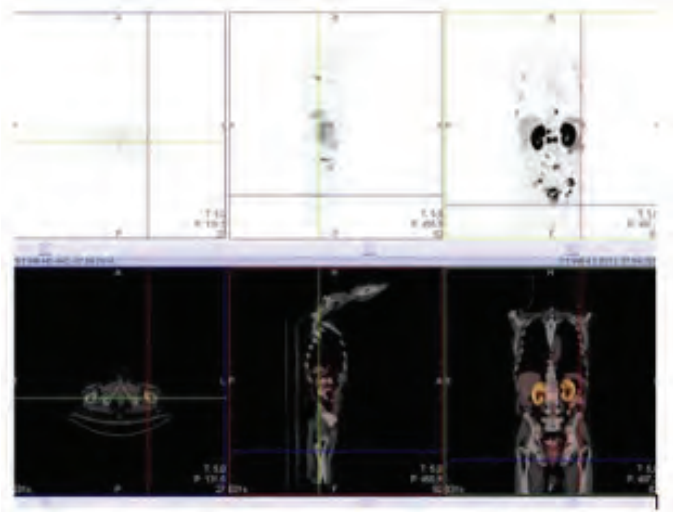

Figure 1. Axial, sagittal, and coronal PET and fusion images showing metastatic lesion located proximal to the upper femur and entering the routine area of acquisition
PET: Positron emission tomography

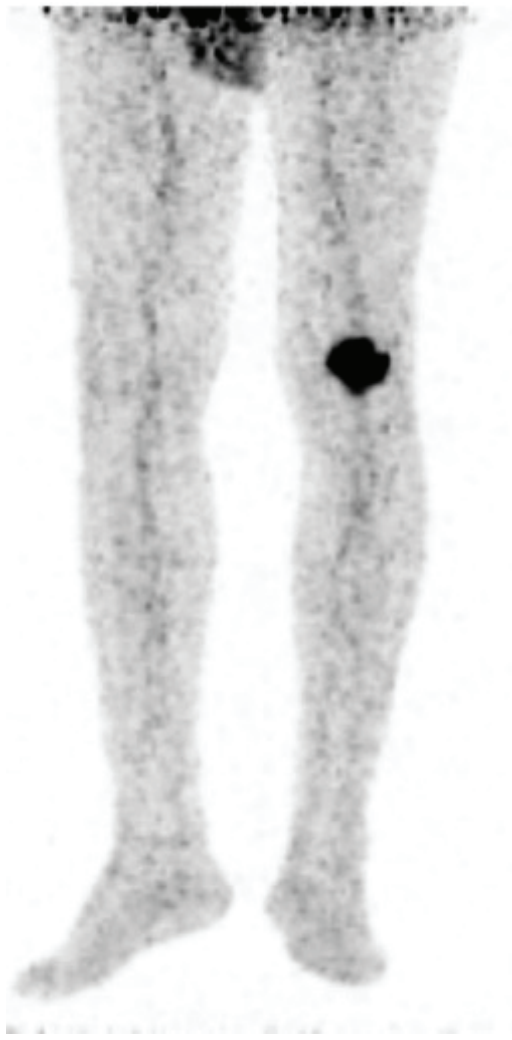

Figure 2. Maximum intensity projection image of ^{68}Ga-PSMA PET showing isolated patellar involvement not proven to be metastatic
PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography

Results of patients who underwent lower-extremity acquisition with the suspicion of metastasis (group 1) and as part of routine acquisition (group 2) were shown in Table 2, excluding the case with suspicious metastasis. In the 1st group consisting of 46 cases, lower-extremity metastasis was detected in 14 patients (31.11%), whereas in the 2nd group consisting of 13 patients, only one case (7.69%) was detected with lower-extremity metastasis. No statistically significant difference was found between these two groups ($p>0.04$).

DISCUSSION

Not many studies in the literature are evaluating the clinical benefit of additional acquisition for the lower extremity; however, this issue is extremely important for the workflow of nuclear medicine clinics. Implementing acquisitions that have no clinical effect complicates the daily work plans of nuclear

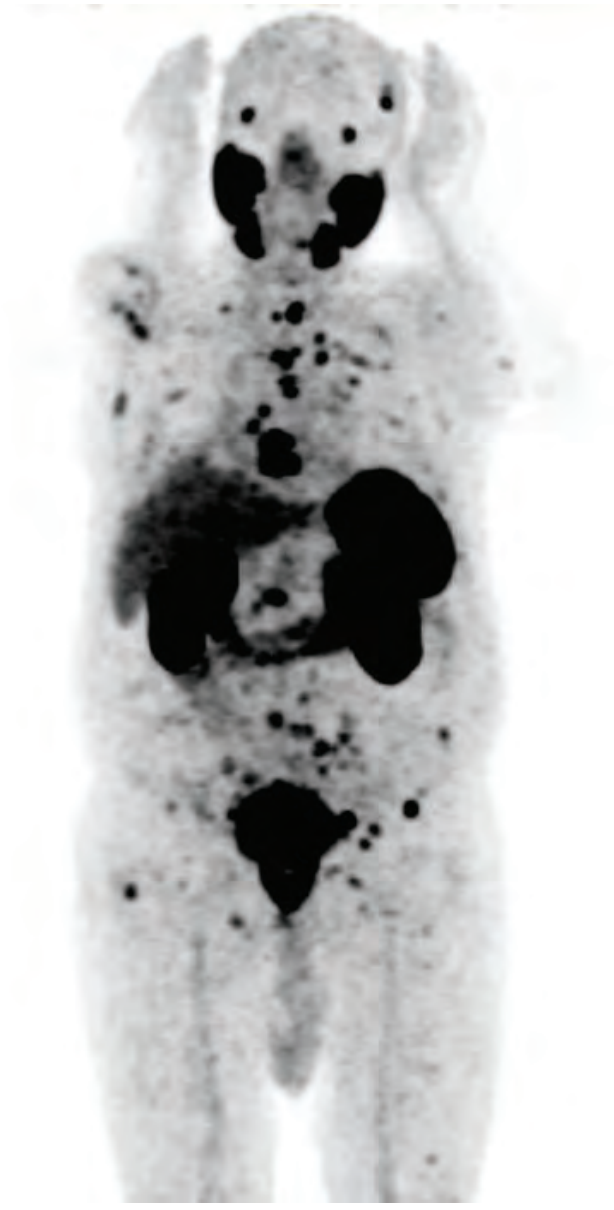

Figure 3. Maximum intensity projection image of 68Ga-PSMA PET/CT showing diffuse metastatic involvement.
PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography, CT: Computed tomography

medicine clinics in terms of planning the imaging studies and using time efficiently. In addition, taking additional acquisitions that will not affect the management of the patient, thus, exposing the patient to additional radiation caused by the PET/CT's tomography component is one of the issues that should be considered. Discussing the necessity of additional acquisition of the lower extremities is important since giving the lowest radiation dose to patients is our main approach in our daily practice depending on the as low as reasonably achievable (ALARA) principle (9).

In the current literature, several studies are reported on the necessity and effectiveness of adding the lower extremity to routine acquisition, especially in diseases with atypical metastatic patterns such as malignant melanoma and sarcoma (10-12); however, only few studies are reported about prostate cancer. Only 15 (25.4%) of 59 patients included in our study had metastases in the bones of lower extremity that were not detected by routine imaging. Many studies were reported in the literature evaluating the effectiveness of ^{68}Ga-PSMA PET/CT in detecting metastases of prostate cancer (13-15). Some of these studies have also included the metastases rates observed in the lower extremity (16); however, few articles are evaluating the contribution of detection of metastases in the lower extremities to its treatment. Simsek et al. (17) reported that lesions were detected in the lower extremity in 61 out of 701 cases (8.7%). Comparing these two studies is impossible, since the cases in our study were divided into two different groups according to clinical suspicion, not the presence of symptoms.

However, in both studies, it was observed that additional lower-extremity acquisition either with clinical suspicion or symptoms caused a detection of significantly higher rate of metastasis than others. In our study, metastases were detected in 31.1% of patients who underwent additional lower-extremity acquisition with clinical suspicion and 7.69% of patients who routinely underwent PET/CT examination with lower extremity involved.

Table 1. Detected lesions and their distribution

Groups	Existence of lesions in the lower extremity						Lesions detected only in additional images		
	Femoral head	Proximal femur	Distal extremity	Patella	No lesion	Total	Positive	Negative	Total
Group 1	**0**	**2**	**14**	**1**	**29**	**46**	**15**	**31**	**46**
Staging	0	1	7	1	21	30	8	22	30
Restaging	0	1	7	0	8	16	7	9	16
Group 2	**1**	**0**	**1**	**0**	**11**	**13**	**1**	**12**	**13**
Staging	0	0	1	0	5	6	1	5	6
Restaging	1	0	0	0	6	7	0	7	7

Table 2. Effects of additional acquisitions			
Group	Number of patients	Cases in which metastases were detected with extra images	
		Number	%
Group 1	45	14	31.1%
Group 2	13	1	7.69%
Total	58	15	25.86%

The common result of both studies is that metastases detected in the lower extremity did not cause any change in treatment. From this point of view, it can be beneficial to use less acquisition that does not contribute to patient management by considering the ALARA principle.

The retrospective structure of the study and the narrow sample size are the main drawbacks in our study. Narrow sample size also makes it difficult to evaluate statistical differences between groups. We believe that the proportional differences between the groups will be statistically significant in studies to be conducted in larger case groups. In addition, the treatment of patient groups included in the study with different treatment modalities, being at different stages of their treatment and not being homogenous in terms of treatment response make it difficult to make a comparison based on PSA for these patients. Therefore, a statistical evaluation on PSA values could not be performed in our study.

CONCLUSION

The addition of lower limbs to the routine acquisition areas, which did not cause any significant changes in the detection of distribution of metastases that eventually affect the treatment protocol of the patients, does not seem to be very suitable according to the data obtained in our study. However, in cases that are symptomatic and considered to be of clinical benefit, it may be wise to consider the additional lower extremities acquisition.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Turkey, Okmeydani Training and Research Hospital (04/10/2018-996).

Informed Consent: All patients signed a written informed consent form for evaluation purposes and data publication.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424. Erratum in: CA Cancer J Clin 2020;70:313.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
3. T.C. Halk Sağlığı Kurumu. Türkiye Kanser İstatistikleri 2015. T.C. Sağlık Bakanlığı Halk Sağlığı Müdürlüğü. 2018.
4. Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol 2000;31:578-83.
5. Shou J, Zhang Q, Wang S, Zhang D. The prognosis of different distant metastases pattern in prostate cancer: a population based retrospective study. Prostate 2018;78:491-7.
6. Hupe MC, Philippi C, Roth D, Kümpers C, Ribbat-Idel J, Becker F, et al. Expression of prostate-specific membrane antigen (PSMA) on biopsies is an independent risk stratifier of prostate cancer patients at time of initial diagnosis. Front Oncol 2018;8:623.
7. Hope TA, Goodman JZ, Allen IE, Calais J, Fendler WP, Carroll PR. Metaanalysis of 68Ga-PSMA-11 PET accuracy for the detection of prostate cancer validated by histopathology. J Nucl Med 2019;60:786-93.
8. Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific membrane antigen PET: clinical utility in prostate cancer, normal patterns, pearls, and pitfalls. Radiographics 2018;38:200-17.
9. Munro L. Basics of Radiation Protection How to Achieve ALARA: Working Tips and Guidelines. Ostensen H, Ingolfsdottir G, editors. World Health Organization. 2004.
10. Plouznikoff N, Arsenault F. Clinical relevance of 18F-FDG PET/CT lower-limb imaging in patients with malignant cutaneous melanoma. Nucl Med Commun 2017;38:1103-8.
11. Webb HR, Latifi HR, Griffeth LK. Utility of whole-body (head-to-toe) PET/CT in the evaluation of melanoma and sarcoma patients. Nucl Med Commun 2018;39:68-73.
12. Querellou S, Keromnes N, Abgral R, Sassolas B, Le Roux PY, Cavarec MB, et al. Clinical and therapeutic impact of 18F-FDG PET/CT whole-body acquisition including lower limbs in patients with malignant melanoma. Nucl Med Commun 2010;31:766-72.
13. Perera M, Papa N, Christidis D, Wetherell D, Hofman MS, Murphy DG, et al. Sensitivity, specificity, and predictors of positive 68Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70:926-37.
14. Sachpekidis C, Bäumer P, Kopka K, Hadaschik BA, Hohenfellner M, Kopp-Schneider A, et al. 68Ga-PSMA PET/CT in the evaluation of

bone metastases in prostate cancer. Eur J Nucl Med Mol Imaging 2018;45:904-12.

15. Löfgren J, Mortensen J, Rasmussen SH, Madsen C, Loft A, Hansen AE, et al. A prospective study comparing 99mTc-hydroxyethylene-diphosphonate planar bone scintigraphy and whole-body SPECT/CT with 18F-fluoride PET/CT and 18F-fluoride PET/MRI for diagnosing bone metastases. J Nucl Med 2017;58:1778-85.
16. Pyka T, Okamoto S, Dahlbender M, Tauber R, Retz M, Heck M, et al. Comparison of bone scintigraphy and 68Ga-PSMA PET for skeletal staging in prostate cancer. Eur J Nucl Med Mol Imaging 2016;43:2114-21.
17. Simsek DH, Sanli Y, Kuyumcu S, Engin MN, Buyukkaya F, Demirci E. Clinical impact of lower-limb imaging in 68Ga-PSMA PET/CT for patients with prostate cancer. J Nucl Med Technol 2019;47:233-7.

ORIGINAL ARTICLE

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Duration of Labor with Meperidine Versus Placebo in Singleton Term Pregnancies: A Randomized Placebo Controlled Study

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Abstract

Objective: Meperidine, a synthetic opioid analgesic, is used empirically in many birth centers due to its effect on the duration of labor as well as pain relief during labor. In this study, we examine the effect of meperidine administration on the duration of labor.

Methods: This study was designed as a prospective randomized placebo-controlled study; 250 patients were randomized into two groups where the study group received 0.5 mL-25 mg i.v. meperidine and the control group received 0.5 mL i.v. saline solution, all at the start of the active phase. The start of the active phase of labor was defined as 4 cm cervical dilatation and 60%-70% cervical effacement. The primary outcome was determined as the duration of the active phase (DAP). This study is registered on ClinicalTrials.gov (identifier: NCT01555671).

Results: Women randomized to the meperidine group had a shorter total duration of labor (TDL) and shorter duration of the DAP compared to the control group, both in the total patient population women (mean ± standard deviation (SD): 273±129 min vs. 331±177 min, p=0.033; 249±122 min vs. 304±167 min, p=0.029, respectively) and in primiparous (mean ± SD: 372±134 min vs. 400±179 min, p=0.026; 296±126 min vs. 363±170 min, p=0.024, respectively). No statistically significant difference was found between the total patient population and primiparous group in terms of the second stage of labor (DSS) (p=0.930, p=0.229; respectively). Multiparous women in meperidine and control groups, did not show a statistically significant difference in terms of the TDL, DAP and the DSS (p=0.170, p=0.157, p=0.498; respectively). No statistically significant difference was found between the two study groups in terms of age (p=0.126), parity (p=0.427), body mass index (p=0.163), cesarean rates (p=0.511) and mean gestational weeks (p=0.845).

Conclusion: Our findings revealed that meperidine administration was associated with a shorter duration of active phase of labor in primiparous women.

Keywords: Active phase, apgar, duration labor, labor analgesia, meperidine, pethidin

INTRODUCTION

The onset of labor is characterized by regular, painful uterine contractions that increase in frequency and intensity resulting in progressive cervical dilatation and effacement. Historically, the stages of labor are based on the observations first made by Friedman and Kroll (1). Because of these observations, the first stage of the labor process was defined as the completion of cervical dilatation, and the second stage as the descent and expulsion of the fetus. With the demonstration of the labor curves for the progression of normal birth and the definition of stages of labor, Friedman's work still constitutes the benchmark for the diagnosis of prolonged labor in today's obstetric practice (2). Prolongation in the first and second stages of labor may lead to increased cesarean rates, operative delivery, and low Apgar scores (3). Shortening of labor duration or preventing labor prolongation, can reduce these adverse outcomes, besides the

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advantage of shorter exposure of the mothers to labor stress and pain. Although labor augmentation is used routinely in some crowded labor wards to avoid complications due to labor prolongation, this practice is not evidence-based (4).

Many non-pharmacological and pharmacological methods have been used for augmentation of labor. These relationships have been tried to be explained by more than one mechanism (5). There is some evidence that the administration of meperidine (another common name is pethidine) (6,7) , which is a method for augmentation, may affect the duration of labor besides its analgesic effect, although the literature is contradictory (8,9). There are some studies showing that meperidine increases uterine contractions (6). Based on its association with uterine contractility (direct or via pain relief) and changes in cervical proteases, meperidine is considered amongst the methods of accelerating labor by stimulating uterine contractions and facilitating cervical dilation (10,11). Another important fact in the widespread use of meperidine is the scarcity of epidural analgesia in public hospitals in Turkey; therefore, many clinicians frequently use meperidine to reduce pain during labor or to accelerate duration of labor. However, few studies have found no association between the drug and uterine contractions and cervical changes (12,13).

Furthermore, there are very-limited numbers of placebo-controlled studies and inconsistent data regarding the efficacy of meperidine on shortening of the duration of labor. This prospective randomized placebo-controlled study was therefore designed to evaluate the impact of meperidine administration on the duration of active labor in relation to parity and neonatal outcomes in singleton term pregnancies.

METHODS

This prospective, randomized, double-blind, placebo-controlled study included 250 consecutive women who gave birth at University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Resarch Hospital, Istanbul-Turkey between January 2012 and May 2012. The hospital is a tertiary referral center with an average of greater than 15,000 deliveries per year. The sample size was calculated using Number Cruncher Statistical System/PASS 2007, based on the active phase labor duration of minimal critical importance (30 min) (14) and mean [standard deviation (SD)] 296.04 min (170.02) values obtained from first 20 control subjects revealing that for statistical power of 80% and significance (α) of 0.05, at least 200 patients (100 patients in each group) should be included in the study.

Nulliparous or multiparous women aged 18-40 years with a singleton pregnancy of 37-42 weeks that were in active labor, with 4 cm cervical dilatation, 60%-70% effacement and fetal head engagement or Bishop score 6 were included in the study. The presence of maternal hypertension, comorbid chronic diseases (i.e. diabetes, thyroid disease), fetal developmental problems, abnormal external fetal cardiotocography findings (i.e. uterus hyperactivity, lack of continuous reactivity), cephalo-pelvic disproportion, vaginal bleeding, past history of uterine surgery or preterm delivery, early membrane rupture, and obstetric complications such as preeclampsia were the exclusion criteria of the study.

In the meperidine group, meperidine 25 mg IV bolus injection (0.5 mL) was administered when the cervical dilatation was 6 cm with 60%-70% effacement. The same amount (0.5 mL) of saline solution was given IV to the subjects in the control group. Enrolled women were randomly assigned to two groups as the study (meperidine group) and placebo group (control group). Randomization was performed according to a computer-generated list of numbers which were recorded in sealed envelopes, containing identical syringes containing either 0.5 mL of meperidine 25 mg or 0.5-mL saline, prepared by a nurse who was not involved in the study. Envelopes were chosen randomly by the principal investigator randomly, both the patient and investigators were blinded for the intervention. All participants underwent a general physical examination and an obstetric examination. The vaginal was examined every hour to assess the progress of labor. In our delivery unit, labor augmentation is performed with oxytocin in accordance with the routine protocol of our hospital. Starting from 6 mU/min, oxytocin is increased by 6 mU/min every 20 min to achieve a regular contraction pattern to a maximum infusion rate of 42 mU/min. Uterine activity of 200-250 Montevideo units is considered adequate. Routine amniotomy was performed in all patients with cervical dilatation of 6 cm or more if spontaneous rupture of membranes had not occurred.

All patients were followed up with external cardiotocography. The delivery procedure is routinely performed according to our hospital's delivery protocol. During delivery, episiotomy is performed by the doctor in line with his or her clinical approach when deemed necessary. The duration of the active phase of labor was recorded as the time (min) from a cervical dilatation of 4 cm until the cervical dilatation was completed. The duration of the second phase of labor was recorded as the time (min) from full cervical dilatation to the delivery of the fetus. In our hospital, cesarean delivery indication and decision is in the responsibility of the obstetrician who is in charge of the labor ward, the same protocol was followed throughout the study. Patients who delivered by cesarean were excluded from the study.

The primary outcome measures were defined as the time from 4 cm with more than 60% effacement to full cervical dilatation duration of the active phase (DAP). Secondary outcome measures were defined as duration of second stage of labor (DSS), (total labor duration: DAP + DSS), need for episiotomy, birth weight, 1-min and 5-min Apgar scores, and presence of meconium aspiration. Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Yeditepe University Faculty of Medicine Clinical Research Ethics Committee (date of approval: 02/11/2011; reference number/protocol no: 2011/121) (ClinicalTrials.gov Identifier: NCT01555671).

Statistical Analysis

Data analyses were made using statistical software SPSS (version 11.5, IBM, New York, USA). Fischer's Exact test and Pearson χ^2 tests were used for the comparison of categorical data. Numerical variables were analyzed using the Student's t-test for parametric variables or the non-parametric Mann-Whitney U test when data were not normally distributed. Data were expressed as "mean ± SD," "median [minimum (min) - maximum (max)]"and "n (%)", where appropriate. P<0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

A total of 449 consecutive singleton pregnancies admitted to the labor ward with the complaint of labor pain and the diagnosis of onset of labor were included in the study. One hundred ninety nine patients who were ineligible for the study were excluded and 250 patients, 125 laboring women in the study group and 125 laboring women in the control group, were included in the study (Figure 1). The mean age was 25.2±5.1 years in the meperidine group, 26±4.8 years in the placebo group, and the differences were not significant (p=0.126). In terms of gestational weeks, median gestational week was 39 weeks 2 days (min-max: 37-42) in the control group, and 39 weeks (min-max: 37-42) in the meperidine group. No statistically significant difference was found between the groups (p=0.845). Twenty (16%) patients in the study group and 25 (25%) patients in the control group had to deliver by cesarean section. Although cesarean section rates were higher in the control group, the difference was not statistically significant (p=0.511). Likewise, there was no difference between the two groups in terms of body mass index (mean ± SD; study group: 28.85±4.52, control group: 27.95±3.43, p=0.163). When

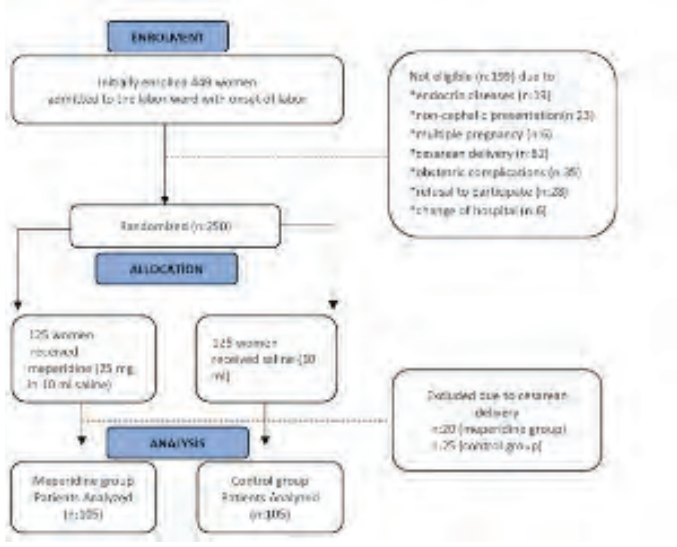

Figure 1. Consort statement flow diagram

the groups were subdivided in terms of parity (primiparous and multiparous), the mean number of patients in the groups was similar. No significant difference was observed in terms of subgroup numbers between meperidine and control groups and in terms of subgroup demographic parameters between multiparous and primiparous women in the overall study population. The demographic and obstetric characteristics of the participants are shown in Table 1.

Labor Characteristics and Neonatal Outcomes

TDL and DAP were found to be statistically significantly shorter in the meperidine group compared to the control group, both in primiparous (mean ± SD: 372±134 min vs. 400±179 min, p=0.026; 296±126 min vs. 363±170 min, p=0.024) and in the total patient population (mean ± SD: 273±129 min vs. 331±177 min, p=0.033; 249±122 min vs. 304±167 min, p=0.029). In contrast, for the DSS, no statistically significant difference in mean duration time was observed between meperidine and control groups in the total patient population, multiparous and primiparous women groups (mean ± SD: 24±15 min vs. 27±22 min, p=0.930; 15±8 min vs. 16±15 min, p=0.498; 30±15 min vs. 36±23 min, p=0.229, respectively). Although the meperidine group had shorter durations in terms of TDL and DAP in the multiparous patient population, no statistically significant difference was found between the groups (mean ± SD; 197±72 min vs. 258±144 min, p=0.170; 181±69 min vs. 241±139 min, p=0.157, respectively). No significant difference was noted between meperidine and control groups regarding total population and subgroups as primiparous and multiparous in terms of need for episiotomy, birth weight, 1-min and 5-min Apgar scores and presence of meconium aspiration (Table 2).

Table 1. Demographic characteristics of patients in the placebo and study groups by parity										
Control (n=100)		Total (n=205)			Multiparous women (n=91)			Primiparous women (n=114)		
		Meperidine (n=105)	p value	Control (n=48)	Meperidine (n=43)	p value	Control (n=52)	Meperidine (n=62)	p value	
Maternal characteristics										
Age (year)	Mean ± SD	26.03± 4.8	25.21±5.17	0.126[1]	28.08±4.63	28.70±4.70	0.593[1]	24.13±4.15	23.1±3.98	0.533[1]
BMI (kg/m^2), mean (min-max)		28.85 (19.47-47.23)	27.95 (14.5-40.16)	0.163[1]	29.88 (22.04-47.3)	28.11 (14.5-40.16)	0.073[1]	27.88 (19.47-37.32)	27.83 (20.2-34.45)	0.928[1]
Parity; mean ± SD		0.74±0.95	0.66±0.93	0.427[1]	1.54±0.80	1.60±0.76	0.550[1]			
Cesarean rates		25/125 (20%)	20/125 (16%)	0.511[1]	12/48	9/43	0.665[1]	13/52	11/62	0.767[1]
Gestational week, mean ± SD, mean (min-max)		39.3±1.51	39.3±1.29	0.845[1]	39.6 (37-41.6)	39.40 (37-41.5)	0.344[1]	39.0 (37.0-41.2)	39.0 (37.0-41.5)	0.421[1]
Parite	Primipar	52	62	0.310[2]	-	-	-	-	-	-
	Multipart	48	43							

[1]Mann-Whitney U test, p<0.05 were considered statistically significant, [2]Pearson χ^2 test. BMI: Body-mass index, SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Labor characteristics and neonatal outcomes in study groups with respect to parity										
		Total (n=205)			Multiparous women (n=91)			Primiparous women (n=114)		
		Control (n=100)	Meperidine (n=105)	p value	Control (n=48)	Meperidine (n=43)	p value	Control (n=52)	Meperidine (n=62)	p value
Labor characteristics										
Duration of labor (min), mean ± SD										
Active phase		304±167	249±122	**0.029[1]**	241±139	181±69	0.157[1]	363±170	296±129	**0.024[1]**
Second stage		27±22	24±15	0.930[1]	16±15	15±8	0.498[1]	36±23	30±15	0.229[1]
Total		331±177	273±129	**0.033[1]**	258±144	197±72	0.170[1]	400±179	372±134	**0.026[1]**
Need for episiotomy, n (%)	No	25 (27.0)	28 (28.6)	0.785[3]	25 (52.1)	28 (65.1)	0.296[3]	0 (0.0)	2 (3.2)	0.499[3]
	Yes	75 (73.0)	77 (71.4)		23 (47.9)	15 (34.9)		52 (100.0)	60 (96.8)	
Neonatal outcomes										
Birth weight (g)	Mean ± SD	3270±480	3210±397	0.330[2]	3405±485	3378±398	0.450[1]	3217±408	3204±316	0.603[1]
	Median (min-max)	3295 (2050-4400)	3200 (2250-4400)		(2050-4400)	(2790-4400)		(2360-3871)	(2223-3860)	
Apgar score										
1 min	Mean ± SD	7.56±0.69	7.81±0.59	0.512[1]	7.66±0.64	7.84±0.5	0.537[1]	7.52±0.7	7.76±0.6	0.145[1]
	Median (min-max)	8.0 (6.0-9.0)	8.0 (6.0-9.0)		8.0 (6.0-9.0)	8.0 (7.0-9.0)		8.0 (6.0-9.0)	8.0 (6.0-9.0)	
5 min*	Mean ± SD	9.08±0.44	9.12±(0.43)	0.550[1]	9.0±(0.37)	9.1±(0.34)	0.640[1]	9.1±0.5	9.2±0.5	0.317[1]
	Median (min-max)	9.0 (7.0-10.0)	9.0 (8.0-10.0)		9.0 (8.0-10.0)	9.0 (8.0-10.0)		9.0 (7.0-10.0)	9.0 (8.0-10.0)	
Meconium aspiration, n (%)	No	81 (80.8)	84 (80.0)	0.884[3]	35 (75.0)	35 (81.4)	0.592[3]	45 (86.5)	52 (83.9)	0.422[3]
	Yes	19 (19.2)	21 (20.0)		12 (25.0)	8 (18.6)		7 (13.5)	10 (16.1)	

[1]Mann-Whitney U test, [2]Student's t-test, [3]Pearson χ^2 test, [4]Fisher's Exact test, where appropriate. P<0.05 was considered statistically significant. Bold written numbers: Statistically significant, *All infants' Apgar score was 7-10. SD: Standard deviation

DISCUSSION

In this study, we tested the hypothesis that meperidine administration shortened labor time in nulliparous women who had labor augmentation, and we found that in primiparous labor duration was shorter with meperidine administration compared to placebo administration. Sosa et al. (9) conducted a randomized controlled study to determine whether meperidine administration reduced the duration of labor in women diagnosed with dystocia in the first stage of labor; however, they

could not find a statistically significant difference between the 100 mg meperidine i.v. and placebo groups in terms of labor duration. Furthermore, El-Refaie et al. (15) also conducted a similar randomized controlled study with 50 mg meperidine i.v. in pregnant women diagnosed with dystocia, but they could not show a statistically significant decrease in labor duration with the use of meperidine. Both studies are inconsistent with our findings. These different results regarding the use of meperidine on the progression of labor, may be a consequence of disparity between the administration of meperidine in patients with labor dystocia and in patients who undergo routine augmentation during a normally progressing labor. Another study from Turkey, conducted with a patient population of 53 primiparous women, revealed that administration of meperidine (50 mg, slow i.v. infusion) at 4-6 cm cervical dilation significantly shortened the total duration of labor by 38% (119.8 min vs. 192.2 min for placebo) and the first stage of labor by 41% (103 min vs. 173 min for placebo) with no difference between meperidine and placebo in terms of duration of the second stage of labor (8). In the same study, no statistically significant difference was found between meperidine administration and placebo in the second stage of labor. These findings were similar to the findings in our study. We also consider that these similar results may be evaluated due to genetic similarities.

The progression of labor is considered faster in multiparous women than in primiparas, as it enables an earlier onset of stronger uterine contractions, associated with the higher sensitivity of the uterus to endogenous and exogenous oxytocin (16). Accordingly, there is a significant negative correlation between parity and duration of both active and second stages of labor in multiparous women in studies (17,18). In this context, in our study, primiparous women who received meperidine had a statistically significant shorter duration of active labor than primiparous women who received placebo, in contrast, the same effect was not observed in multiparous women. The lack of effect in multiparous women can be explained by the fact that the effect of parity on the duration of labor may mask the effect of meperidine.

Maternal safety remains a concern with any opioid-based analgesic technique used during labor. Meperidine has been associated with an adverse effect on neonatal outcome, including low Apgar scores and respiratory depression in neonates (19,20). However, a few previous studies (21,22) suggest that the risk of adverse neonatal outcome is related to 1) the dose of meperidine and 2) the time between meperidine administration and the delivery of the baby. Although studies show inconsistent results, 50 mg meperidine applications can be considered an upper limit (8,9,23). Therefore, given that fetal meperidine exposure is maximum 2-3 hours after maternal administration, the optimal time for delivery may be considered to be within the first hour or after the third hour of the dose of meperidine (23). However, it may be proper to be skeptical about this issue.

Generally, no significant difference was observed in terms of Apgar scores between the control and meperidine groups in our study. Sosa et al. (9) showed that lower Apgar scores and more neonatal intensive care needs were required in the meperidine group. This difference may be because the patient population was selected from patients with labor dystocia or those who needed active management in the second stage of labor and the dose of meperidine administered was higher. In this regard, 25 mg i.v. meperidine administration may be safe. More studies are needed on neonatal effects.

Study Limitations

It must be admitted that some confounding factors were not noticed at first due to the study. In particular, determining the onset of the active phase of labor and subjective measurement of cervical dilatation are among these factors. In this respect, studies using more objective measurement methods and strict criteria should be conducted. Another limitation of our study was that the acid-base status of the arterial and venous umbilical cord blood samples at birth was not determined in our study. The fact that maternal side effects (nausea, vomiting, dizzinesss, cooperation disorder, etc.) were not evaluated in the study and control groups may be another weakness of our study. Additionally, the follow-up of the newborns in the first days after delivery could not be evaluated in our study due to the working conditions of the hospital. Besides, it would be appropriate to evaluate maternal pain in each group using the post-intervention visual analog score test.

Our study is the first randomized-controlled study that we know of, examining the effects of meperidine on labor duration during normally progressing labor without additional conditions such as labor dystocia. It is also the first study that used a lower dose (25 mg) of meperidine than other studies, demonstrating that it shortens the duration of labor in primiparous pregnant women.

CONCLUSION

In conclusion, our findings revealed that meperidine administration was associated with a shorter duration of active phase of labor in primiparous women. No significant impact on and no deterioration in Apgar scores with meperidine administration was observed in both primiparous and

multiparous women. There is a need for further larger scale randomized clinical studies addressing the impact of meperidine on duration of labor and neonatal outcomes among primiparous and multiparous women by different doses at various stages of cervical dilatation with a thorough and comprehensive neonatal assessment.

Ethics

Ethics Committee Approval: Yeditepe University Faculty of Medicine Clinical Research Ethics Committee (date of approval: 02/11/2011; reference number/protocol no: 2011/121).

Informed Consent: Informed consent forms were signed by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: O.Ş., Design: O.Ş., Data Collection or Processing: O.Ş., N.Ç., Analysis, or Interpretation: O.Ş., G.Y., S.G., V.M., N.Ç., A.İ.T., Literature Search: O.Ş., G.Y., Writing: O.Ş.

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REFERENCES

1. Friedman EA, Kroll BH. Computer analysis of labour progression. J Obstet Gynaecol Br Commonw 1969;76:1075-9.
2. Friedman EA, Kroll BH. Computer analysis of labor progression. II. distribution of data and limits of normal. J Reprod Med 1971;6:20-5.
3. Nabhan A, Boulvain M. Augmentation of labour. Best Pract Res Clin Obstet Gynaecol 2020;67:80-9.
4. Wei S, Wo BL, Qi HP, Xu H, Luo ZC, Roy C, et al. Early amniotomy and early oxytocin for prevention of, or therapy for, delay in first stage spontaneous labour compared with routine care. Cochrane Database Syst Rev 2013:CD006794.
5. Mastrogiannis DS, Knuppel RA. Labor induced using methods that do not involve oxytocin. Clin Obstet Gynecol 1995;38:259-66
6. Sica-Blanco Y, Rozada H, Remedio MR. Effect of meperidine on uterine contractility during pregnancy and prelabor. Am J Obstet Gynecol 1967;97:1096-100.
7. Ballas S, Toaff ME, Toaff R. Effects of intravenous meperidine and meperidine with promethazine on uterine activity and fetal heart rate during labor. Isr J Med Sci 1976;12:1141-7.
8. Yilmaz B, Kart C, Kelekci S, Gokturk U, Sut N, Tarlan N, et al. Meperidine versus valethamate bromide in shortening the duration of active labor. Int J Gynaecol Obstet 2009;107:126-9.
9. Sosa CG, Balaguer E, Alonso JG, Panizza R, Laborde A, Berrondo C. Meperidine for dystocia during the first stage of labor: a randomized controlled trial. Am J Obstet Gynecol 2004;191:1212-8.
10. Nacitarhan C, Sadan G, Kayacan N, Ertugrul F, Arici G, Karsli B, et al. The effects of opioids, local anesthetics and adjuvants on isolated pregnant rat uterine muscles. Methods Find Exp Clin Pharmacol 2007;29:273-6.
11. Milwidsky A, Finci-Yeheskel Z, Mayer M. Direct stimulation of urokinase, plasmin, and collagenase by meperidine: a possible mechanism for the ability of meperidine to enhance cervical effacement and dilation. Am J Perinatol 1993;10:130-4.
12. Eskes TKAB. Effect of morphine upon uterine contractility in late pregnancy. Am J Obstet Gynecol 1962;84:281-89.
13. Pajntar M, Valentincic B, Verdenik I. The effect of pethidine hydrochloride on the cervical muscles in the active phase of labour. Clin Exp Obstet Gynecol 1993;20:145-50.
14. Díaz AG, Schwarcz R, Fescina R, Caldeyro-Barcia R. Vertical position during the first stage of the course of labor, and neonatal outcome. Eur J Obstet Gynecol Reprod Biol 1980;11:1-7.
15. El-Refaie TA, El-Said MM, Shoukry AA, Khafagy SM, El-Din AS, Badawy MM. Meperidine for uterine dystocia and its effect on duration of labor and neonatal acid-base status: a randomized clinical trial. J Obstet Gynaecol Res 2012;38:383-9.
16. Nesheim BI. Duration of labor. An analysis of influencing factors. Acta Obstet Gynecol Scand 1988;67:121-4.
17. Laughon SK, Branch DW, Beaver J, Zhang J. Changes in labor patterns over 50 years. Am J Obstet Gynecol 2012;206:419.e1-9.
18. Ijaiya MA, Aboyeji AP, Fakeye OO, Balogun OR, Nwachukwu DC, Abiodun MO. Pattern of cervical dilatation among parturients in Ilorin, Nigeria. Ann Afr Med 2009;8:181-4.
19. Sosa CG, Buekens P, Hughes JM, Balaguer E, Sotero G, Panizza R, et al. Effect of pethidine administered during the first stage of labor on the acid-base status at birth. Eur J Obstet Gynecol Reprod Biol 2006;129:135-9.
20. Smith LA, Burns E, Cuthbert A. Parenteral opioids for maternal pain management in labour. Cochrane Database Syst Rev 2018;6:CD007396.
21. Mattingly JE, D'Alessio J, Ramanathan J. Effects of obstetric analgesics and anesthetics on the neonate: a review. Paediatr Drugs 2003;5:615-27.
22. Petrie RH, Yeh SY, Murata Y, Paul RH, Hon EH, Barron BA, et al. The effect of drugs on fetal heart rate variability. Am J Obstet Gynecol 1978;130:294-9.
23. Phillips SN, Fernando R, Girard T. Parenteral opioid analgesia: does it still have a role? Best Pract Res Clin Anaesthesiol 2017;31:3-14.

ORIGINAL ARTICLE

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Assessment of the Relationship of REMS and MEWS Scores with Prognosis in Patients Diagnosed with COVID-19 Admitted to the Emergency Department

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Abstract

Objective: The current study predicts their clinical termination and the mortality rate at the end of the first-month with rapid scoring systems such as rapid emergency medicine score (REMS) and modified early warning score (MEWS) of Coronavirus disease-2019 (COVID-19) patients admitted to the emergency department.

Methods: A total of 392 patients diagnosed with COVID-19 admitted to the emergency department in 1-month included in the study. REMS and MEWS were calculated for each case. Demographic data of patients, clinical outcomes [discharge, service or intensive care unit (ICU) hospitalization] and first-month mortality were analysed with receiver operating characteristic (ROC) curves to determine the cut-off value based on these scores.

Results: The 1-month mortality rate of our patients was 4.3% (n=17). REMS was higher in the mortality of patients who are (7.24±3.77) with COVID-19 than survival (2.87±3.09), and there was a statistically significant difference between them ($p<0.01$). Similarly, the average of the MEWS was higher in the mortality of patients (2.76±1.86) than in patients who are survival (1.65±1.35), and there was a statistically significant difference ($p<0.01$). The REMS of patients admitted to the service was higher than that of patients discharged ($p<0.01$). When the REMS score was determined as 3 cut-off value in ROC analysis, service hospitalization was 5 times higher in patients with a REMS score of 3 and above than in those who were discharged (odds ratio: 1: 5.022 95% confidence interval: 3.088-8.168). Also, REMS and MEWS were higher in ICU patients than in discharged patients ($p<0.01$).

Conclusion: In predicting the 1-month mortality of patients with ED diagnosed with COVID-19, REMS, and MEWS scoring systems can be useful and guiding in determining the patients who need hospitalization for emergency physicians. The use of these scoring systems in emergency departments can help predict the clinical outcomes of patients at the time of the initial evaluation and can also be a practical method for predicting the prognosis of the patients.

Keywords: COVID-19, infectious diseases, viral, triage, emergency department

INTRODUCTION

Coronaviruses are RNA viruses that may cause diseases by affecting multiple systems in humans and other living things (1). Until the last few years, six types of coronaviruses that have caused the disease in humans. A novel type of coronavirus was discovered in Wuhan, China, in the last months of 2019, after an increase in pneumonia cases with an unknown factor. This virus was named Coronavirus disease-2019 (COVID-19). Some patients infected with the virus were asymptomatic, and some were admitted to the hospital with symptoms, such as fever, cough, weakness, rhinorrhoea, chest pain, diarrhea and respiratory failure (2,3).

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The clinical course of patients being affected by COVID-19 infection was linked to several risk factors, such as age, gender, presence of comorbid disease and smoking history, in some studies (4-7). Many scoring systems have also been investigated in these patient groups to predict the clinical course and the course of patients after hospitalization. To date, the use of scores that predict early mortality in emergency departments has been a rational approach, as it ensures close follow-up and treatment of patients. Examples of these scorings are rapid emergency medicine score (REMS) and modified early warning score (MEWS) scoring (8). Research on early warning scores that can predict prognosis during emergency department admission in COVID-19 infection is limited. One of these studies has been conducted only to predict the mortality of patients in intensive care, and the other has been conducted to predict 48-hour and 7-day mortality with some scoring systems (9,10).

This study aims to evaluate the availability of REMS and MEWS scores to predict 1-month mortality and emergency department clinical outcomes of the patients with COVID-19 infection admitted to the emergency department.

METHODS

Study Design

This study was designed as a single-centered, prospective, and observational study. To conduct this study, ethical approval was obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Local Ethical Committee (no: 48670771-514.10). Patients diagnosed with COVID-19 who were admitted to University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital Emergency Medicine Clinic were included in this study. Our hospital emergency department is a tertiary, multidisciplinary hospital where approximately 500,000-550,000 patients are cared for annually. Our study was completed within one month on patients diagnosed with COVID-19 out of patients admitted to the emergency department pandemic area of our hospital. Our hospital has about 400 patients applying daily with the suspicion of COVID-19 to the emergency department pandemic area, and about 40 patients have been diagnosed with COVID-19 as of daily. Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Study Subjects and Settings

Patients diagnosed with COVID-19 and admitted to our hospital's emergency medicine clinic between 07/06/2020 and 07/07/2020 were included in this study. All patients over the age of 18 who were clinically, radiologically or laboratory diagnosed with COVID-19 and who gave consent to participate in this study were included. Pregnant patients, patients under 18, patients who did not give consent to participate in this study, patients who had suffered from trauma, and patients on drugs that were primarily effective on the central nervous system, such as antidepressants and antipsychotics, were excluded from this study. This study was also in line with the Declaration of Helsinki. University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Local Ethical Committee (no: 48670771-514.10).

Data Analysis and Measurement

Demographic data of the patients included in this study, their symptoms during admission, and information about their clinical outcome in the emergency department, such as hospitalization or discharge, were collected and analysed. The data contained all the information needed to calculate REMS and MEWS scores. REMS to calculate the score; the state of consciousness, Glasgow Coma scale (GCS), Average blood pressure (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), fever (°C), partial oxygen saturation (%) and patient age (years) information to calculate MEWS score; state of consciousness, systolic blood pressure (mmHg), heart rate (beats/min), body temperature (°C) and respiratory rate (breath/min) data were used. REMS and MEWS scores calculated based on these data were recorded. The 1-month mortality information of patients enrolled in this study was examined and analysed through hospital data.

Statistical Analysis

The NCSS (number Cruncher Statistical System) (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used while evaluating the study data. The suitability of quantitative data for normal distribution was tested with the Kolmogorov-Smirnov, Shapiro-Wilk test, and graphical evaluations. Student's t-test was used in two-group comparisons of quantitative data with a normal distribution, and the Mann-Whitney U test was used in two-group comparisons of data without normal distribution. Kruskal-Wallis test and Bonferroni Dunn test were used for binary comparisons of three and above groups that did not show normal distribution. Pearson chi-square test, Fisher-Freeman-Halton Exact test and Fisher's Exact test was used to compare qualitative data. Diagnostic screening tests (sensitivity, specificity, PKD, NKD) and receiver operating characteristic (ROC) curve analyses were used to determine cut-off for parameters. Significance was evaluated at a level of at least $p<0.05$.

RESULTS

Our study included 455 patients. A total of 63 patients whose data were recorded incomplete and who were using antidepressants were excluded from this study. Of the 392 patients included in our study, 43.4% (n=170) were female and 56.6% (n=222) were male. The average age of our patients was 48.98±19.49 years. The age of the cases with mortality at the end of the first-month was higher ($p<0.01$). However, no statistically significant differences were found between gender distributions and 1-month mortality ($p>0.05$). The most common additional disease of our patients was hypertension, followed by diabetes mellitus (DM) and ischemic heart disease (IHD). The most common symptoms were shortness of breath and cough. These symptoms were followed by fever, headache, and myalgia. Information about our patient's vital signs, average REMS and MEWS scores, states of consciousness, comorbid diseases, symptoms and mortality rates are indicated in Table 1.

The mortality rate of our patients at the end of the first-month was 4.3% (n=17). At the end of the first-month, the mortality of patients with a comorbid disease - was 20.8 times higher than those without a comorbid disease, and a statistically significant difference was found between them ($p<0.01$) [odds ratio (OR): 1:20.810 (95% confidence interval (CI): 2.731-158.539]. The average REMS score was higher in patients who died (non-survival) (7.24±3.77) than in patients who survived (2.87±3.09), and there was a statistically significant difference between them ($p<0.01$). The average MEWS score was also higher in non-survival patients (2.76±1.86) than in survivor patients (1.65±1.35), and there was a statistically significant difference between them ($p<0.01$). In other words, at the end of the first-month of the disease, REMS and MEWS scores were higher in cases with mortality (Table 2). Based on this significance, calculating the cut-off point for REMS and MEWS scores was considered.

The cut-off point of groups for REMS score was determined as 5 and above. When 1-month mortality for 5 cut-off values of REMS score was examined, sensitivity was 82.35%, specificity 71.47%, positive estimation 11.57%, negative estimation 98.89% and accuracy was 71.94%. In the ROC curve obtained (Figure 1), area under the curve (AUC) 81.8% standard error was determined as 5.3%. A statistically significant association was found between mortality at the end of the first-month and the 5 cut-off values of the REMS score ($p<0.01$), and the risk of mortality was 11.7 times higher in patients with REMS score 5 and above [OR: 11.688 (95% CI: 3.293-41.493)]. For the MEWS score, the cut-off point was 3 and higher, and for this estimated value, sensitivity was 52.94%, specificity was 82.40%, the positive estimate was 12.0%, the negative estimate

Table 1. The distribution of demographic characteristics

		N (%) or min-max (median) mean ± SD
Age (years)		18-101
		48.98±19.49
Sex	**Female**	170 (43.4%)
	Male	222 (56.6%)
Comorbid diseases	**No**	213 (54.3%)
	Yes	179 (45.7%)
Comorbidities (n=179)	**Hypertension**	95 (53.1%)
	Diabetes mellitus	61 (34.1%)
	Coronary arter disease	46 (25.7%)
	COPD	42 (23.5%)
	Congestive heart failure	18 (10.1%)
	Chronic kidney disease	14 (7.8%)
	Others	32 (23.4%)
Symptom	**Asymptomatic/contact**	16 (4.1%)
	Sympmtomatic	376 (95.9%)
Symptoms (n=376)	**Dyspnea**	164 (43.6%)
	Cough	143 (38%)
	Fever	112 (29.8%)
	Fatigue-myalgia	110 (29.3%)
	Diarrhea	30 (8%)
	Headache	30 (8%)
	Nausea-vomiting	27 (7.2%)
	Loss of taste or smell	22 (5.9%)
	Throat ache	15 (4%)
	Chest pain	10 (2.7%)
	Others	33 (8.7%)
Systolic heart pressure, mmHg	-	17-233 (130)
	-	131.78±24.87
Diastolic heart pressure, mmHg	-	34-124 (75)
	-	76.45±13.06
Beats/minute	-	47-192 (90)
	-	93.20±17.21
Respiratory rate/ minute	-	12-96 (18)
	-	18.80±5.75
Fever, °C	-	35.3-40 (36.7)
	-	36.79±0.65
SpO_2, %	-	18-980 (97)
	-	97.60±45.07
REMS score	-	0-15 (2)
	-	3.06±3.24
MEWS score	-	0-10 (1)
	-	1.69±1.40

Contunuet Table 1		
Glasgow Coma score	-	3-15 (15)
	-	14.71±1.55
AVPU (n=390)	**A**	374 (95.9%)
	V	8 (2.1%)
	P	4 (1%)
	U	4 (1%)
Clinical outcome	**Admitted to ICU**	24 (6.1%)
	Admitted to service	108 (27.6%)
	Discharged	260 (66.3%)
Mortality status after 1-month	**Mortality (-)**	375 (95.7%)
	Mortality (+)	17 (4.3%)

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, REMS: Rapid emergency medicine score, MEWS: Modified early warning score, ICU: Intensive care unit, A: Awake, V: Verbal, P: Pain, U: Unresponsive, min: Minimum, max: Maximum

Table 2. The evaluation of mortality results after 1-month according to demographic characteristics and comorbid diseases

		Mortality status after 1-month		p
		No (n=375)	Yes (n=17)	
		n (%)	n (%)	
Age (years)	Min-max (median)	10-101 (48)	45-88 (80)	[a]**0.001****
	Mean ± SD	47.83±18.98	73.76±15.01	
Sex	**Female**	164 (43.7)	6 (35.3)	[b]**0.492**
	Male	211 (56.3)	11 (64.7)	
Comorbid disease	**No**	212 (56.5)	1 (5.9)	[b]**0.001****
	Yes	163 (43.5)	16 (94.1)	
REMS score	Min-max (median)	0-15 (2)	0-14 (7)	[d]**0.001****
	Mean ± SD	2.87±3.09	7.24±3.77	
MEWS score	Min - max (median)	0-10 (1)	0-7 (3)	[d]**0.007****
	Mean ± SD	1.65±1.35	2.76±1.86	

[a]Student t-test, [b]Pearson chi-square test, [d]Mann-Whitney U test, *p<0.05, **p<0.01. REMS: Rapid emergency medicine score, MEWS: Modified early warning score, SD: Standard deviation, min: Minimum, max: Maximum

was 97.48%, and accuracy was 81.12%. In the obtained ROC curve, AUC 68.1% standard error was determined as 7.5%. At the end of the first-month, a statistically significant relationship was found between the mortality rate and the 3 cut-off values of the MEWS score (p<0.01). In patients with a MEWS score of 3 and above, the risk of mortality at the end of the first-month was 5.3 times higher [OR: 1:5.267 (95% CI: 1.960-14.157)] (Table 3).

In the study of clinical outcome of the patients with ED, the incidence of comorbid disease was higher in intensive care

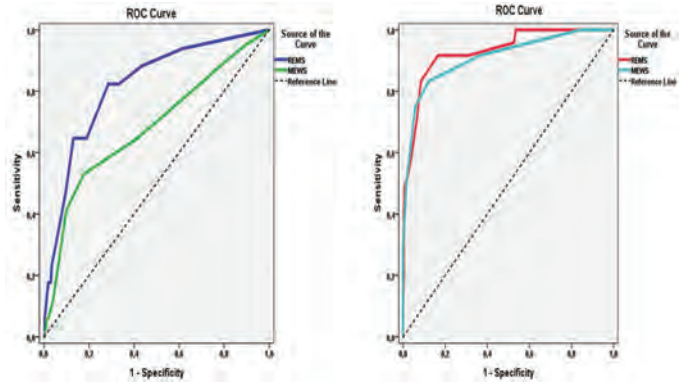

Figure 1. ROC curve for REMS and MEWS scores based on mortality (left) and ICU hospitalization and discharge (right) after 1-month
ROC: Receiver operating characteristic, REMS: Rapid emergency medicine score, MEWS: Modified early warning score, ICU: Intensive care unit

unit (ICU) and hospitalized patients than in discharged patients (p=0.001; p=0.001 p<0.01, respectively). The most common comorbid disease in ICU patients was hypertension, which was followed by DM, IHD and chronic obstructive pulmonary disease. REMS scores of ICU and service hospitalization cases are higher than those of discharge cases (p<0.01). Similarly, MEWS scores in ICU and service hospitalization were higher than in discharged cases (p=0.001; p=0.031; p<0.05, respectively). Additionally, REMS and MEWS scores of patients admitted to ICU were also higher than patients admitted to the service (p<0.01).

A statistically significant relationship was found between ICU admission and the discharge status and the 5 cut-off values of the REMS score (p<0.01). In patients with a REMS score of 5 and above, the risk of ICU hospitalization is 55.5 times higher than in those who were discharged [OR: 1:55.512 95% (CI: 12.586-244.847)] (Table 3).

According to ICU hospitalization and discharge groups, the cut-off point for MEWS score was determined as 3 and higher. For 3 cutting values of the MEWS score, sensitivity was 83.33%, specificity was 87.69%, positive estimation was 38.46%, negative estimation was 98.28%, and accuracy was 87.32%. In the obtained ROC curve, the underlying area was 91.1% standard error of 3.6% (Figure 1).

REMS and MEWS scores were higher in ICU hospitalization cases than in service hospitalization cases (p<0.01) (Table 4). Based on this significance, it was considered to calculate the cut-off point for REMS and MEWS scores. The cut-off point for REMS score was determined as 7 and above for ICU hospitalization and service hospitalization groups. For 7 cut-off values of REMS score, sensitivity was 70.83%, specificity was 75.93%, positive estimation was 39.53%, negative estimation was 92.13% and accuracy was 75.0%. In the obtained ROC curve, the underlying area was 81.5% standard error 5.1% (Figure 2). A statistically

Table 3. Diagnostic tests and ROC curve results for REMS and MEWS scores					
		Patient's clinical outcome			p
		Admitted to ICU (n=24)	Admitted to service (n=108)	Discharged (n=260)	
		n (%)	n (%)	n (%)	
Comorbid diseases	**No**	3 (12.5)	34 (31.5)	176 (67.7)	[b]**0.001****
	Yes	21 (87.5)	74 (68.5)	84 (32.3)	
Comorbidities	**HT**	14 (58.3)	39 (36.1)	42 (16.2)	[b]**0.001****
	DM	7 (29.2)	28 (25.9)	26 (10.0)	[b]**0.001****
	COPD	5 (20.8)	15 (13.9)	22 (8.5)	[b]**0.079**
	CAD	8 (33.3)	22 (20.4)	16 (6.2)	[b]**0.001****
	CKD	3 (12.5)	6 (5.6)	5 (1.9)	[e]**0.015***
	CHF	4 (16.7)	10 (9.3)	4 (1.5)	[e]**0.001****
	Malignancy	2 (8.3)	5 (4.6)	7 (2.7)	[e]**0.203**
	CVD	5 (25.0)	5 (4.6)	0 (0)	[e]**0.001****
	Others	2 (8.3)	7 (6.5)	8 (3.1)	[e]**0.145**
REMS score	Min-max (median)	1-15 (9)	0-12 (5)	0-13 (2)	[f]**0.001****
	Mean ± SD	8.88±3.77	4.40±3.00	1.97±2.41	
MEWS score	Min-max (median)	1-10 (4.5)	0-6 (1)	0-5 (1)	[f]**0.001****
	Mean ± SD	4.63±2.12	1.74±1.13	1.40±1.06	

[b]Pearson chi-square test, [e]Fisher-Freeman-Halton Exact test, [f]Kruskal-Wallis test, *p<0.05, **p<0.01, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CAD: Coronary arter disease, CKD: Chronic kidney disease, CHF: Congestive heart failure, ICU: Intensive care unit, REMS: Rapid emergency medicine score, MEWS: Modified early warning score, SD: Standard deviation, min: Minimum, max: Maximum, CVO: Cerebro vascular disease

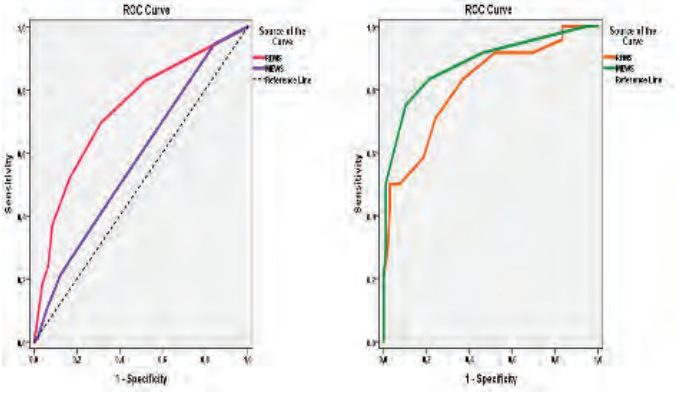

Figure 2. ROC curve for REMS and MEWS scores according to service admission or discharge (left) and ICU hospitalization or service hospitalization (right)

ROC: Receiver operating characteristic, REMS: Rapid emergency medicine score, MEWS: Modified early warning score, ICU: Intensive care unit

significant relationship was found between ICU hospitalization, service hospitalization and the 7 cut-off values of the REMS score (p<0.01). In patients with a REMS score of 7 and above, the risk of ICU hospitalization was 7.66 times higher than in those with a service hospitalization [OR: 1:7.659 (95% CI: 2.862-20.501)] (Table 5).

A statistically significant relationship was found between ICU admission/discharge status and the 3 cut-off values of the MEWS score (p=0.001; p<0.01). In patients with a MEWS score of 3 and above, the risk of ICU hospitalization was 35.63 times higher than in those who were discharged [OR: 1:35.625 (95% CI: 11ch445-110.890)] (Table 5).

REMS and MEWS scores were higher in patients with service hospitalization than in patients who were discharged (p<0.01, p<0.05). Based on this significance, the calculation of the cut-off point for REMS and MEWS scores was considered. The cut-off point for REMS score was determined as 3 and higher for groups who were hospitalized and discharged. For 3 cut-off values of REMS score, sensitivity was 69.44%, specificity was 68.85%, positive estimation was 48.08%, negative estimation was 84.43% and accuracy was 69.02%. In the obtained ROC curve, the underlying area was determined as 73.7% standard error 2.9% (Figure 2). In patients with a REMS score of 3 and above, service admission was 5.022 times higher than those discharged [OR 1:5.022 (95% CI: 3.088-8.168)]. The cut-off point for the MEWS score was determined as 1 and above in the same groups. For the 1 cut-off value of the MEWS score, sensitivity was 94.44%, specificity was 15.77%, positive estimation was 31.78%, negative estimation was 87.23% and accuracy was 38.86%. In the resulting ROC curve, the underlying area was 58.4% and standard error was 3.2% (Figure 2). A statistically significant relationship was

found between service hospitalization and discharge status and the MEWS score cut-off value of 1 (p<0.01). In cases with a MEWS score of 1 and above, service hospitalization was 3.183 times higher than in those discharged [OR: 1: 3.183 (95% CI: 1.309-7.737)] (Table 5).

The cut-off point for MEWS score for ICU hospitalization and service hospitalization groups was determined as 4 and above. Sensitivity was 75.00%, specificity was 89.81%, positive estimation was 62.07%, negative estimation was 94.17% and accuracy was 87.12% for 4 cut-off values of the MEWS score. In the resulting ROC curve, the underlying area was 88.4% and the standard error to be 4.4% (Figure 2). A statistically significant relationship was found between ICU hospitalization, service hospitalization and the 4 cut-off values of the MEWS score (p=0.001; p<0.01). In patients with a MEWS score of 4 and above, the risk of ICU hospitalization was 26.46 times higher than in those with a service hospitalization [OR: 1:26.455 (95% CI: 8.678-80.648)] (Table 5).

DISCUSSION

Our study has shown that there is no special rapid scoring system used to predict the prognosis of COVID-19. In this study, we have tried determining the prognosis of these patients using REMS and MEWS scoring systems. We have found that COVID-19 patients with high REMS and MEWS scores had higher hospitalization, ICU admission and 1-month mortality rate. Additionally, both

Table 4. Evaluations according to the patient's clinical outcome

	Diagnostic scan					ROC curve		p
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area	95% confidence interval	
Mortality at the end of 1-month								
REMS	**≥5**	82.35	71.47	11.57	98.89	**0.818**	0.714-0.921	**0.001****
MEWS	**≥3**	52.94	82.40	12.00	97.48	**0.681**	0.534-0.828	**0.012***
According to ICU admission and discharge status								
REMS	**≥5**	91.67	83.46	33.85	99.09	**0.930**	0.876-0.984	**0.001****
MEWS	**≥3**	83.33	87.69	38.46	98.28	**0.911**	0.840-0.982	**0.001****
According to service admission and discharge status								
REMS	**≥3**	69.44	68.85	48.08	84.43	**0.737**	0.680-0.795	**0.001****
MEWS	**≥1**	94.44	15.77	31.78	87.23	**0.584**	0.521-0.647	**0.012***
ICU hospitalization and service hospitalization status								
REMS	**≥7**	70.83	75.93	39.53	92.13	**0.815**	0.715-0.915	**0.001****
MEWS	**≥4**	75.00	89.81	62.07	94.17	**0.884**	0.798-0.970	**0.001****

*p<0.05, **p<0.01. ROC: Receiver operating characteristic, ICU: Intensive care unit, REMS: Rapid emergency medicine score, MEWS: Modified early warning score

Table 5. Relationship between REMS and MEWS scores (cut-off values)

	REMS <5	REMS ≥5	p	MEWS <3	MEWS ≥3	p
Mortality (-)	268 (71.5)	107 (28.5)	[b]**0.001****	309 (82.4)	66 (17.6)	[c]**0.001****
Mortality (+)	3 (17.6)	14 (82.4)		8 (47.1)	9 (52.9)	
	REMS <5	REMS ≥5		MEWS <3	MEWS ≥3	
Discharged	217 (83.5)	43 (16.5)	[b]**0.001****	228 (87.7)	32 (12.3)	[c]**0.0011****
Admitted to ICU	2 (8.3)	22 (91.7)		4 (16.7)	20 (83.3)	
	REMS <3	REMS ≥3		MEWS <1	MEWS ≥1	
Discharged	179 (68.8)	81 (31.2)	[b]**0.001****	41 (15.8)	219 (84.2)	[b]**0.008****
Admitted to service	33 (30.6)	75 (69.4)		6 (5.6)	102 (94.4)	
	REMS <7	REMS ≥7		MEWS <4	MEWS ≥4	
Admitted to service	82 (75.9)	26 (24.1)	[b]**0.001****	97 (89.8)	11 (10.2)	[b]**0.001****
Admitted to ICU	7 (29.2)	17 (70.8)		6 (25)	18 (75)	

[b]Pearson chi-square test, [c]Fisher's Exact test, **p<0.01, REMS: Rapid emergency medicine score, MEWS: Modified early warning score, ICU: Intensive care unit

mortality and hospitalization rates of patients with comorbidity were higher. In previous studies, it has been emphasized that comorbidity is important for hospitalization and admission to intensive care (4,11,12). Consistent with previous studies, patients with comorbidity had higher mortality at the end of the first-month in our study.

MEWS is a modified version (13) of the EWS developed by Subbe et al. (14) in 2000. As an easily computable per-patient tool in a busy clinical area, MEWS can help identify the need for early intervention while evaluating emergency patients. Moreover, MEWS is a scoring system that uses vital parameters calculated using systolic blood pressure, heart rate, respiratory rate, body temperature and AVPU scale (14). However, REMS is a scoring system developed by Olsson et al. (15), and which uses the GCS instead of AVPU, unlike MEWS; the age of the patient is also included in the scoring while using REMS. The main reason we have received high scores in these two scoring systems is that the score points increase as the vital signs deteriorate. The study of Hu et al. (10) supports the findings of our study. Hu et al. (10) used the REMS and MEWS rapid scoring systems, which are normally used in the emergency department, on patients with COVID-19 in critical condition. Their study included 105 patients and they noted that mortality would be high at certain cut-off values in the REMS score and MEWS score. Considering these data, they have argued that the REMS scoring system is better than MEWS in predicting mortality in critical patients (10,16,17). In our study, we tried to predict mortality and prognosis in all patients with COVID-19 admitted to the emergency department using these two scoring systems.

The advantage of our study compared to other studies is that this study has examined all applications and reviewed service hospitalization, intensive care hospitalization and mortality altogether. Hu et al. (10) evaluated only mortality for each cut-off value in critical patients in intensive care. In our study, it has been determined that the patient's prognosis can be defined based on the cut-off values obtained.

When we compared REMS and MEWS scores in our study, we found that REMS score of 5 points and above was superior to the MEWS score of 3 points and above. A positive value as AUC value 0.818 was determined for REMS score 5 points and above. Although the high REMS score was not compelling in determining mortality (PPV: 11.57), it was very successful in determining that there would be no mortality of patients below 5 points (NPV: 98.89). We can attribute this to the fact that the number of patients we lost was only 17. A MEWS score of 3 or higher is also a useful method for determining patient mortality, but it is not as strong as REMS (AUC: 0.681).

The finding obtained in our study suggest that REMS is again superior to the MEWS score to distinguish when the patients will be admitted to intensive care or when they will be discharged. Patients with a REMS score of 5 points and above are more likely to be admitted to intensive care (AUC: 0.930). This value was as strong as the REMS score for 3 points and above values for the MEWS score (AUC: 0.911). Therefore, note that patients above 5 and 3 points in REMS and MEWS scores, respectively, are more likely to be admitted to intensive care.

Also, another substantial discovery we made was that the MEWS score slightly exceeded the REMS score when patients admitted to the service and admitted to the ICU were compared. Patients with a MEWS score of 4 points and above and patients with a REMS score of 7 points and above were mostly admitted to intensive care. Therefore we believe that the MEWS score is a good scoring system that will be used in the emergency department to be admitted to the ICU.

Study Limitations

The most important limitation of our study is that our number of patients and mortality rate are low. However, to our knowledge, this study has the largest number of patients in the literature. Our second limitation is that in our study, we did not separate the age groups of our patients based on decades. If we grouped patients based on their ages, we would probably find different mortality scores depending on the age group, given that in the REMS scoring system, different scores are received from different age groups. Another limitation is that we have not determined the mortality based on the treatment administered to our patients. Keeping this factor in mind for other prospective studies on this subject will contribute to the literature.

CONCLUSION

To sum up, our study has shown that REMS and MEWS scoring systems can be useful and guiding for emergency physicians in determining the 1-month mortality of COVID-19 diagnosed patients and in determining which patients need to be hospitalized. The use of these scoring systems in emergency departments can help predict the clinical endings of patients in the initial evaluation and can also be a practical method for predicting the prognosis of patients.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Local Ethical Committee (no: 48670771-514.10).

Informed Consent: Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
2. Corman VM, Lienau J, Witzenrath M. Coronaviren als Ursache respiratorischer Infektionen [Coronaviruses as the cause of respiratory infections]. Internist (Berl) 2019;60:1136-45.
3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-280. e8.
4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.
5. Sakurai A, Sasaki T, Kato S, Hayashi M, Tsuzuki SI, Ishihara T, et al. Natural history of asymptomatic SARS-CoV-2 infection. N Engl J Med 2020;383:885-6.
6. Bajema KL, Oster AM, McGovern OL, Lindstrom S, Stenger MR, Anderson TC, et al. Persons evaluated for 2019 novel coronavirus - United States, January 2020. MMWR Morb Mortal Wkly Rep 2020;69:166-70.
7. Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395:514-23.
8. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation 2013;84:465-70.
9. Ciceri F, Castagna A, Rovere-Querini P, De Cobelli F, Ruggeri A, Galli L, et al. Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy. Clin Immunol 2020;217:108509.
10. Hu H, Yao N, Qiu Y. Comparing rapid scoring systems in mortality prediction of critically ill patients with novel coronavirus disease. Acad Emerg Med 2020;27:461-8.
11. Chen Z, Cheng Z, Zhang X, et al. Clinical manifestations and CT characteristics sa corona virus disease 2019 (COVID-19). Radiol Pract. 2020; 3:286-90.
12. Zhu YC, Tan L, Liu L, Li KZ, Qi WY, Hu X. Comparative analysis of characteristics and medications between corona virus disease 2019 and several acute reproductive syndrome. Clin Med J. 2020; 18:15-23.
13. Covino M, Sandroni C, Santoro M, Sabia L, Simeoni B, Bocci MG, et al. Predicting intensive care unit admission and death for COVID-19 patients in the emergency department using early warning scores. Resuscitation 2020;156:84-91.
14. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified early warning score in medical admissions. QJM 2001;94:521-6.
15. Olsson T, Terent A, Lind L. Rapid emergency medicine score can predict long-term mortality in nonsurgical emergency department patients. Acad Emerg Med 2004;11:1008-13.
16. Montenegro SMSL, Miranda CH. Evaluation of the performance of the modified early warning score in a Brazilian public hospital. Rev Bras Enferm 2019;72:1428-34. Erratum in: Rev Bras Enferm 2019;72(Suppl 3):373. Rodrigues, Carlos Henrique Miranda [corrected to Miranda, Carlos Henrique].
17. Olino L, Gonçalves AC, Strada JKR, Vieira LB, Machado MLP, Molina KL, et al. Effective communication for patient safety: transfer note and modified early warning Score. Rev Gaucha Enferm 2019;40:e20180341.

ORIGINAL ARTICLE

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Radiotherapy for Patients with Cancer and Connective Tissue Disease

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Abstract

Objective: This research aimed to evaluate acute and late toxicities of radiotherapy for patients with connective tissue disease (CTD).

Methods: A retrospective review was performed with the medical records of patients with a diagnosis of both cancer and CTD, who have undergone radiotherapy at our institution between January 2010 to December 2020. Acute and chronic adverse effects of radiotherapy were analyzed.

Results: The mean age of the patients at time of RT was 58 years (45-74) and 50 years (35-68) at CTD diagnosis. Fourteen of patients were female (77.7%). Primary tumor location was as; breast 8 (44.7%), cervix 2 (11.1%), rectum 2 (11.1%), prostate 2 (11.1%), brain 1 (5.5%), lung 1 (5.5%), larynx 1 (5.5%) and endometrium 1 (5.5%). Nine patients (50%) had Behçet's disease, 5 (28%) systemic lupus erythematosus, 2 (11%) systemic sclerosis and 2 (11%) dermatomyositis. Patients in the curative group receiving higher doses of radiation have experienced more acute toxic effects than the others. Thirteen (72%) patients had any grade 1 and 6 (33%) patients had any grade 2 acute toxicities while only 3 (17%) patients with cervical and brain cancers had chronic grade 2 hematological toxicity due to concomitant chemoradiotherapy. The most common acute toxicities were radiation dermatitis, nausea, fatigue and diarrhea. No acute or chronic toxicities higher than grade 2 were recorded. There was not any interruption occured during radiotherapy treatment because of acute toxicities and all patients completed their prescribed course of radiotherapy.

Conclusion: With new radiotherapy techniques there was no increased incidence of acute and chronic risk of toxicity observed and radiotherapy was generally well-tolerated for patients with CTD during the treatment and follow-up. Individualizing treatment strategy for each patient will help improve the results for this group of patients with increased treatment efficacy and decreased toxicity.

Keywords: Connective tissue diseases, adverse effects radiotherapy, toxicity radiotherapy, collagen vascular diseases, complications

INTRODUCTION

Connective tissue diseases (CTD) are a group of autoimmune diseases,including systemic lupus erythematosus (SLE), systemic sclerosis (SS), dermatomyositis (DM), polymyositis, rheumatoid arthritis (RA) and Behçet's disease (BD) that have potential to affect multiple organ systems leading to diverse clinical conditions like renal dysfunction alongside vasculitis, malar or discoid rash, arthritidies, serositis and ulceration (1). Symptoms appear in flares with active and non-active phases of disease with relapsing and remission course, which require different therapeutic approaches including non-steroidal anti-inflammatory drug (NSAID), systemic glucocorticoids, antimalarials and cytotoxic drugs (2).

Inflammatory reactions at the organs with a tendency of elevated immunologic response and poor wound healing affected the decision of radiotherapy (RT) for CTD known as relative contraindication for years because of the possibility of increased toxicity. Early publications of several case reports, with severe radiation-induced toxicity in the setting of CTD after receiving radiation treatment have taken place in the scientific literature

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(3-10). Regarding these case reports, the American College of Radiology published guidelines defined CTD as a relative contraindication to breast conservation treatment (11). Although previous studies with case series about RT toxicities for patients with CTDs are heterogeneous in terms of tumor type, anatomical region, radiation site, radiation dose and therapeutic modalities; several relatively large and homogeneous retrospective studies have been published suggesting that RT of CTD patients have a toxicity risk potency which should be held carefully (12-17). While one matched control study did not observe any increased risk of complications in patients with CTD (18), two matched control studies concluded that patients with SS have a significantly increased incidence of complications differing from the rest of CTD (19,20). In an other aspect, there are studies suggesting an increased risk of developing malignancies with CTD that leads RT as a component of multimodality treatment and it is essential forming strategies for this group of patients (21,22). Our goal was to evaluate a 10 year's period of our data of CTD patients with cancer who received RT for assessing both acute and chronic treatment toxicity by presenting a retrospective study.

METHODS

We identified patients by electronically searching a central computer database with ICD-10 codes (23) for the diagnosis of both cancer and CTD between January 2010 to December 2020. Patients who were indicated RT cross-referenced with records from the department of radiation oncology. RA and patients who have diagnosis of CTD after the completion of RT were excluded from our search. Medical records were reviewed for the following characteristics: Age, sex, CTD type, date of CTD diagnosis, concurrent medications, date of cancer diagnosis, primary of cancer site and dose schedule of RT, acute and late toxicity, pattern of failure, and survival.

Toxic effects were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0 (24) (Table 1). Symptoms that developed within 90 days from the start of radiation were considered acute toxicities, while those that occurred later than 90 days were considered chronic toxicities.

This study was conducted in accordance with the ethical standards provided by the Helsinki Declaration and informed consent documents, obtained before treatment from each patient are available in patient files. This study was accepted by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (date: 07.06.2021, decision no: 227).

Table 1. Common terminology criteria for adverse events version 5.0 grading scale

Grade 1	Mild adverse event	Asymptomatic or mild symptoms intervention not indicated
Grade 2	Moderate adverse event	Minimal, local or non-invasive intervention indicated
Grade 3	Severe or medically significant but not immediately life-threatening	Hospitalization or prolongation of hospitalization indicated, disabling, limiting self care
Grade 4	Life-threatening consequences	Urgent intervention indicated
Grade 5	Death related to adverse event	Death related to adverse event

Statistical Analysis

During the evaluation of the study data, descriptive statistical methods such as mean, median, frequency, ratio, minimum and maximum value were used.

RESULTS

The mean age of the patients at time of RT was 58 years (45-74) and 50 years (35-68) at CTD diagnosis. Fourteen of 18 patients were female (77.7%). Primary tumor location was as; breast 8 (44.7%), cervix 2 (11.1%), rectum 2 (11.1%), prostate 2 (11.1%), brain 1 (5.5%), lung 1 (5.5%), larynx 1 (5.5%) and endometrium 1 (5.5%). CTD subtypes were nine patients (50%) BD, 5 (28%) SLE, 2 (11%) SS and 2 (11%) DM. Most seen CTD symptoms were arthritis, skin lesions, oral ulcerations, uveitis, genital ulcerations, renal and neurologic disorders (Table 2). For CTD treatment; twelve patients were medicated NSAIDs, 6 patients with colchicine, 5 patients with hydroxychloroquine and 3 patients with corticosteroids. At the time of analysis 15 (83%) patients were alive and 3 (17%) patients had died; two because of lung metastasis, one because of SLE nephritis with a median follow-up time of 4.05 years (range, 1.2-9.7 years).

All patients were evaluated carefully and discussed in tumor council for indication of RT and consulted with their rheumatologists for phase, current CTD treatment and individual recommendation. Patients received 18 courses of RT with external beam radiation therapy (EBRT), one course of intraoperatif boost RT and three courses of intracavitary brachytherapy after EBRT. Three patients had concomitant chemoradiotherapy. All EBRT was administered with megavoltage linear accelerators and ten patients treated with conformal while 8 patients with intensity modulated radiotherapy (IMRT). RT treatment characteristics are summarized in Table 3.

Table 2. Demographic, rheumatologic and tumor characteristics of patients	
Criteria	**Value (n=18) %**
Demographic	
Sex	
Female	14 (77.7)
Male	4 (22.3)
Age, y, median (range)	
At radiotherapy	58 (45-74)
At CTD diagnosis	50 (35-68)
Primary tumor location	
Breast	8 (44.7)
Cervix	2 (11.1)
Rectum	2 (11.1)
Prostate	2 (11.1)
Brain	1 (5.5)
Lung	1 (5.5)
Larynx	1 (5.5)
Endometrium	1 (5.5)
CTD type	
Behçet's disease	9 (50)
Systemic lupus erythematosus	5 (28)
Systemic sclerosis	2 (11)
Dermatomyositis	2 (11)
CTD symptoms	
Arthritis	7 (38.8)
Skin lesions	6 (33.3)
Oral ulcerations	5 (27.7)
Uveitis	3 (16.6)
Genital ulcerations	1 (5.5)
Renal disorders	1 (5.5)
Neurologic disorders	1 (5.5)
CTD: Connective tissue diseases	

Table 3. Characteristics of radiotherapy	
Treatment criteria	**Value (%)**
Intent of treatment per radiotherapy course	
Definitive	17 (94)
Palliative	1 (6)
Anatomical target	
Breast	8 (44)
Pelvis	7 (38)
Brain	1 (6)
Neck	1 (6)
Bone	1 (6)
Radiotherapy dose, median (range)	
Dose per fraction, Gy	2 (1.80-4.00)
No of fractions	30 (5-35)
Total dose, Gy	60 (20-70)

Thirteen (72%) patients had any grade 1 and 6 (33%) patients had any grade 2 acute toxicities while only 3 (17%) patients with cervical and brain cancers had chronic grade 2 hematological toxicity due to concomitant chemoradiotherapy. The most common acute toxicities were radiation dermatitis, nausea, fatigue and diarrhea. No interruption occurred during RT treatment because of acute toxicities and all patients completed their prescribed course of RT. Patients in the receiving higher doses of radiation have experienced more acute toxic effects than the others as expected. No acute or chronic toxicities higher than grade 2 were recorded (Table 4).

Table 4. Acute and chronic adverse events		
	Acute adverse events	**Chronic adverse events**
Grade 1		
Behçet's disease	7/9	1/9
Systemic lupus erythematosus	3/5	0/5
Systemic sclerosis	2/2	0/2
Dermatomyositis	1/2	0/2
Total	13 /18	1/18
Grade 2		
Behçet's disease	3/9	1/9
Systemic lupus erythematosus	1/5	1/5
Systemic sclerosis	1/2	0/2
Dermatomyositis	1/2	1/2
Total	6/18	3/18

DISCUSSION

The management of RT for patients with CTD has always known as challenging approach for radiation oncologists requiring an additional attention. In this retrospective study, cancer patients with CTD completed their treatment with acceptable toxicity so that we suggest RT can be performed safely for this group of patients.

Similarity between CTD and malignancy as TGF-β has been shown to be a key molecular component, which is responsible for effective wound healing and is commonly disrupted at the pathophysiology of both groups; wound healing is impaired in severe CTD (25). At the same time localized fibrosis and inflammation, mediated by TGF-β, can be intensified by RT which reactivates systemic CTD (26) and it could be difficult to manage the complexity of pro-inflammation promotion of RT in patients with autoimmune disease (27).

Lin et al. (28) studied with 73 CTD patients and concluded that although they appear to predispose to a greater risk of late RT toxicity, treatment is generally well tolerated, with a relatively low incidence of severe acute or late toxicity but CTD subtype, the site of irradiation, RT dose and the use of concurrent chemotherapy should be carefully evaluated. In a review Wo and Taghian (29), commented that although numerous case reports reported increased risk of acute and late toxicities; a large retrospective series stay controversial in this patient population. Ma evaluated cervical cancer patients with SLE treated by IMRT

that was generally well tolerated by decreasing the prescribed dose to the normal tissues and established that SLE was not a risk factor for radiation complications (14). Chen et al. (20) showed that CTD subtype like scleroderma with a significantly increased incidence of complications after breast-conserving surgery and radiation therapy and different organ involvement, radiation dose and the use of immunosuppressants might be risk factors for severe complications from radiation treatment. Hölscher et al. (30) concluded in a review that although there are some methodological problems with the studies there can be association with an increased risk of late radiation-induced reaction and CTD patients. Unlike these studies acute toxicity were more recorded than chronic toxicity in our study.

With an international systematic review and meta-analysis, Lin et al. (31) evaluated toxicity after radiotherapy in patients with historically accepted contraindications to treatment (CONTRAD) briefly analyzing 417 patients and suggested that CTD is not an absolute contraindication and should not prevent RT for curable cancer therapy. Our patients had all RT with exact indication and did not compromised of their oncology treatment because of CTD.

Shah et al. (32) from two centers, in a retrospective study of scleroderma patients with breast cancer, showed no significant acute skin toxicity from radiation, but approximately 50% chronic radiation-induced cutaneous fibrosis localized to the field of radiation. Benk et al. (33) suggested that RT have been inappropriately withheld from patients with SLE with cancer for fear of severe late complications traditionally and should always be taken to consideration if indicated. Lee et al. (26) recommended a national record system of registration for toxicity recording to understand true incidence of CTD patients being referred for RT at different centers. They also suggested close liaison with the rheumatologist during the decision of indication, monitoring acute effects, reducing the total dose by >10%, considering smaller treatment volumes, conventional fraction sizes and caution with concurrent chemoradiotherapy (26). In our group similar to late retrospective studies which were treated with new RT techniques there was no increased incidence of acute or late complications observed and RT was generally well tolerated for patients with CTD during the treatment and follow-up. Individualizing treatment strategy for each patient will help improve the results for this group of patients. Although its retrospective nature, data were evaluated carefully from well-recorded toxicity profile from patient files and treatment charts.

Study Limitations

The most significant limitation of this retrospectively designed study is small sample size with heterogeneous patient population and RT treatment schedules but it should be taken consideration that as CTD patients receiving RT is a rare group for a single institution. Further multi-institutional studies may help to enlarge the study group with detailed analysis of toxicities

CONCLUSION

Factors including CTD subtype and disease activity, site of irradiation, RT dose, technique and the use of concurrent chemotherapy can increase the risk of toxicity and should be considered carefully. While interfering RT, a multidisciplinary discussion including rheumatologist should be administered between the treating modalities. Recent advances in RT have shown superiority in decreasing the prescribed dose to the normal tissues with decreased toxicity for all groups of cancer patients. Even in the presence of a CTD, RT with modern techniques is generally well tolerated, with a relatively low incidence of severe acute or late toxicity so that CTD patients will not be excluded from RT regimens when indicated because of the risk of toxicities.

Ethics

Ethics Committee Approval: This study was accepted by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (date: 07.06.2021, decision no: 227).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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REFERENCES

1. Mulhearn B, Tansley SL, McHugh NJ. Autoantibodies in connective tissue disease. Best Pract Res Clin Rheumatol 2020;34:101462.
2. Diamond B, Lipsky PE. Autoimmunity and autoimmune diseases. Jameson J, Fauci AS, Kasper DL, eds. Harrison's Principles of Internal Medicine. New York: McGraw Hill; 2018. p. 2510-15.
3. Robertson JM, Clarke DH, Pevzner MM, Matter RC. Breast conservation therapy. Severe breast fibrosis after radiation therapy in patients with collagen vascular disease. Cancer 1991;68:502-8.

4. Aref I, Cross P, Nair B. Case report: severe fibrosis in a patient with scleroderma and previous radiotherapy--a case report and literature review. Br J Radiol 1996;69:1055-6.

5. Fleck R, McNeese MD, Ellerbroek NA, Hunter TA, Holmes FA. Consequences of breast irradiation in patients with pre-existing collagen vascular diseases. Int J Radiat Oncol Biol Phys 1989;17:829-33.

6. Varga J, Haustein UF, Creech RH, Dwyer JP, Jimenez SA. Exaggerated radiation-induced fibrosis in patients with systemic sclerosis. JAMA 1991;265:3292-5.

7. Ransom DT, Cameron FG. Scleroderma--a possible contra-indication to lumpectomy and radiotherapy in breast carcinoma. Australas Radiol 1987;31:317-8.

8. Hareyama M, Nagakura H, Tamakawa M, Hyodo K, Asakura K, Horikoshi T, et al. Severe reaction after chemoradiotherapy of nasopharyngeal carcinoma with collagen disease. Int J Radiat Oncol Biol Phys 1995;33:971.

9. Olivotto IA, Fairey RN, Gillies JH, Stein H. Fatal outcome of pelvic radiotherapy for carcinoma of the cervix in a patient with systemic lupus erythematosis. Clin Radiol 1989;40:83-4.

10. Mayr NA, Riggs CE Jr, Saag KG, Wen BC, Pennington EC, Hussey DH. Mixed connective tissue disease and radiation toxicity. A case report. Cancer 1997;79:612-8.

11. Winchester DP, Cox JD. Standards for diagnosis and management of invasive breast carcinoma. American College of Radiology. American College of Surgeons. College of American Pathologists. Society of Surgical Oncology. CA Cancer J Clin 1998;48:83-107.

12. Pinn ME, Gold DG, Petersen IA, Osborn TG, Brown PD, Miller RC. Systemic lupus erythematosus, radiotherapy, and the risk of acute and chronic toxicity: the Mayo Clinic Experience. Int J Radiat Oncol Biol Phys 2008;71:498-506.

13. Cengiz M, Altundag MK, Zorlu AF, Güllü IH, Ozyar E, Atahan IL. Malignancy in Behçet's disease: a report of 13 cases and a review of the literature. Clin Rheumatol 2001;20:239-44.

14. Ma J, Wang W, Shen J, Hou X, Lian X, Yan J, et al. Radiotherapy for cervical cancer in patients with systemic lupus erythematosus. Cancer Manag Res 2020;12:8675-83.

15. Morris MM, Powell SN. Irradiation in the setting of collagen vascular disease: acute and late complications. J Clin Oncol 1997;15:2728-35.

16. Chon BH, Loeffler JS. The effect of nonmalignant systemic disease on tolerance to radiation therapy. Oncologist 2002;7:136-43.

17. Gold DG, Miller RC, Petersen IA, Osborn TG. Radiotherapy for malignancy in patients with scleroderma: the Mayo Clinic experience. Int J Radiat Oncol Biol Phys 2007;67:559-67.

18. Ross JG, Hussey DH, Mayr NA, Davis CS. Acute and late reactions to radiation therapy in patients with collagen vascular diseases. Cancer 1993;71:3744-52.

19. Phan C, Mindrum M, Silverman C, Paris K, Spanos W. Matched-control retrospective study of the acute and late complications in patients with collagen vascular diseases treated with radiation therapy. Cancer J 2003;9:461-6.

20. Chen AM, Obedian E, Haffty BG. Breast-conserving therapy in the setting of collagen vascular disease. Cancer J 2001;7:480-91.

21. Abu-Shakra M, Buskila D, Ehrenfeld M, Conrad K, Shoenfeld Y. Cancer and autoimmunity: autoimmune and rheumatic features in patients with malignancies. Ann Rheum Dis 2001;60:433-41.

22. Bernatsky S, Ramsey-Goldman R, Clarke A. Malignancy and autoimmunity. Curr Opin Rheumatol 2006;18:129-34.

23. WHO. International Statistical Classification of Diseases and Related Health Problems. 10th revision. Geneva, Switzerland: World Health Organisation; 2004.

24. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Published: November 27, 2017.

25. Valluru M, Staton CA, Reed MW, Brown NJ. Transforming growth factor-β and endoglin signaling orchestrate wound healing. Front Physiol 2011;2:89.

26. Lee CE, Prabhu V, Slevin NJ. Collagen vascular diseases and enhanced radiotherapy-induced normal tissue effects--a case report and a review of published studies. Clin Oncol (R Coll Radiol) 2011;23:73-8.

27. Marazzi F, Masiello V, Franceschini G, Bosello S, Moschella F, Smaniotto D, et al. Adult onset still's disease and radiotherapy treatment for breast cancer: case report about management of this rare association and literature review. Rep Pract Oncol Radiother 2020;25:527-32.

28. Lin A, Abu-Isa E, Griffith KA, Ben-Josef E. Toxicity of radiotherapy in patients with collagen vascular disease. Cancer 2008;113:648-53.

29. Wo J, Taghian A. Radiotherapy in setting of collagen vascular disease. Int J Radiat Oncol Biol Phys 2007;69:1347-53.

30. Hölscher T, Bentzen SM, Baumann M. Influence of connective tissue diseases on the expression of radiation side effects: a systematic review. Radiother Oncol 2006;78:123-30.

31. Lin D, Lehrer EJ, Rosenberg J, Trifiletti DM, Zaorsky NG. Toxicity after radiotherapy in patients with historically accepted contraindications to treatment (CONTRAD): an international systematic review and meta-analysis. Radiother Oncol 2019;135:147-52.

32. Shah DJ, Hirpara R, Poelman CL, Woods A, Hummers LK, Wigley FM, et al. Impact of radiation therapy on scleroderma and cancer outcomes in scleroderma patients with breast cancer. Arthritis Care Res (Hoboken) 2018;70:1517-24.

33. Benk V, Al-Herz A, Gladman D, Urowitz M, Fortin PR. Role of radiation therapy in patients with a diagnosis of both systemic lupus erythematosus and cancer. Arthritis Rheum 2005;53:67-72.

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COVID-19 Pneumonia: Variation of Chest Computed Tomographic Findings at Different Phases of Disease

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Abstract

Objective: We determined the temporal changes on thoracic computed tomography (CT) in patients with Coronavirus disease-2019 (COVID-19) pneumonia, during the disease.

Methods: Our sample included 55 patients (29 men, 26 women) who were admitted to our hospital between March 10 and May 10 2020 with COVID-19, diagnosed by reverse-transcription polymerase chain reaction, who underwent at least two CT examinations in our hospital. From the onset of the symptoms, the disease process was divided into six stages, and CT patterns at each stage were analyzed. Additionally, we calculated the CT score by using a semiquantitative method to measure the involvement in all five lung lobes.

Results: The most common CT patterns in all stages were ground-glass opacification, crazy-paving pattern, and consolidation. The total CT scores were highest between the 10th and 21st days. This pattern continued similarly for a while later. Residual signs of disease were found in 92% of the patients who underwent CT after the 28th day.

Conclusion: CT findings in COVID-19 pneumonia progress in a certain time-dependent pattern. CT findings of the disease is most severe between the 10th and 21st days. Residual disease findings are observed even after 28 days in most patients.

Keywords: COVID-19, computed tomography, ground-glass opacity

INTRODUCTION

In December 2019, cases of pneumonia caused by a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan, China. The resulting disease, Coronavirus disease-2019 (COVID-19) quickly spread worldwide within 3 to 4 months (1). By December 29, 2021, COVID-19 had been diagnosed in 281,808,270 patients worldwide, and 5,411,759 patients had died (2).

Computed tomography (CT) plays an important role in the diagnosis and management of COVID-19 pneumonia (3). CT findings continue to be analyzed. A better understanding of the changes in CT findings during the disease will facilitate the diagnosis of the disease, help determine the stage of the disease at the time of the CT examination and help identify complications that may develop. Serial CT scans of the thorax help clinicians better understand the development and progression of the disease. Our aim was to evaluate the temporal changes in thoracic CT findings during the disease.

METHODS

Patients

This study was approved by the Ethics Committee of University of Health Seciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (protocol number: 192) and the Republic of Turkey Ministry of

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Health, COVID-19 Scientific Research Committee. All patients gave informed consent. In 78 patients who were admitted to our hospital between March 10 and May 10 2020, COVID-19 was confirmed in the first or control reverse-transcription polymerase chain reaction, and at least two CT scans were performed in our hospital during the diagnosis and follow-up processes; the scans were retrospectively evaluated. Inclusion criteria were (1) known date of onset of the patient's symptoms and (2) two or more thoracic CT evaluations performed in our hospital as of the date of admission. An age of younger than 18 was an exclusion criterion. Of the 78 patients, 23 were excluded from the study because their symptom onset dates were unknown. Data from 55 patients were included in the final analysis.

Computed Tomographic Imaging

Patients underwent at least two CT examinations in our picture archiving and communication system. All CT scans were performed without intravenous contrast material with the patients in the supine position during end inspiration. A Philips Ingenuity Core (Philips Medical Systems, Amsterdam, The Netherlands) was used for all chest CT examinations. The tube voltage was set at 120 kV with automatic tube current modulation. Thin-section CT slices were reconstructed by a lung algorithm with a slice thickness of 1.5 mm.

Image Evaluation

CT images were evaluated by two radiologists with 6 and 15 years of experience, respectively. Final decisions were reached by consensus. For the cases in which the radiologists disagreed, a third thoracic radiologist with 20 years of experience made a final decision. Ground-glass opacification (GGO), consolidation, the tree-in-bud sign, a crazy-paving pattern, and septal thickening were defined as elsewhere (4). GGO, honeycombing, consolidation, linear opacities, air bronchogram, bronchiectasis, pleural effusion, and mediastinal lymphadenopathy were among the findings recorded on thin-section CT. The extent of disease evident on thin-section CT was also evaluated. The distribution of abnormalities was also recorded. Lesions are involving mainly the peripheral one-third of the lung as peripheral, and lesions involving mainly the central two-third of the lung as central.

We quantified the CT images by using a previously published method (5-7) of scoring (0-5) for each lobe; the total possible score ranged from 0 to 25 (Table 1).

We categorized the CT scans according to the period between the onset of initial symptoms and the date when they were performed: Stages 1 (0-4 days, in 43 patients), 2 (5-9 days, in 31 patients), 3 (10-14 days, in 18 patients), 4 (15-21 days, in 8 patients), 5 (22-28 days, in 7 patients), and 6 (>28 days, in 25 patients) (6,7).

Statistical Analysis

To perform statistical analysis, we used NCSS 10 software (NCSS, LLC, East Kaysville, UT, USA). Normal distribution was checked with the Shapiro-Wilk test, histograms, Q-Q plots, and box plot graphics. The data were calculated as means and standard deviations, medians, minimums and maximums, frequencies, and percentages. We used Kruskal-Wallis One-Way analysis of variance to compare the total CT scan scores in each stage, and we used Dunn's test for multiple comparisons. Intragroup variables were evaluated with Friedman's repeated measures analysis of variance, and multiple comparisons were made with the Bonferroni-corrected Wilcoxon test (limit of significance was set as $p<0.0167$). Intragroup paired comparisons were evaluated with the Wilcoxon test. Fisher's Exact probability test was used to compare nominal variables. A p value of less than 0.05 indicated bidirectional statistical significance.

RESULTS

Data from 55 patients (26 women and 29 men) were included in the analysis; the patients' mean age was 44.6±11.5 years. Each patient had a median of 2.62±0.9 chest CT scans (Table 2). In total, 132 CT scans were evaluated.

The most prevalent symptoms at presentation were dry cough [in 40 patients (73%)] and fever [in 28 (51%)]. The distribution of lesions and changes in CT patterns at the six different disease stages were evaluated. At all stages, most of the lesions were peripheral and subpleural in location and in most patients, involvement was bilateral. The most common CT findings in all stages were GGO, consolidation, and crazy-paving patterns (Table 3).

Four of the 55 patients showed no pneumonia in the initial CT scan (Figure 1). Of the 43 patients in whom CT scans were performed in stage 1, 13 (30.2%) showed a unilateral

Table 1. Scoring system

Score	Definition
0	None
1	<5% of lobe
2	5%-25% of lobe
3	26%-49% of lobe
4	50%-75% of lobe
5	>75% of lobe

involvement, and 9 (20.9%) showed a single lobe involvement (Table 3). The most common abnormalities in stage 1 were GGO, in 39 patients (91%); crazy-paving pattern, in 12 (28%); and consolidation, in 11 (26%). The incidence of crazy-paving pattern differed between stages ($p<0.001$) and was observed mostly in stages 2 and 3 (Figure 1). The frequency of consolidation also differed between the stages ($p<0.001$); it was observed least in stage 6 and most in stages 3 and 4 (Figure 2). The frequency of linear opacification differed between stages as well ($p=0.04$) and was observed mostly in stages 4, 5, and 6. Of the 25 patients who underwent CT examinations in stage 6, 22 (88%) exhibited GGO, 8 (32%) exhibited linear opacities, and only 2 (8%) exhibited no radiological abnormality (Figure 3).

Table 2. Characteristics of the patient cohort

	All patients (n=55)
Age (y)	46.64±12.50 (21-81)
Gender	
Male	29 (52.7%)
Female	26 (47.3%)
Initial symptoms	
Throat pain	3 (5.5%)
Cough	40 (72.7%)
Fever	28 (50.9%)
Headache	10 (18.2%)
Myalgia	15 (27.3%)
Fatigue	13 (23.6%)
Numbers of scans	2.62±0.9 (2-5)
The frequency of CT scans	
2 scans	39
3 scans	12
4 scans	2
5 scans	2
Total number of the CT scans	132
Examination day	14.06±16.19 (0-91)
Clinical outcomes	
Discharged	50
Died	5

CT: Computed tomography

Total CT scores differed between stages ($p<0.001$; Table 4). The total CT scores were highest in stages 3 (9.0±3.4) and 4 (10.5±6.2). The score of stage 1 was lower than those of stages 2, 3, and 4 ($p<0.001$). When we evaluated 43 patients in whom first CT scans were performed in stage 1, again total CT scores were highest in stages 3 and 4. Evaluation of the score differences between lobes revealed that the right middle lobe scores were lower than the other lobe scores. Right lower lobe scores were higher than the right upper and middle lobe scores ($p=0.011$ and $p<0.001$, respectively) and left lower lobe scores were higher than left upper lobe scores ($p<0.001$).

DISCUSSION

In our study, we evaluated the changes in CT patterns in pneumonia caused by COVID-19 from the onset of symptoms throughout the disease process.

In the early stage of the disease (0-4 days), GGO was the main radiological abnormality; crazy-paving patterns and

Table 3. Distribution and frequency of the pulmonary lesions on CT at different stages

	Stage 1 (n=43)	Stage 2 (n=31)	Stage 3 (n=18)	Stage 4 (n=8)	Stage 5 (n=7)	Stage 6 (n=25)
Distribution of pulmonary lesions						
No lesion	4 (9.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
Peripheral	34 (79.1%)	27 (87.1%)	16 (88.9%)	6 (75.0%)	7 (100%)	23 (92.0%)
Central	3 (7.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diffuse	2 (4.7%)	4(12.9%)	2 (11.1%)	2 (25.0%)	0 (0.0%)	0 (0.0%)
Involvement of the lung						
No involvement	4 (9.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
Unilateral	13 (30.2%)	4 (12.9%)	1 (5.6%)	0 (0.0%)	2 (28.6%)	2 (8.0%)
Bilateral	26 (60.5%)	27 (87.1%)	17 (94.4%)	8 (100%)	5 (71.4%)	20 (84%)
GGO	39 (90.7%)	31 (100.0%)	18(100.0%)	7 (87.5%)	7 (100%)	22 (88.0%)
Crazy-paving pattern	12(27.9%)	19 (61.3%)	11 (61.1%)	2 (25.0%)	2 (28.6%)	1 (4.0%)
Consolidation	11 (25.6%)	19 (61.3%)	15 (83.3%)	7 (87.5%)	2 (28.6%)	0 (0.0%)
Linear opacities	3 (7.0%)	4 (12.9%)	5 (27.8%)	3 (37.5%)	3 (42.9%)	8 (32.0%)

CT: Computed tomography, GGO: Ground-glass opacification

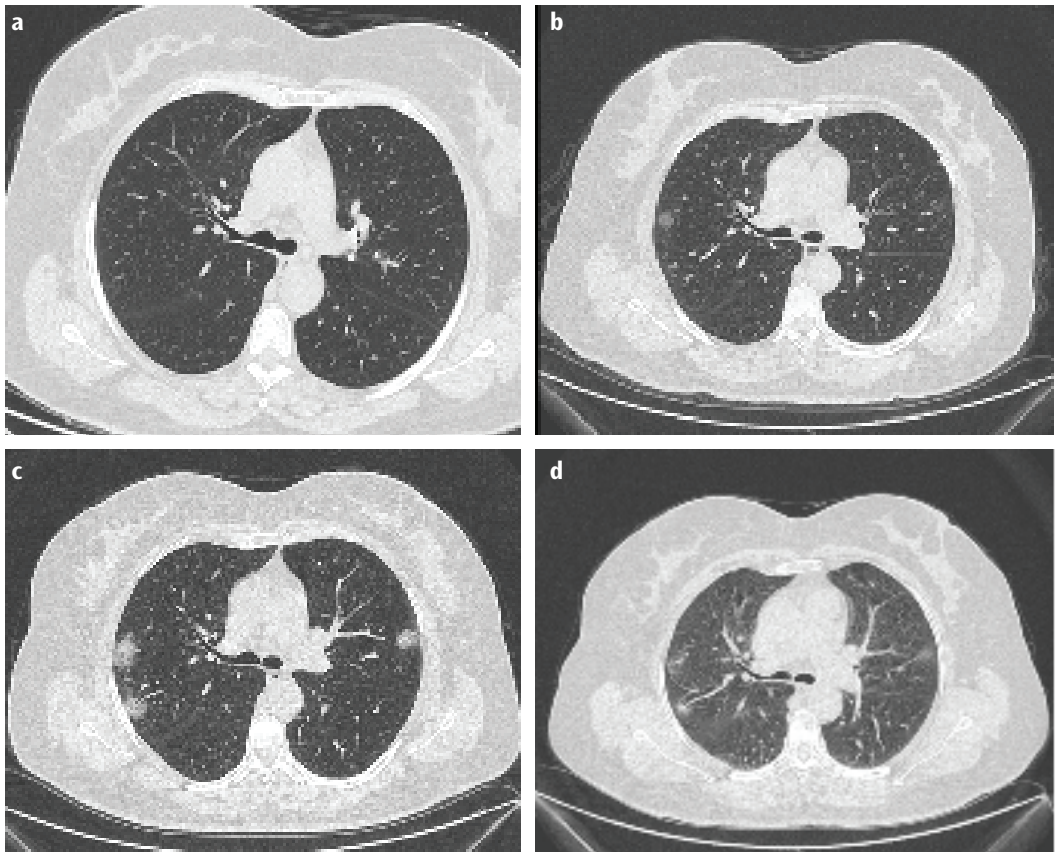

Figure 1 a-d. CT scans in a 48-year-old woman with coronavirus 2019 pneumonia. Axial CT image (a) obtained 3 days after the onset of initial symptoms (stage-1) shows no abnormal findings . Axial CT image (b) obtained 7 days after the onset of initial symptoms (stage-2) shows a round and patchy GGO around the subpleural area of right upper lobe. Axial CT image (c) obtained 12 days after the onset of initial symptoms (stage-3) shows crazy-paving pattern appear within the GGOs with increased extent, GGO and crazy-paving pattern also appeared in the left upper lobe. Axial CT image (d) obtained 34 days after the onset of initial symptoms (stage-6) shows small residual GGOs in both upper lobes

CT: Computed tomography, GGO: Ground-glass opacification

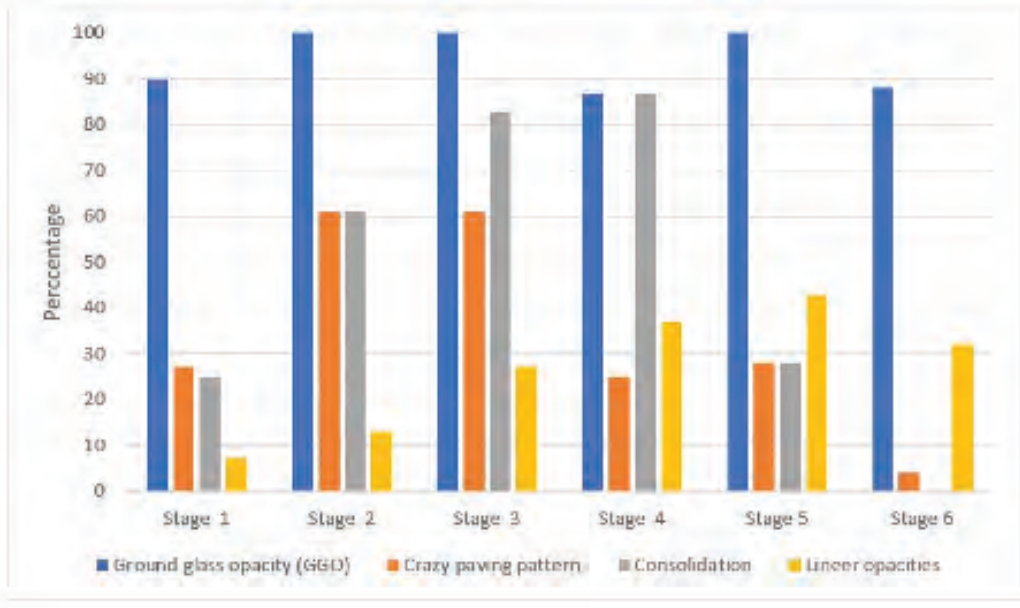

Figure 2. The frequency of major CT findings at different stages

CT: Computed tomography

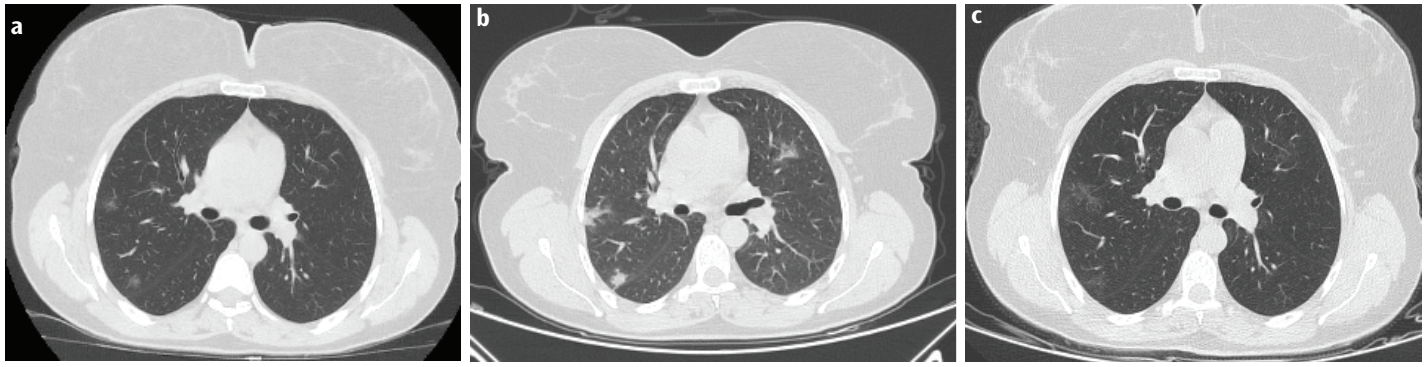

Figure 3 a-c. CT scans in a 49-year-old woman with coronavirus 2019 pneumonia. Axial CT image (a) obtained 3 days after the onset of initial symptoms (stage-1) shows round and patchy GGOs distributed around the subpleural area of right upper and middle lobes . Axial CT image (b) obtained 7 days after the onset of initial symptoms (stage-2) shows increased density on right lobe lesions which mainly became consolidations and a patchy ground-glass opacity is newly developed in left upper lobe. Axial CT image (c) obtained 30 days after the onset of initial symptoms (stage-6)) shows patchy residual GGOs in both upper lobes and right middle lobe
CT: Computed tomography, GGO: Ground-glass opacification

Table 4. The CT score of the pulmonary involvement in six stages

	Stage 1 (n=43)	Stage 2 (n=31)	Stage 3 (n=18)	Stage 4 (n=8)	Stage 5 (n=7)	Stage 6 (n=25)
Total CT score of the pulmonary involvement	3.7±2.9 (0-12)	6.8±2.5 (1-11)	9±3.4 (1-14)	10.5±6.2 (4-24)	4.4±2.8 (1-8)	5±3 (0-10)
CT score in each lobe						
Left upper lobe	0.6±0.7 (0-2)	1.1±0.7 (0-2)	1.7±0.7 (0-3)	2.0±1.5 (0-5)	0.8±0.9 (0-2)	0.8±0.6 (0-2)
Left lower lobe	0.9±0.8 (0-2)	1.6±0.8 (0-3)	2.0±0.9 (0-3)	2.1±1.1 (1-4)	1.0±1.0 (0-3)	1.2±0.7 (0-2)
Right upper lobe	0.8±0.8 (0-3)	1.3±0.7 (0-3)	1.9±1.10 (0-4)	2.2±1.3 (1-5)	1.0±0.8 (0-2)	0.9±0.6 (0-2)
Right middle lobe	0.5±0.6 (0-2)	1.0±0.5 (0-2)	1.3±0.9 (0-3)	1.7±1.5 (1-5)	0.4±0.5 (0-1)	0.7±0.8 (0-2)
Right lower lobe	0.8±0.7 (0-3)	1.8±0.8 (0-3)	2.1±0.9 (0-3)	2.2±1.0 (1-4)	1.1±0.6 (0-2)	1.2±0.9 (0-3)

consolidation were less common. This followed in prior reports (6-8). In stage 2 (5-9 days), the CT abnormalities became more diverse; crazy-paving patterns and consolidation increased significantly. In stages 3 and 4, the frequency of consolidation peaked (83.3% and 87.5%, respectively); then it decreased gradually. Again, GGO was the most prominent abnormality in the late stages (5 and 6). Findings of residual disease persisted in 23 (92%) of the 25 patients who underwent imaging in stage 6.

The highest total CT scores were recorded in stages 3 and 4. This result was different from that in Pan et al.'s (6) study; they reported that after 14 days, the infection was brought under control and that the consolidations started to be absorbed. The reason for this difference in results may be that only patients with mild COVID-19 pneumonia were included in Pan et al.'s (6) study. Our finding of the persistence of high CT scores was different finding from that of Pan et al. (6), but it was similar to those of Wang et al. (8). The increase in the incidence of GGO in the late stages was also similar to findings in Wang et al.'s (8) study. Increases in GGO in the late stages were also shown in patients with SARS (9). Moreover, in our study, the incidence of linear lines increased in the late stages (4, 5, and 6). Pan et al. (6) did not observe crazy-paving patterns after 14 days; in our study, in contrast, crazy-paving patterns were observed in stages 4 (25%) and 5 (28.6%).

CT scores were higher in both lower lobes, which followed in previous studies (6,7). Other results in our study that corroborated the results of previous studies included peripheral-subpleural lesions and predominant GGO and consolidation. This pattern of involvement was also similar to those in SARS and Middle East respiratory syndrome (MERS). CT findings in COVID-19 pneumonia showed typical lung damage from viral pneumonia, as in SARS and MERS (9,10).

Study Limitations

This study had two major limitations. First, group analysis of patients with mild and severe pneumonia was not performed. Second, scanning intervals among patients were not uniform because of the retrospective nature of this study.

CONCLUSION

In conclusion, the most common CT finding in COVID-19 pneumonia is bilateral peripheral GGO. On CT, lung involvement increases rapidly after the onset of the symptoms, peaks at approximately 10-14 days and continues at relatively high levels for some time thereafter. CT findings thus show a specific pattern during the disease process. On the basis of these patterns, clinicians can determine whether the disease is progressing or whether the patient is recovering. Knowing which pattern is dominant at which stage can help clinicians predict the course of the disease and determine the prognosis of the patient.

- The most common CT appearances in all stages were GGO, crazy-paving pattern, and consolidation.
- Most of the lesions were peripheral and subpleural in location, and in most patients, involvement was bilateral.
- Residual signs of disease were found in 92% of the patients who underwent CT after the 28th day.

Ethics

Ethics Committee Approval: Ethics Committee of University of Health Seciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (protocol number: 192) and the Republic of Turkey Ministry of Health, COVID-19 Scientific Research Committee.

Informed Consent: All patients gave informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.D.Ö., R.Y.B., Design: D.K., Data Collection or Processing: D.K., Analysis or Interpretation: D.K., Literature Search: S.D.Ö., Writing: S.D.Ö., F.Ş.

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

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REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
2. World Health Organization. Novel coronavirus (2019-nCoV). Weekly Epidemiological Update Coronavirus Diseaseat:https://covid19.who.int
3. Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, et al.Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. Eur Radiol 2020;30:3306-9.
4. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697-722.
5. Chang YC, Yu CJ, Chang SC, Galvin JR, Liu HM, Hsiao CH, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. Radiology 2005;236:1067-75.
6. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology 2020;295:715-21.
7. Ding X, Xu J, Zhou J, Long Q. Chest CT findings of COVID-19 pneumonia by duration of symptoms. Eur J Radiol 2020;127:109009.
8. Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, et al. Temporal changes of CTfindings in 90 patients with COVID-19 pneumonia: Alongitudinalstudy. Radiology 2020;296:E55-64.
9. Ooi GC, Khong PL, Müller NL, Yiu WC, Zhou LJ, Ho JC, et al. Severe acute respiratory syndrome: temporal lung changes at thin-section CT in 30 patients. Radiology 2004;230:836-44.
10. Das KM, Lee EY, Enani MA, AlJawder SE, Singh R, Bashir S, et al. CT correlation with outcomes in 15 patients with acute Middle East respiratory syndrome coronavirus. AJR Am J Roentgenol 2015;204:736-42.

ORIGINAL ARTICLE

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The Effects of Joint Hypermobility on Quality of Life in Healthy School Children

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Abstract

Objective: This study aimed to determine the prevalence of joint hypermobility in healthy primary school children and to investigate the quality of life differences between children with and without joint hypermobility.

Methods: Joint hypermobility was investigated in healthy children aged 8-12 years. The "Beighton" score was evaluated for the diagnosis of joint hypermobility. According to these scores, children were divided into three groups as "joint hypermobility," "increased joint mobility" and "no joint hypermobility." All children were evaluated by the Pediatric Quality of Life Inventory (PedsQL) version 4 and quality of life scores were measured. The PedsQL results were compared between the groups in terms of statistical significance.

Results: The mean Beighton score of 378 students enrolled in the study was 2.4±2.2. The PedsQL mean total score was 77±13.3. Age, sex distribution, pediatric PedsQL total score, psychosocial score and physical health score did not differ significantly between groups.

Conclusion: Our results show that joint hypermobility does not affect the quality of life in healthy children but more extensive studies in this field are needed.

Keywords: Beighton score, joint hypermobility, quality of life, school

INTRODUCTION

Musculoskeletal pain is often seen in childhood. Sometimes it can be long-lasting and repetitive. One of the major causes of these pains is joint hypermobility. Joint hypermobility is defined as having a joint range of motion greater than normal limits (1,2). Joint hypermobility and joint laxity are used by some authors interchangeably (3). Although there are no definitive definitions, hypermobility is the ability of the joint to exceed its normal limits within its motion axis (especially in extension), and hyperlaxity is the ability of the joint to move in unusual motion axes (4). When more than one joint exceeds the joint motion limits within its own motion axes it is called generalized joint hypermobility. In hypermobility syndrome, the patient should have joint hypermobility as well as muscle and skeletal system symptoms and should not have hereditary connective tissue disease (5).

The incidence of joint hypermobility and benign joint hypermobility syndrome may differ greatly in different publications. This may be caused by the differences between the tests and the criteria used in the diagnosis of joint hypermobility. The lack of consensus on the cut-off value of the Beighton score, which is one of the most commonly used diagnostic

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tests, may also lead to different incidence rates. In his original article, Beighton accepted the score of 4 and for the diagnosis of hypermobility (6). Some authors accepted scores higher than 4 as the cut-off value (7-9). The frequency of joint hypermobility varies according to age, sex, and race (6,10,11). The frequency of asymptomatic hypermobility varies between 5 and 10% (11,12). In children, this rate was found as 10%-25% (13,14).

The measurement of quality of life is preferred today to evaluate the treatment results of rheumatic diseases in children (15). To assess the quality of life related to health, version 4 of the Pediatric Quality of Life Inventory (PedsQL) was created in 1999 by Varni et al. (16). There are different versions according to age groups. This scale, which is applied in the form of a questionnaire and can be completed by children aged 8-12 years, includes 23 questions about 4 different topics (16).

This study aimed to determine the prevalence of joint hypermobility in healthy primary school children and to investigate the quality of life differences between children with and without joint hypermobility.

METHODS

A total of 378 students, 211 (55.8%) females, 167 (44.2%) males, were included in the study. The mean age was 9.87 (range, 8-12) years. The criteria for inclusion (aged between 8-12 years, student of selected primary school, not having a physical, mental or developmental chronic disease and having informed consent) and exclusion (having a trauma in the last month which makes the patient unsuitable for evaluating joint movements or having sequela in extremities due to a recent trauma that limit joint movements) were applied to the students.

The students' Beighton scores were measured. All measurements were performed by two pediatric physicians using a goniometer. The Beighton score was established by Beighton in 1973 by modifying the Carter and Wilkinson criteria (6). Passive dorsiflexion of the little fingers beyond 90°, passive apposition of the thumbs to the flexor aspects of the forearms, hyperextension of the elbows beyond 10°, hyperextension of the knees beyond 10°, and forward flexion of the trunk with knees straight so that the palms of the hands rested easily on the floor, score points in the test. A total of nine points are evaluated. In his original article, Beighton accepted 4 as the cut-off value (6). Scores above 4 are required for the diagnosis of hypermobility.

The PedsQL version 4 questionnaire was then given to the students. In this survey, there were 23 questions under 4 main headings. In this questionnaire, the general health and activities of children (8 questions), emotional status (5 questions), social relations (5 questions), and school status (5 questions) were questioned. The answers and scores were as follows: No problems: 0 points; almost no problems: 1 point; problems sometimes: 2 points; problems often: 3 points; almost always problems: 4 points. The total score was inverted and was rated on a 0-100 scale. The mean score of the eight questions related to the "my health and activities" section was taken for the mean score of physical health, and the total mean score of the emotional status, social relations, and school status sections were taken for the psychosocial mean score.

The cut-off Beighton score for the diagnosis of joint hypermobility was accepted as 7. Children with ≥7 Beighton scores were diagnosed with joint hypermobility (group 3). Children with ≤4 Beighton scores were accepted as normal (group 1). Children with 5-6 Beighton scores were included in the "increased joint mobility" group (group 2). The difference between these groups in terms of the PedsQL results was investigated.

The study was approved by University of Health Sciences Turkey, Okmeydani Training and Research Hospital Ethics Committee (approval no: 25/10/2016-535) and a permission certificate was issued by the Istanbul Provincial Directorate of National Education (date: 13/12/2016, no: 14083890). Then, a "Child Consent Form for Research Purposes" and an "Informed Consent Form" for the approval of their families were distributed to the classes of students aged between 8 and 12 years in a public primary school.

Statistical Analysis

The mean, standard deviation, median, maximum, frequency, and ratio values were used in descriptive statistics (Table 1). The distribution of variables was measured using the Kolmogorov-Smirnov test. The Kruskal-Wallis test was used to analyze quantitative data. The chi-square test was used for the analysis of qualitative independent data. The SPSS 22.0 program was used for analysis.

RESULTS

The mean Beighton score was 2.39±2.2 (0-9) (Table 2). Positivity of apposition of the thumbs was found in 90 children, passive dorsiflexion of the little fingers in 118 children, hyperextension of the elbows in 85 children, hyperextension of the knees in 108 children, and resting of the palms of the hands on the floor with flexion of the trunk in 160 children (Table 3).

There was no difference between groups 1, 2, and 3 in terms of age and sex ($p>0.05$) (Figure 1). The PedsQL total score,

Table 1. Descriptive statistics				
		Min-max	Median	Mean ± SD
Age		8.0- 12.0	10.0	9.9±1.2
Sex	**Female**	-	-	211±55.8%
	Male	-	-	167±44.2%
Beighton scoring		0.0-9.0	2.0	2.4±2.2
Apposition of the right thumb		-	-	84±22.2%
Apposition of the left thumb		-	-	79±20.9%
Dorsiflexion of the right little finger		-	-	115±30.4%
Dorsiflexion of the left little finger		-	-	108±28.6%
Hyperextension of the right elbow		-	-	81±21.4%
Hyperextension of the left elbow		-	-	69±18.3%
Hyperextension of the right knee		-	-	108±28.6%
Hyperextension of the left knee		-	-	106±28.0%
Placing the palms of the hands on the floor		-	-	160±42.3%
Pediatric quality of life inventory total score		24-100	78.3	77.0±13.3
Physicosocial score		22-100	79.2	77.1±14.6
Physical total score		28-100	78.1	76.7±15.4
General health and activities question (GHAQ) 1		0-100	75.0	72.8±29.5
GHAQ 2		0-100	100.0	73.3±31.1
GHAQ 3		0-100	100.0	87.2±22.3
GHAQ 4		0-100	50.0	58.0±34.5
GHAQ 5		0-100	100.0	89.5±23.7
GHAQ 6		0-100	100.0	86.8±23.3
GHAQ 7		0-100	100.0	75.3±29.4
GHAQ 8		0-100	75.0	70.6±29.8
Emotional status question (ESQ) 1		0-100	100.0	75.5±29.6
ESQ 2		0-100	100.0	78.4±27.0
ESQ 3		0-100	100.0	75.5±29.1
ESQ 4		0-100	100.0	73.1±34.1
ESQ 5		0-100	100.0	74.9±30.7
Social relations question (SRQ) 1		0-100	100.0	83.9±25.8
SRQ 2		0-100	100.0	83.7±26.9
SRQ 3		0-100	100.0	85.7±25.2
SRQ 4		0-100	100.0	80.1±26.2
SRQ 5		0-100	100.0	77.6±31.4
School status question (SSQ) 1		0-100	100.0	80.3±28.5
SSQ 2		0-100	75.0	73.3±28.1
SSQ 3		0-100	100.0	82.6±25.6
SSQ 4		0-100	100.0	74.2±30.5
SSQ 5		0-100	50.0	58.1±33.6
SD: Standard deviation, min: Minimum, max: Maximum				

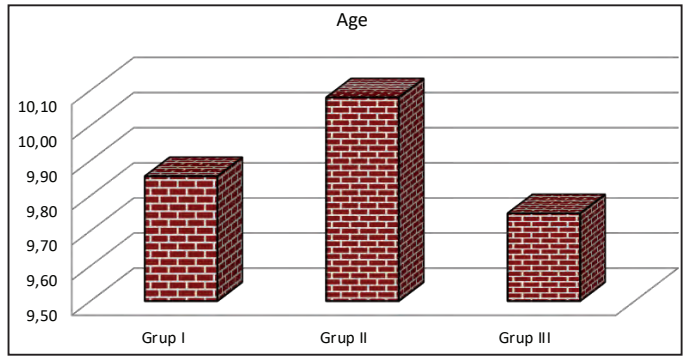

Figure 1. Distribution of age in the groups

Table 2. The distribution of students according to the Beighton score		
Beighton score	**Number of students**	**Percentage in all students**
9	11	2.91
8	4	1.06
7	29	7.67
6	18	4.76
5	32	8.47
4	16	4.23
3	51	13.49
2	29	7.67
1	30	7.94
0	158	41.8

psychosocial score, and physical health score did not differ significantly between groups 1, 2, and 3 ($p>0.05$). There was no difference between groups 1, 2, and 3 in terms of sections in the PedsQL ($p>0.05$) (Table 4).

DISCUSSION

Beighton et al. (6) determined the cut-off value for the diagnosis of joint hypermobility as 4 and it was reported that joint range of motion reduced with age from childhood. According to this, the Beighton cut-off value for the diagnosis of joint hypermobility in children should be a higher value than the cut-off value for adults. Jansson et al. (10) scanned hypermobility in 1.845 children and stated that the Beighton cut-off should be 8 for children aged 9 years; 7 for girls and 6 for boys aged 12 years; and 8 for girls and 6 for boys aged 15 years to be able to define 95% of the children as normal. Mikkelsson et al. (7) stated that the cut-off was 6 in hypermobility scans in 1.637 students. Remvig et al. (17) stated in a literature review of generalized joint hypermobility and benign joint hypermobility that the cut-off value of the Beighton score ranged from 2 to 7 in several publications. To investigate the validity and reproducibility of

Table 3. The rate of the Beighton score positivity among all students				
Beighton score	**Positivity in the right**	**Positivity in the left**	**Bilateral positivity**	**Total**
Apposition of the thumbs	11 (2.91%)	6 (1.59%)	73 (19.31%)	90 (23.8%)
Passive dorsiflexion of the little fingers	10 (2.64%)	3 (0.79%)	105 (27.78%)	118 (31.21%)
Hyperextension of the elbows	16 (4.23%)	4 (1.05%)	65 (17.19%)	85 (22.48%)
Hyperextension of the knees	2 (0.52%)	0 (0%)	106 (28.04%)	108 (28.57%)
Placing the palms of the hands on the floor with lomber flexion	-	-	-	160 (42.32%)

Table 4. The distribution of the pediatric quality of life scores in the groups								
	Group 1		**Group 2**		**Group 3**		**p**	
	Mean ± SD	**Median**	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**		
The pediatric quality of life inventory								
Total score	76.7±13.1	78.3	77.6±13.5	77.7	77.8±14.9	79.3	0.719	[K]
Psycosocial score	76.7±14.3	78.3	78.8±14.8	80.0	78.0±16.4	80.0	0.454	[K]
Physical health score	76.8±15.1	78.1	75.3±16.3	78.1	77.3±6.5	79.7	0.776	[K]
[K]Kruskal-Wallis test, SD: Standard deviation								

the Beighton score, Smits-Engelsman et al. (18) conducted this test on 551 children aged between 6 and 12 years and reported a cut-off value of 7. Hypermobility frequency is reported to vary according to age, sex, and race in various publications (10,19,20).

In a study conducted in our country, Koldaş Doğan et al. (21) accepted the cut-off value of the Beighton score as 4 in children aged 7-12 years with attention-deficit/hyperactivity disorder. Yazgan et al. (22) accepted the cut-off value of the Beighton score as 4 in a study of 922 children aged between 5 and 10 years and 363 (39.3%) children were accepted as having joint hypermobility. Yıldırım (23) accepted the Beighton cut-off value as 6, and 118 (13.8%) of 857 children were diagnosed with joint hypermobility.

In our study, to distinguish children with joint hypermobility from children without joint hypermobility, children were divided into three groups according to their Beighton scores as Smits-Engelsman et al. (18) did and a group of children with increased joint mobility was added to the groups comprising children with and without joint hypermobility. The proportion of children diagnosed with joint hypermobility was found to be consistent with the literature.

The presence of hypermobility in females is higher than in males (10,20). In our study, although the ratio of girls in the group with joint hypermobility was higher, there was no statistically significant difference test between the groups. We think that this is because of differences in the children's age. Jansson et al. (10) determined different Beighton score cut-off values in different age groups according to sex in their publication. In our study, we believe that the use of the same cut-off value for all children aged between 8 and 12 years without regard to sex and age increased the rate of the girls in the group with joint hypermobility.

A decrease in the frequency of joint hypermobility with age has been reported in several publications (6,20). In spite of this, Mikkelsson et al. (7) and Ruperto et al. (24) were unable to confirm this in their studies. In our study, the age range in the inclusion criteria was narrow. We believe that the mean age between the groups was not different due to our inclusion criteria.

The frequency of joints with hypermobility in the Beighton scoring system varies in studies. El-Garf et al. (25) reported that the most frequently observed hypermobile joint was the finger joint, and the least frequently observed hypermobile joint was knee joint in 997 children in Egypt. Lamari et al. (26) and Silman et al. (27) indicated that the most frequently observed hypermobile joint was finger joint in children and adolescents. Adib et al. (28) indicated that the most frequently observed hypermobile joint the knee joint in children. In our study, 160 of 378 (42.32%) children rested easily on the floor with the palms of the hands with forward flexion of the trunk and with knees straight, and they scored points from this criterion in the Beighton score. The least frequently observed hypermobile joint was the elbow in our study. The apposition of the thumb was found in 90 (23.8%) children, passive hyperextension of the little finger in 118 (31.2%) children, hyperextension of the elbow in 85 (22.48%) children, and hyperextension of knee in 108 (28.5%) children; all these score points in the test.

The validity and reliability of the Turkish PedsQL 4 was tested in 2008 by Çakın Memik et al. (29). The total score, psychosocial score and physical health score did not differ significantly between the 3 groups in our study. When we examined each question, we found that the 4th question (Is it hard for me to lift something heavy?) of the "My Health and My Activities" section, which examines physical health, was the question with lowest average score in all three groups. Çakın Memik et al. (29) also encountered this finding and stated that this could be because the child perceived to be carrying more weight than the weight they could lift. The average score of the last question about school functionality (Are there times you can't go to school because you go to doctor or hospital?) was lower than other questions in all 3 groups. It was stated that this could be because the child perceived as they could not go to school when they became sick.

In the literature, the quality of life scores were found to be statistically lower in patients with joint hypermobility syndrome compared with the control group (15,30,31). Pacey et al. (30) correlated this difference in quality of life with pain, fatigue, and incontinence. Mastoroudes et al. (31) showed a significantly higher prevalence of urinary incontinence in females with joint hypermobility than controls and correlated the difference in quality of life with incontinence. Fatoye et al. (15) compared the quality of life of 29 children with hypermobility syndrome between the ages of 8 and 15 years and 37 healthy children and found that the quality of life score was lower in children with hypermobility syndrome. Although Beighton et al. (6) mentioned a positive relationship between mobility scores and musculoskeletal symptoms, we found no difference between the groups with and without joint hypermobility in terms of quality of life total scores, physical scores, emotional scores, and school scores. This may be due to "pain in four or more joints for 3 months or longer," a major Beighton criterion for the diagnosis of joint hypermobility syndrome. Russek and Errico (32) showed a statistically significantly higher frequency of sprain and back pain in patients with joint hypermobility syndrome than the control group, but they found no difference between patients with generalized joint hypermobility and the control group in terms of sprain and back pain. McCluskey et al. (33) observed no relation between musculoskeletal pain and joint hypermobility in European children, but they did find a relation in Afro-Asians in their meta-analysis on the relation between musculoskeletal pain and joint hypermobility in children. In a study of 1230 children aged between 7 and 15 years, Leone et al. (34) found no positive correlation between joint hypermobility and pain.

CONCLUSION

In conclusion, our results show that joint hypermobility does not affect the quality of life in healthy children. More extensive prospective studies on relation between joint hypermobility and musculo skeletal pain are needed. The appropriateness of beighton cut off values for age, sex and race can reduce the high prevalence rates of joint hypermobility.

Ethics

Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, Okmeydani Training and Research Hospital Ethics Committee (approval no: 25/10/2016-535) and a permission certificate was issued by the Istanbul Provincial Directorate of National Education (date: 13/12/2016, no: 14083890).

Informed Consent: Consent was received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: O.Ö., A.S., Design: O.Ö., A.S., Data Collection or Processing: M.S.S., A.S., B.Y.D., Analysis or Interpretation: O.Ö., E.T., A.S., B.Y.D., M.S.S., Literature Search: B.Y.D., A.S., M.S.S., Writing: A.S.

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REFERENCES

1. Grahame R. Hypermobility and hypermobility syndrome. Keer R, Grahame R, editors. Hypermobility syndrome - recognition and management for physiotherapists. London: Butterworth-Heinemann; 2003:1-14.
2. Rowe DW, Shapiro JR. Heritable disorders of structural proteins. Kelley WN, Haris ED, Ruddy S, Sledge CB, editors. Textbook of Rheumatology. 4th ed. Philadelphia: Sounders Company; 1993:1567-92.
3. Engelbert RH, Bank RA, Sakkers RJ, Helders PJ, Beemer FA, Uiterwaal CS. Pediatric generalized joint hypermobility with and without musculoskeletal complaints: a localized or systemic disorder? Pediatrics 2003;111:e248-54.
4. Tofts LJ, Elliott EJ, Munns C, Pacey V, Sillence DO. The differential diagnosis of children with joint hypermobility: a review of the literature. Pediatr Rheumatol Online J 2009;7:1.
5. Kirk JA, Ansell BM, Bywaters EG. The hypermobility syndrome. Musculoskeletal complaints associated with generalized joint hypermobility. Ann Rheum Dis 1967;26:419-25.
6. Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. Ann Rheum Dis 1973;32:413-8.

7. Mikkelsson M, Salminen JJ, Kautiainen H. Joint hypermobility is not a contributing factor to musculoskeletal pain in pre-adolescents. J Rheumatol 1996;23:1963-7.

8. Bridges AJ, Smith E, Reid J. Joint hypermobility in adults referred to rheumatology clinics. Ann Rheum Dis 1992;51:793-6.

9. Bulbena A, Duró JC, Porta M, Faus S, Vallescar R, Martín-Santos R. Clinical assessment of hypermobility of joints: assembling criteria. J Rheumatol 1992;19:115-22.

10. Jansson A, Saartok T, Werner S, Renström P. General joint laxity in 1845 Swedish school children of different ages: age- and gender-specific distributions. Acta Paediatr 2004;93:1202-6.

11. Lewkonia RM, Ansell BM. Articular hypermobility simulating chronic rheumatic disease. Arch Dis Child 1983;58:988-92.

12. Şahin S, Kavuncu V. Hipermobilite sendromunun klinik özellikleri. Romatizma 2001;16:169-76.

13. Seçkin U, Tur BS, Yilmaz O, Yağci I, Bodur H, Arasil T. The prevalence of joint hypermobility among high school students. Rheumatol Int 2005;25:260-3.

14. Biro F, Gewanter HL, Baum J. The hypermobility syndrome. Pediatrics 1983;72:701-6.

15. Fatoye F, Palmer S, Macmillan F, Rowe P, van der Linden M. Pain intensity and quality of life perception in children with hypermobility syndrome. Rheumatol Int 2012;32:1277-84.

16. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003;3:329-41.

17. Remvig L, Jensen DV, Ward RC. Epidemiology of general joint hypermobility and basis for the proposed criteria for benign joint hypermobility syndrome: review of the literature. J Rheumatol 2007;34:804-9.

18. Smits-Engelsman B, Klerks M, Kirby A. Beighton score: a valid measure for generalized hypermobility in children. J Pediatr 2011;158:119-24.

19. Doğanavşargil E. Yaşlı, yaşlanma ve yaşlılığın fizyolojik değişiklikleri. Gümüşdiş G, editor. Yaşlılık ve romatizmal hastalıklar, İstanbul: Deniz; 1999:5-20.

20. Cheng JC, Chan PS, Hui PW. Joint laxity in children. J Pediatr Orthop 1991;11:752-6.

21. Koldaş Doğan S, Taner Y, Evcik D. Benign joint hypermobility syndrome in patients with attention deficit/hyperactivity disorders. Turkish Journal of Rheumatology 2011;26:187-93.

22. Yazgan P, Geyikli I, Zeyrek D, Baktiroglu L, Kurcer MA. Is joint hypermobility important in prepubertal children? Rheumatol Int 2008;28:445-51.

23. Yıldırım Y. Sağlıklı okul çocuklarında eklem hipermobilitesi sıklığı. Türk Pediatri Arşivi 2005;2.

24. Ruperto N, Malattia C, Bartoli M, Trail L, Pistorio A, Martini A, et al. Functional ability and physical and psychosocial well-being of hypermobile schoolchildren. Clin Exp Rheumatol 2004;22:495-8.

25. El-Garf AK, Mahmoud GA, Mahgoub EH. Hypermobility among Egyptian children: prevalence and features. J Rheumatol 1998;25:1003-5.

26. Lamari NM, Chueire AG, Cordeiro JA. Analysis of joint mobility patterns among preschool children. Sao Paulo Med J 2005;123:119-23.

27. Silman AJ, Day SJ, Haskard DO. Factors associated with joint mobility in an adolescent population. Ann Rheum Dis 1987;46:209-12.

28. Adib N, Davies K, Grahame R, Woo P, Murray KJ. Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? Rheumatology (Oxford) 2005;44:744-50.

29. Çakın Memik N, Ağaoğlu B, Coşkun A, Karakaya I. The validity and reliability of Pediatric Quality of Life Inventory in 8-12 year old Turkish children. Turk J Child Adolesc Ment Health 2008;15:87-98.

30. Pacey V, Tofts L, Adams RD, Munns CF, Nicholson LL. Quality of life prediction in children with joint hypermobility syndrome. J Paediatr Child Health 2015;51:689-95.

31. Mastoroudes H, Giarenis I, Cardozo L, Srikrishna S, Vella M, et al. Lower urinary tract symptoms in women with benign joint hypermobility syndrome: a case-control study. Int Urogynecol J 2013;24:1553-8.

32. Russek LN, Errico DM. Prevalence, injury rate and, symptom frequency in generalized joint laxity and joint hypermobility syndrome in a "healthy" college population. Clin Rheumatol 2016;35:1029-39.

33. McCluskey G, O'Kane E, Hann D, Weekes J, Rooney M. Hypermobility and musculoskeletal pain in children: a systematic review. Scand J Rheumatol 2012;41:329-38.

34. Leone V, Tornese G, Zerial M, Locatelli C, Ciambra R, Bensa M, et al. Joint hypermobility and its relationship to musculoskeletal pain in schoolchildren: a cross-sectional study. Arch Dis Child 2009;94:627-32.

ORIGINAL ARTICLE

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The Metastatic Lymph Node Ratio is a Crucial Criterion in Colorectal Cancer Therapy Management and Prognosis

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Abstract

Objective: Every year, 1.8 million people are diagnosed with colon cancer. The presence of lymph node (LN) metastases is a key prognostic factor in adjuvant treatment planning and follow-up. The tumor-node-metastasis (TNM) classification can be used to assist in prognostic cancer staging. However, TNM-classification may not always compromise the necessary prognostic information. Therefore, guidelines are updated regarding prognostic value and new prognostic parameters are investigated. One of these parameters is metastatic lymph node ratio (mLNR), which is calculated by dividing the number of metastatic lymph nodes (mLNs) by the total number of lymph nodes excised. Similar publications have already reported on the prognostic value of the mLNR in gastric, pancreatic, and bladder cancer.

Methods: Pathology reports of 496 stage II and stage III patients treated for colorectal cancer (CRC) in our hospital in the last decade were retrospectively reviewed. Factors such as age, gender, tumor location, tumor size, T stage, lymphovascular invasion, perineural invasion, tumor budding, tumor deposit, total and mLN count were evaluated for overall survival.

Results: The mean tumor size was 53.8 mm. The patients who had an average of 2 LN involvement among those who had 23 lymph nodes excised were followed up for an average of 66.8 months. Receiver operating characteristic test presented the cut-off value of mLNR on overall survival was 0.028, with a sensitivity of 42% and a specificity of 71%. Gender, tumor's localization, and size of ≥6 cm had no significant impact on survival. However, survival was related to age >60, lymphovascular, and perineural invasion, tumor deposit/budding, and mLNR >0.028 ($p \leq 0.05$). Furthermore, multivariate analysis revealed that only mLNR ($p=0.034$) affected overall survival independently.

Conclusion: We believe that mLNR that does not require additional costs will gain more value in diagnosis and treatment. Based on our results, mLNR may be a useful to assess prognosis in CRC patients.

Keywords: Metastatic lymph node ratio, colorectal cancer, prognostic factor

INTRODUCTION

Over 1.8 million new colorectal cancer (CRC) cases and 881,000 deaths were observed in 2018 worldwide, accounting for almost one-tenth of all cancer cases and deaths (1). The mortality rate varies depending on tumor stage and/or the treatment availability (2).

Accurate staging is essential for managing the disease. According to the 8th American Joint Committee on Cancer (AJCC) cancer staging guideline, the assessment for lymph node (LN) metastases in CRC is conducted via involved regional lymph nodes. This guideline is updated over time due to evolving needs and technical developments. Although the basic structure was preserved in the evaluation in AJCC 8, some new parameters such as status for micrometastasis and isolated tumor cells were added (3). For evaluating LN metastasis, a minimum of 12 lymph nodes must be removed (4,5). Less than this number of removed lymph nodes may cause false LN negativity or a lower N grade (5).

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CRC is defined as stage III in the current staging method when there are regional LN metastases. Additional treatment alternatives, such as adjuvant chemotherapy, should be used at this stage (6). Although tumor staging according to the AJCC guide helps assess prognosis, prognosis estimation for IIIA and II stages cannot be performed precisely. According to the current staging method, the prognosis of stage IIIA can be better than that of the lower stages. According to several authors, stage IIIA has a better prognosis than stages IIB and IIC (2,4,6,7).

As a result, a more specific and thorough technique for assessing nodal metastasis would be beneficial. It has been discovered that the metastatic lymph node ratio (mLNR), defined as the ratio of the number of metastatic lymph nodes (mLNs) to the number of inspected lymph nodes (LNs) and not included in the AJCC guidance, is crucial in assessing prognosis in gastric and pancreatic tumors (8,9).

Considering this information, we retrospectively investigated parameters such as age, gender and tumor size, stage, location, LN status, perivascular-perineural involvement, tumor deposit and tumor budding such as mLNR from pathology reports that may impact the overall survival of CRC patients without distant metastasis.

METHODS

Patients' data was collected from the archives of the department of pathology from 01/01/2011 to 01/01/2021. Approval was obtained on 24.11.2021 from the Local Ethics Committee of University of Health Sciences Turkey, Istanbul Prof. Dr. Cemil Tascioglu City Hospital with the number E-48670771-514.99. Retrospectively 496 patients with stage II and III were included with the following criteria: ≥ age 18, male/female, surgery due to CRC, adequate clinical record and follow-up, excision of at least 12 lymph nodes. Stage I and IV patients, as well as those with postoperative mortality of at least one month or patients with multiple primary tumors and rectum cancer treated with neo-adjuvant therapies were excluded. Patient staging was made after 8th AJCC cancer staging guideline and tumor budding in CRC was reported accordingly to The International Tumor Budding Consensus Conference (ITBCC) (10).

Statistical Analysis

Data are presented as the mean with interquartile range and minima and maxima, if not as stated in the figure legend. Categorical variables were compared using Fisher's Exact test. Survival analysis was performed using the Kaplan-Meier method and Cox proportional hazards regression modeling.

The area under the receiver operating characteristic curve (ROC) was generated to define diagnostic test's accuracy and a cut-off point of age, tumor size, mLNR for survival. The log-rank test as a non-parametric test was used for comparing survival curves. Missing data were omitted when clinical records were not complete. An overall alpha value of $p<0.05$ was applied to reject the null hypothesis. SPSS [version 18.0, SPSS Inc, Chicago (IL), United States)] for Windows was used for statistical analysis.

RESULTS

Totally 496 patients are included in the study. The mean age of 197 (39.7%) female and 299 (60.3%) male patients was 61.5. For each patient, a mean of 23 LN was excised, on average 2 LN were metastatic. The mean tumor diameter was found to be 53.8 mm in patients with a mean follow-up of 66.8 months (Table 1). Of the total CRC, 171 (34.5%) were detected in the rectum, 129 (26%) in the right colon, 98 (19.8%) in the sigmoid colon, 68 (13.7%) in the left colon and 9 (1.8%) in the transverse colon. Multiple foci were detected in 21 (4.2%) patients (Table 2). It was observed that 403 (81.3%) patients were in T3 stage, 81 (16.3%) patients were in T4 and 12 (2.4%) patients were in T2 (Table 3). It was observed that 310 (62.5%) patients did not show a LN involvement, therefore rated stage II. The remaining 186 (37.5%)

Table 1. General characteristics of patients

	n	Minimum	Maximum	Mean	Standard deviation
Age/years	496	21.7	89.8	61.51	13.27
Longest diameter/mm	496	10	200	53.79	23.91
Survey/month	496	1	179	66.80	46.21
Total excised lymph node	496	12	73	23.09	11.48
Metastatic lymph node	496	0	66	2.14	5.73

Table 2. Tumor anatomical localization

Location	Frequency (n)	Percentage (%)
Right colon	129	26.0
Transverse colon	9	1.8
Left colon	68	13.7
Sigmoid colon	98	19.8
Rectum	171	34.5
Multifocal	21	4.2
Total	496	100

Table 3. T stage distribution

	T2	T3	T4	Total
Frequency (n)	12	403	81	496
Percentage (%)	2.4	81.3	16.3	100

patients showed a LN involvement and reported as stage III.

While 355 (71.6%) patients showed lymphovascular invasion (LVI), 374 (75.4%) individuals exhibited perineural invasion. Out of 130 patients evaluated for extranodal tumor deposits, which was not addressed as a prognostic factor in the 8th AJCC despite its negative impact on overall survival and disease-free survival (11), 28 (21.5%) were positive. Another important prognostic factor tumor budding was reported in 35 patients via the scoring system according to ITBCC and 11 (31.4%) patients were positive for budding.

Since there is no consensus on the cut-off values including the age of the patient, the largest tumor size and the mLNR of the patients we determined these cut-off values for patients admitted to our hospital with a ROC test. These values were reported as 60.2 years for age (sensitivity: 0.66; specificity: 0.56), 57.8 mm (sensitivity: 0.4; specificity: 0.63) for the largest tumor size and 0.028 (sensitivity: 0.42; specificity: 0.71) for mLNR (Figure 1).

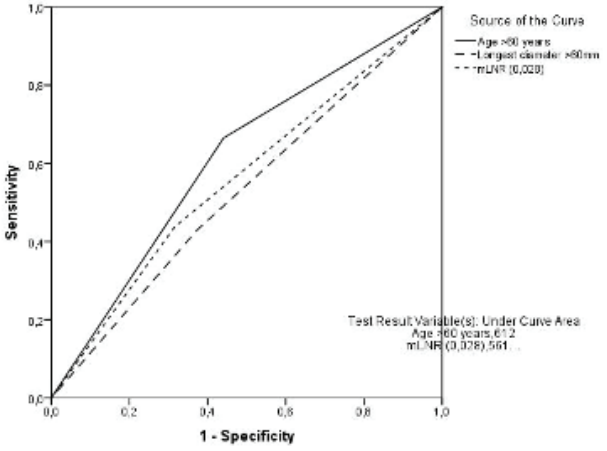

Figure 1. Cut-off values for age, diameter and mLNR
mLNR: Metastatic lymph node ratio

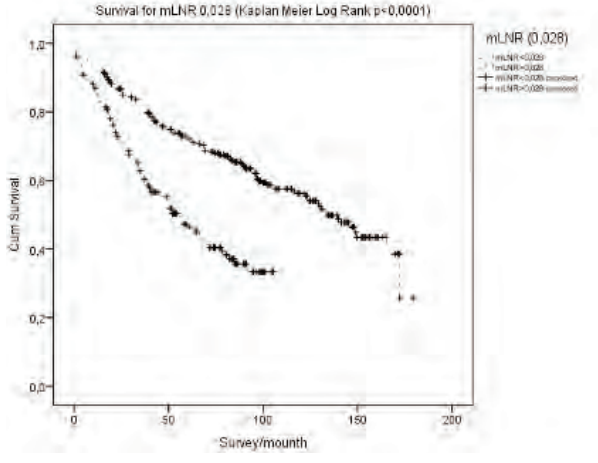

Figure 2. Survival mLNR stages
mLNR: Metastatic lymph node ratio

When survival analysis was performed for these factors; there was no statistically significant difference in overall survival in terms of gender, tumor diameter, tumor localization and tumor perforation (p>0.05). For patient age (60/year), tumor stage, LN metastasis, mLNR (0.028) (Figure 2), LVI, perineural invasion (p<0.0001), tumor deposit (p<0.001) and tumor budding (p=0.016) significant survival difference was detected (Table 4). There was a survival difference between stage IIIA and IIB and IIC, but it could not be statistically proven (p=0.078) (Figure 3). When multivariate analysis was performed for survival, only mLNR (p=0.034) was found to be an independent prognostic factor (Table 5).

DISCUSSION

In a study with 1.837 patients diagnosed with CRC it was reported that there is no difference in survival rate in different sexes when the other causes of death than cancer are excluded. The same finding was also discovered in our study (12).

Table 4. Factors affecting survival with results of univariate analysis

Parameters (n)	Negative (%)	Positive (%)	Log rank (Mantel-Cox) p
Age >60 years (496)	225 (45.4)	271 (54.6)	p<0.0001
Longest diameter >60 mm (496)	298 (60.1)	198 (39.9)	p=0.120
Lymph node (496)	310 (62.5)	186 (37.5)	p<0.0001
Lymphovascular invasion (496)	355 (71.6)	141 (28.4)	p<0.0001
Perineural invasion (496)	374 (75.4)	122 (24.6)	p<0.0001
Tumor deposit (130)	102 (78.5)	28 (21.5)	p=0.001
Tumor budding (36)	24 (66.7)	12 (33.3)	p=0.016
mLNR >0.028 (496)	311 (62.7)	185 (37.3)	p<0.0001
mLNR: Metastatic lymph node ratio			

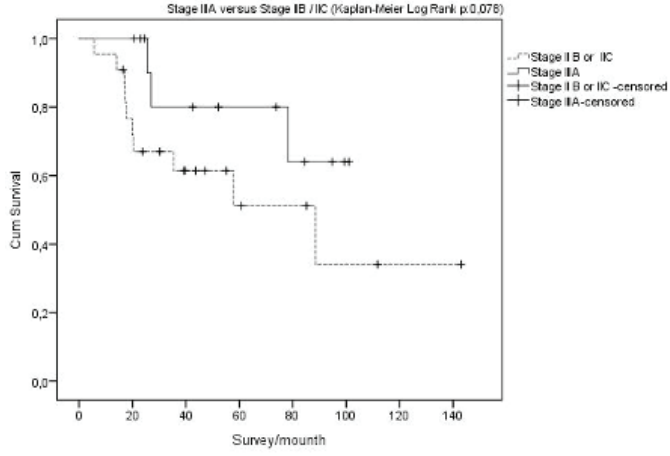

Figure 3. Survival stage IIIA versus stage IIB-IIC

Table 5. Factors affecting survival analysis via multivariate analysis/Cox regression)								
	B	SE	Wald	df	Sig.	Exp (B)	95.0% Cl for Exp (B)	
							Lower	Upper
Age >60 years	-1.117	1.237	0.815	1	0.367	0.327	0.029	3.697
T stage	-	-	1.948	2	0.378	-	-	-
T stage (1)	-2.311	194.926	0.000	1	0.991	0.099	0.000	8.277E+164
T stage (2)	-4.019	194.931	0.000	1	0.984	0.018	0.000	1.513E+164
Lymph node positive	-12.508	86.834	0.021	1	0.885	0.000	0.000	3.026E+68
Lymphovascuar invasion	16.167	86.834	0.035	1	0.852	10499330.74	0.000	8.940E+80
Perineural invasion	0.457	1.219	0.141	1	0.708	1.580	0.145	17.226
Tumor deposit	-	-	2.559	2	0.278	-	-	-
Tumor deposit (1)	-21.781	115.592	0.036	1	0.851	0.000	0.000	8.559E+88
Tumor deposit (2)	2.566	1.614	2.527	1	0.112	13.016	0.550	308.031
Tumor budding	-11.707	86.825	0.018	1	0.893	0.000	0.000	6.628E+68
mLNR (0.028)	-3.376	1.595	4.479	1	0.034	0.034	0.002	0.779
mLNR: Metastatic lymph node ratio, CI: Confidence interval								

In a study from Kornprat et al. (13) with 369 patients, tumor size proved to be an independent prognostic parameter for patients with CRC. In this study it was also reported that the cut-off points differed among the colon locations. However, there was no certain coherence found between the tumor size and prognosis in other studies (14-16).

Our cut-off value was found at 60 mm and at this level there was no difference in survival in our patients.

Some studies showed, that a cancer in the left colon had a worse prognosis than in the right colon, yet other studies could not support the same effect of tumor location on the prognosis (17). In a study from 2020, the general differences among survival rate was compared between the right and left colon cancers. Right and left colon cancers showed differences in microbiom, clinical presentation and molecular features. Separate therapy regimes were recommended (18). We did not see the effect of tumor location on the survival.

Assessing the relationship between perforation and the survival rate did not show any significant difference in multivariate analysis, even if a tendency was inspected in univariate analysis (19-21). Our univariate analysis did not show a relationship between perforation and survival either.

Patients of higher age are admitted and operated most of the time as emergency cases, hence they show a higher mortality (22). In a study from Steele et al. (23) in 2014 with 7.948 patients, the effect of age on overall survival was conducted and younger patients showed at the time of diagnosis higher grades of the cancer and higher recurrence, meanwhile no significant difference in survival compared to the older patients. In our study we observed a lower survival rate in patients older than 60 (based on ROC analysis)

Staging is vital in the assessment of the prognosis and the therapeutic goals in CRC. Progress in the grade shows bad prognosis (24). A study of Zielinski et al. (20) proved higher age, advanced T stage and high American Society of Anesthesiologists score effected the survival independently. In our study the T stage showed significant effects on survival in univariate analysis.

AJCC staging system is also essentially adopted by World Health Organization and updated regularly with the AJCC-8 version being the most up-to-date. A novelty in the latest edition is the detailed description of Tis dysplasia. It is lesions penetrating lamina propria with probable invasion of muscularis mucosa are defined as intramucosal carcinoma. While in other malignant entities only the basal membrane penetration is assessed as invasive, in CRCs even lesions advanced into the submucosa have the potential of metastasizing (3).

In a study from 2016, the survival rate differed between the patients in stages IIB-IIC and IIIA, in favor of IIIA, where the older AJCC-7 system was used for the staging (25). Isolated tumor cells, which had not been mentioned in the N grading of the colorectal tumors in the earlier editions, are also available in the AJCC-8. Isolated tumor cells in subcapsular or marginal sinus lymph nodes (<20 cells or <0.2 mm tumor cell group) and micro-metastasis (20 cells or more and metastasis diameter between 0.2-2 mm) are being described in detail. LN containing isolated tumor cells are being registered as N0 (or N0i) and these cells do not upstage the disease to stage III. Patients with micro-

metastasis are registered as N1, as they show a worse prognosis. Since we did not have a patient diagnosed with micrometastasis and isolated tumor cell, these findings were not taken into account in our study.

Tumor deposits, being one of the important histopathological factors, are seen in 20% of the CRCs and are related to worse prognosis. The discussion of their consideration in the TNM staging is still not concluded (26). We found in our study that patients with tumor deposits showed lower survival rates.

The definition of tumor deposit in AJCC-7 is a tumor forming a prominent nodule, independent of lymphatic tissue finding. AJCC-8 clarified the interpretation of the tumor nodules found in lymphatic drainage field of primary CRCs. Nodules not containing prominent lymph nodes or vascular/neural constructs are being defined as tumor deposit (N1c). Nodules shape, borders and size are not being taken into consideration. Tumor cells covered by smooth muscle or endothelial cells in contact with erythrocytes are being accepted as vascular invasion. If tumor nodules are seen in the proximity of neural constructs, it is being classified as perineural invasion (11,27-29).

Studies describe a vascular invasion in 65% of the CRC cases. LVI is a significant indicator of advanced stage and is remarkably correlated with worse prognosis in CRC patients (30). LVI was an indicator of more aggressive biological behavior and poor prognosis in patients with stage III CRC (31). Vascular invasion showed a difference in survival in our univariate analysis.

Perineural invasion is a sign of worse prognosis, progress of the disease and are seen in 22% of CRC cases. Studies show independently of other factors a positive perineural invasion reduced the 5-year survival from 75% to 25% (32).

In a meta-analysis of 38 studies and 12,661 patients from 2015 perineural invasion lead to lower survival rates in CRC. Patients in grade 2 and 3 showed the perineural invasion independently an effect on the survival rate. In our study, perineural invasion reduced the survival rate as well (33).

N1c elevates disease to stage III, even in the absence of nodal metastases. The number of tumor deposits is recorded with site-specific factors but does not influence the designation (i.e. a patient with one tumor deposit and a patient with four tumor deposits are both staged as N1c). The number of tumor deposits is not added to the number of positive lymph nodes (34).

Among 20 patients we recruited in our study since 2018, none had the finding of a N1c grade. In this period 4 patients passed away, 2 of them without any lymphatic invasion (in IIA stage). Most our patients were assessed according to the AJCC-7 system. We also found that the prognosis of IIIA stage being better than the II stage, yet showing no statistical significance. Limited invasion depth and early regional LN metastasis show the indecisive character of the stage IIIA colon cancer. These tumors are rather superficial and their mLNs are mostly in the proximity of their main lesion, making them treatable with surgical resection and show good prognosis. However, the fact that they show metastasis although being superficial shows how aggressive their biological character is (25). Hence, there are further parameters in need, in addition to the LN metastasis and tumor invasion depth, to describe their character properly.

Tumor budding is the tumor infiltration in form of single cells or a small cell cluster (<5 cells) in the invasive tumor border and is not being considered by AJCC but required by the College of American Pathologists in the pathological findings. It is accepted as a sign of advanced mobility, invasive phenotype transformation and tumor progression. It is also being considered because of epithelial/mesenchymal transformation of neoplastic cells and a special type of apoptotic escape (35). A multi-center prospective study with 991 patients from 2019 tumor budding correlated with the tumor stage, size and the lymphatic invasion and lowered the survival significantly (36). In a review and meta-analysis from 2016 the value of tumor budding as a prognostic factor was studied. Out of 2.728 studies 34 were included and it was shown that the tumor budding affected the LN metastasis and local recurrence (37).

In the previous studies factors such as surgeons' experience, disease's stage, sample size, tumor size, individual immune response and the pathologist's ability to dissect lymph nodes causing a wide margin of dissected lymph nodes between 6 to 40.

The number of positive lymph nodes has a strong influence on the prognosis of CRC patients. LN assessment in CRC will ensure accurate patient staging. LN metastasis rate was increased in poorly differentiated tumors. It was also shown that higher number of mLNs and their localization in the stems of major vessels reduced the survival rate (38). Another study described the number of harvested mLNs correlated with the possibility of LN metastasis (39). Since the number of minimum harvested lymph nodes plays a defining role in the staging, we only included patients with at least 12 lymph nodes in our study. We speculate that this might be lowering our LNR values sensitivity

LNR is recommended as an additional staging to the pN stage for cancer patients. It is defined as the ratio of positive nodes to LNH and is based on the observation that LNH can affect positive node count and survival. The LNR has been shown in multiple retrospective studies to be an independent prognostic factor in cancer (gastric, pancreatic, euosophagus, bladder) patients (5).

Deployment of LNR can help prevent an over- or understaging. However, the most significant discussion on LNR is the cut-off point. Different authors agree on different cut-off values and a it has not been come to a consensus.

However, both univariate and multivariate analysis (p=0.034) showed LNR efficient. We believe with more upcoming studies on LNR in colorectal and other cancers, LNR will receive an important place among the prognostic factors.

In our study, we found that patient age (more than 60 years); tumor, T stage, N stage, LVI, perineural invasion, deposits, budding and LNR were the factors that influenced prognosis of patients according to the univariate analysis. Patients with a better young age and earlier stage of T staging, N staging and absence of perineural-LVI, tumor deposit-budding, and a lower LNR have improved survival rates.

However, when all eight factors are entered into the Cox proportional-hazards model, the multivariable analysis showed that only LNR showed statistical significance. LNR still had statistical significance in both the univariate and multivariable analysis. Neo-adjuvant therapies used especially in rectum cancer notably reduced the LN invasion. Therefore patients with rectum cancer treated with neo-adjuvant therapies are excluded in our studies and patients with stage II and III are being considered in the same group. Further research is required on only stage III or rectum cancer patients treated with neo-adjuvant therapies and its influence on the LNR should be regarded.

CONCLUSION

Currently, as in other malignities, the personalized approaches of diagnostics and therapies (consideration of somatic and germline mutations leading to microsatellite instabilities, RAS pathway (KRAS, BRAF, NRAS) mutations) come into prominence. We believe that prognostic factors, which do not require further expenses, such as LNR, peritoneal metastasis, tumor budding and tumor deposit are to gain further clinical value in diagnostics and therapy beside the innovative genetic analysis, mentioned earlier. Hence, with the upcoming publications, the mLNR, used already in other malignant diseases, will also become one of the indispensable prognostic factors.

Ethics

Ethics Committee Approval: Approval was obtained on 24.11.2021 from the Local Ethics Committee of University of Health Sciences Turkey, Istanbul Prof. Dr. Cemil Tascioglu City Hospital with the number E-48670771-514.99.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Pei JP, Zhang CD, Fu X, Ba Y, Yue S, Zhao ZM, et al. A Novel TNM classification for colorectal cancers based on the metro-ticket Paradigm. J Cancer 2021;12:3299-306.
3. Weiser MR. AJCC 8th Edition: Colorectal cancer. Ann Surg Oncol 2018;25:1454-5.
4. Horne J, Bateman AC, Carr NJ, Ryder I. Lymph node revealing solutions in colorectal: should they be used routinely? J Clin Pathol 2014;67:383-8.
5. Walker R, Wood T, LeSouder E, Cleghorn M, Maganti M, MacNeill A, et al. Comparison of two novel staging systems with the TNM system in predicting stage III colon cancer survival. J Surg Oncol 2018;117:1049-57.
6. Pyo JS, Kim JH, Lee SY, Baek TH, Kang DW. Metastatic lymph node ratio (mLNR) is a useful parameter in the prognosis of colorectal cancer; a meta-analysis for the prognostic role of mLNR. Medicina 2019;55:673.
7. Kim MJ, Jeong SY, Choi SJ, Ryoo SB, Park JW, Park KJ, et al. Survival paradox between stage IIB/C (T4N0) and stage IIIA (T1-2N1) colon cancer. Ann Surg Oncol 2015;22:505-12.
8. Yamamoto Y, Ikoma H, Morimura R, Konishi H, Murayama Y, Komatsu S, et al. The clinical impact of the lymph node ratio as a prognostic factor after resection of pancreatic cancer. Anticancer Res 2014;34:2389-94.
9. Hou Y, Wang X, Chen J. Prognostic significance of metastatic lymph node ratio: the lymph node ratio could be a prognostic indicator for patients with gastric cancer. World J Surg Oncol 2018;16:198.
10. Lugli A, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol 2017;30:1299-311.
11. Lord AC, D'Souza N, Pucher PH, Moran BJ, Abulafi AM, Wotherspoon A, et al. Significance of extranodal tumour deposits in colorectal cancer: a systematic review and meta-analysis. Eur J Cancer 2017;82:92-102.
12. Samawi HH, Yin Y, Speers CH, Cheung WY. Sex disparities in outcomes of early stage colorectal cancer: a population-based study. Clinical Colorectal Cancer 2018;17:e711-7.
13. Kornprat P, Pollheimer MJ, Lindtner RA, Schlemmer A, Rehak P, Langner C. Value of tumor size as a prognostic variable in colorectal cancer: a critical reappraisal. Am J Clin Oncol 2011;34:43-9.

14. Kamphues C, Andreatos N, Kruppa J, Buettner S, Wang J, Sasaki K, et al. The optimal cut-off values for tumor size, number of lesions, and CEA levels in patients with surgically treated colorectal cancer liver metastases: an international, multi-institutional study. J Surg Oncol 2021;123:939-48.

15. Crozier JE, McMillan DC, McArdle CS, Angerson WJ, Anderson JH, Horgan PG, et al. Tumor size is associated with the systemic inflammatory response but not survival in patients with primary operable colorectal cancer. J Gastroenterol and Hepatol 2007;22:2288-91.

16. Li X, An B, Ma J, He B, Qi J, Wang W, et al. Prognostic value of the tumor size in resectable colorectal cancer with different primary locations: a retrospective study with the propensity score matching. J Cancer 2019;10:313-22.

17. Brouwer NPM, Bos ACRK, Lemmens VEPP, Tanis PJ, Hugen N, Nagtegaal ID, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. Int J Cancer 2018;143:2758-66.

18. Stintzing S, Tejpar S, Gibbs P, Thiebach L, Lenz HJ. Understanding the role of primary tumour localization in colorectal cancer treatment and outcomes. Eur J Cancer 2017;84:69-80.

19. Banaszkiewicz Z, Woda Ł, Tojek K, Jarmocik P, Jawień A. Colorectal cancer with intestinal perforation - a retrospective analysis of treatment outcomes. Contemp Oncol (Pozn) 2014;18:414-8.

20. Zielinski MD, Merchea A, Heller SF, You YN. Emergency management of perforated colon cancers: how aggressive should we be? J Gastrointest Surg 2011;15:2232-8.

21. Kim MS, Lim SW, Park SJ, Gwak G, Yang KH, Bae BN, et al. Survival rate and prognostic factors in perforated colorectal cancer patients: a case-control study. J Korean Soc of Coloproctol 2010;26:69-75.

22. Limam M, Matthes KL, Pestoni G, Michalopoulou E, Held L, Dehler S, et al. Are there sex differences among colorectal cancer patients in treatment and survival? a swiss cohort study. J Cancer Res Clin Oncol 2021;147:1407-19.

23. Steele SR, Park GE, Johnson EK, Martin MJ, Stojadinovic A, Maykel JA, et al. The impact of age on colorectal cancer incidence, treatment, and outcomes in an equal-access health care system. Dis Colon Rectum 2014;57:303-10.

24. van den Berg I, Coebergh van den Braak RRJ, van Vugt JLA, Ijzermans JNM, Buettner S. Actual survival after resection of primary colorectal cancer: results from a prospective multicenter study. World J Surg Oncol 2021;19:96.

25. Huang B, Feng Y, Ni M, Chen C, Cai G. Heterogeneous survival between stage IIA and stage IIIA colon cancer when different numbers of lymph nodes are harvested. ANZ J Surg 2018;88:316-21.

26. Delattre JF, Selcen Oguz Erdogan A, Cohen R, Shi Q, Emile JF, Taieb J, et al. A comprehensive overview of tumour deposits in colorectal cancer: towards a next TNM classification. Cancer Treat Rev 2022;103:102325.

27. Lin Q, Wei Y, Ren L, Zhong Y, Qin C, Zheng P, et al. Tumor deposit is a poor prognostic indicator in patients who underwent simultaneous resection for synchronous colorectal liver metastases. Onco Targets Ther 2015;8:233-40.

28. Nagayoshi K, Ueki T, Nishioka Y, Manabe T, Mizuuchi Y, Hiranashi M, et al. Tumor deposit is a poor prognostic indicator for patients who have stage II and III colorectal cancer with fewer than 4 lymph node metastases but not for those with 4 or more. Dis Colon Rectum 2014;57:467-74.

29. Ueno H, Hashiguchi Y, Shimazaki H, Shinto E, Kajiwara Y, Nakanishi K, et al. Peritumoral deposits as an adverse prognostic indicator of colorectal cancer. Am J Surg 2014;207:70-7.

30. Wang X, Cao Y, Ding M, Liu J, Zuo X, Li H, et al. Oncological and prognostic impact of lymphovascular invasion in Colorectal Cancer patients. Int J Med Sci 2021;18:1721-29.

31. Zhong JW, Yang SX, Chen RP, Zhou YH, Ye MS, Miao L, et al. Prognostic value of lymphovascular invasion in patients with stage III colorectal cancer: a retrospective study. Med Sci Monit: Med Sci Monit 2019;25:6043-50.

32. Liebig C, Ayala G, Wilks J, Verstovsek G, Liu H, Agarwal N, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clin Oncol 2009;27:5131-7.

33. Yang Y, Huang X, Sun J, Gao P, Song Y, Chen X, et al. Prognostic value of perineural invasion in colorectal cancer: a meta-analysis. J Gastrointest Surg 2015;19:1113-22.

34. Dursun N, Paşaoğlu E. Changes and updates in staging colorectal carcinomas at American joint of cancer commitee and cancer reporting protocol of College of American Pathologists. J Curr Pathol 2018;2:78-84.

35. Liotta LA, Kohn E. Anoikis: cancer and the homeless cell. Nature 2004 26;430:973-4.

36. Ueno H, Ishiguro M, Nakatani E, Ishikawa T, Uetake H, Matsuda C, et al. Prospective multicenter study on the prognostic and predictive impact of tumor budding in stage II colon cancer: results from the SACURA trial. J Clin Oncol 2019;37:1886-94.

37. Rogers AC, Winter DC, Heeney A, Gibbons D, Lugli A, Puppa G, et al. Systematic review and meta-analysis of the impact of tumour budding in colorectal cancer. Br J Cancer 2016;115:831-40.

38. Faerden AE, Sjo OH, Bukholm IR, Andersen SN, Svindland A, Nesbakken A, et al. Lymph node micrometastases and isolated tumor cells influence survival in stage I and II colon cancer. Dis Colon Rectum 2011;54:200-6.

39. Ogino S, Nosho K, Irahara N, Meyerhardt JA, Baba Y, Shima K, et al. Lymphocytic reaction to colorectal cancer is associated with longer survival, independent of lymph node count, microsatellite instability, and CpG island methylator phenotype. Clin Cancer Res 2009;15:6412-20.

CASE REPORT

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^{18}F-FDG PET/CT Imaging of an Extramedullary Solitary Plasmacytoma of the Maxillary Sinus; A Case Report

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Abstract

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is successfully used for imaging malignant plasma cell disorders. Solitary plasmacytoma of head and neck is relatively rare. We report a case of 52-year-old male patient with high ^{18}F-FDG uptake of pathologically proven maxillary sinus plasmacytoma that is uncommon. Our case has demonstrated ^{18}F-FDG PET/CT is useful for showing the extent of the disease that affects treatment management in plasmacytoma.

Keywords: Plasmacytoma, maxillary sinus, ^{18}F-FDG PET/CT

INTRODUCTION

Solitary extramedullary plasmacytoma is a plasma cell malignancy without systemic involvement. It is a rare clinical condition and mostly occurs in head and neck region (1). ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been reported to be useful in demonstrating the spread of the disease, it's involvement in the other parts of the body and in follow-up in solitary plasmacytoma (2-4).

CASE PRESENTATION

A-52-year-old male patient has referred to our department for ^{18}F-FDG PET/CT imaging for a body scan. He had complaints of swelling and pain on the left side of his face. After physical examination and CT scan, a lesion was demonstrated inside the left maxillary sinus. Fine needle biopsy revealed malign tumor cells, however excision of the lesion needed to confirm the diagnosis of the patient. Before excision ^{18}F-FDG PET/CT imaging was conducted for a whole body scan. PET/CT images has demonstrated a ^{18}F-FDG avid destructive lesion with high uptake inside the maxillary sinus and extending to the soft tissue surrounding left orbita (Figure 1). There was no pathological ^{18}F-FDG uptake in other parts of the body other than the extravasation of ^{18}F-FDG on the right hand around the side of injection (Figure 2). The patient had a maxillary sinus excision and orbital exenteration operation a week after the PET scan. The histopathology report was compatible with plasmacytoma. Bone marrow biopsy and blood tests were done and reported as normal to rule out multiple myeloma.

DISCUSSION

Solitary extramedullary plasmacytoma is a rare form of plasma cell disorder and the treatment approach may be different. If there is no disease in the other parts of the body, radiotherapy or excision with radiotherapy is recommended for treatment (5,6). Combined therapies with chemotherapy are also recommended for the higher disease-free survival rates (7). ^{18}F-FDG PET/CT imaging has been useful in the initial stage for excluding the metastatic disease and systemic involvement. Furthermore, it has been shown that ^{18}F-FDG uptake of the lesion can

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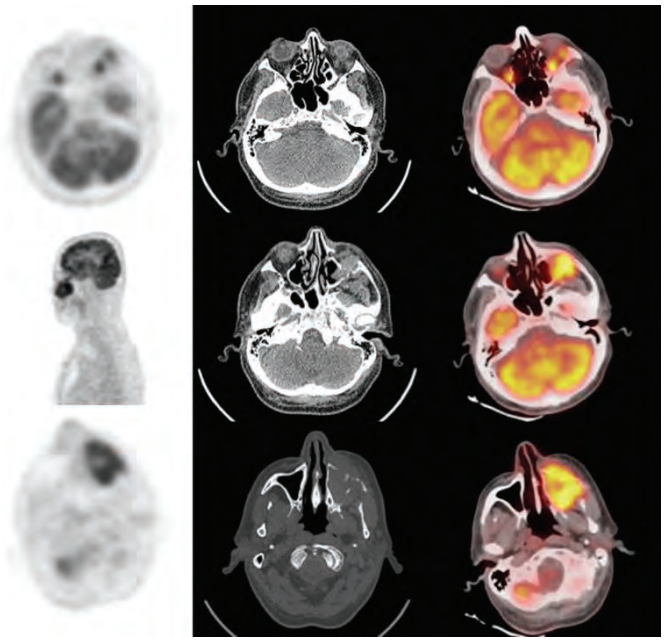

Figure 1. PET/CT images demonstrated a destructive lesion with high FDG uptake inside the maxillary sinus and extending to the soft tissue surrounding left orbita
PET/CT: Positron emission tomography/computed tomography, FDG: Fluorodeoxyglucose

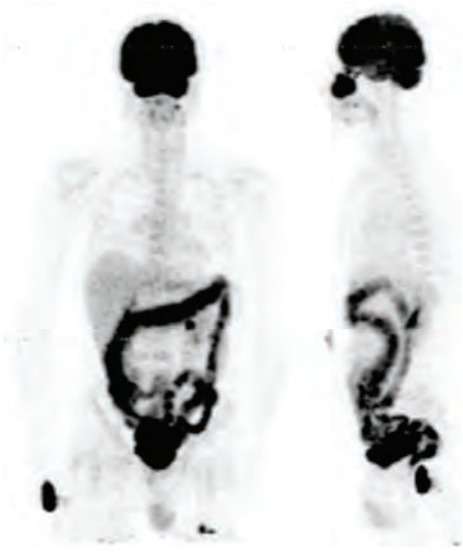

Figure 2. Whole body maximum intensity projection image showed no pathological findings other than primary lesion in the maxillary sinus

have an impact on the prognosis of the diease. [18]F-FDG avid plasmacytoma lesions are more likely to transform multiple myeloma, making follow-up more important in lesions with high uptake (8). There are currently a few cases reported for maxillary sinus plasmacytoma in the literature, however there are fewer reports for the use of [18]F-FDG PET/CT (9,10).

CONCLUSION

Our case has emphasized the importance of [18]F-FDG PET/CT whole body imaging to support clinical decision before starting treatment and during follow-up.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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REFERENCES

1. Dimopoulos MA, Hamilos G. Solitary bone plasmacytoma and extramedullary plasmacytoma. Curr Treat Options Oncol 2002;3:255-9.
2. Zhang L, Zhang X, He Q, Zhang R, Fan W. The role of initial 18F-FDG PET/CT in the management of patients with suspected extramedullary plasmocytoma. Cancer Imaging 2018;18:19.
3. Kato T, Tsukamoto E, Nishioka T, Yamazaki A, Shirato H, Kobayashi S, et al. Early detection of bone marrow involvement in extramedullary plasmacytoma by whole-body F-18 FDG positron emission tomography. Clin Nucl Med 2000;25:870-3.
4. An SY, An CH, Choi KS, Heo MS. Multiple myeloma presenting as plasmacytoma of the jaws showing prominent bone formation during chemotherapy. Dentomaxillofac Radiol 2013;42:20110143.
5. Krause S, Hillengass J, Goldschmidt H, Debus J, Neuhof D. Radiotherapy of solitary plasmacytoma. Ann Hematol 2011;90:1093-7.
6. Vlad D, Trombitas V, Albu S. Extramedullary Plasmacytoma of the Paranasal Sinuses: Combining Surgery with External Radiotherapy. Indian J Otolaryngol Head Neck Surg 2016;68:34-8.
7. Avilés A, Huerta-Guzmán J, Delgado S, Fernández A, Díaz-Maqueo JC. Improved outcome in solitary bone plasmacytomata with combined therapy. Hematol Oncol 1996;14:111-7.
8. Albano D, Bosio G, Treglia G, Giubbini R, Bertagna F. 18F-FDG PET/CT in solitary plasmacytoma: metabolic behavior and progression to multiple myeloma. Eur J Nucl Med Mol Imaging 2018;45:77-84.
9. Erdogan BA, Sekercan O, Dursun N, Tatar G, Bora F. Extramedullary plasmacytoma of maxillary sinus. J Craniofac Surg 2013;24:e85-7.
10. Exarchakos G, Korantzopoulos P, Bai M, Xanthopoulos J, Tzouvara E, Skevas A. Solitary extramedullary plasmacytoma of the maxillary sinus. Case report. Acta Otorhinolaryngol Belg 2003;57:217-20.