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Highlights

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- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

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

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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Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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

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

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

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

Tables

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).

Table 1. Limitations for each manuscript type

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

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

Figures and Figure Legends

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

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

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

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

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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.

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REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

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EDITORIAL

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Happy 100th Anniversary of Our Republic

İsmail Demirkale

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Advanced education is one of the most essential parameters required to elevate the Republic of Turkey to a contemporary and civilized level. Indeed, societies that have drifted away from logic, inquiry, and analytical thinking have not given enough importance to science and art. The best expression that reflects this situation is undoubtedly: "For everything in the world, for materiality, spirituality, and success, the most genuine guide is knowledge, it is science. Seeking a guide other than knowledge and science is negligence, ignorance, and delusion." The author of these words is Mustafa Kemal Atatürk, who is defined by UNESCO as the father of modern Turkey on the occasion of his 100th birth anniversary. Turkey's relentless struggle in the first half of the 20th-century for both social and political development constitutes a particularly remarkable page in modern world history.

While previous modernization efforts were wasted due to wars and uprisings, the Republic established by the great leader Mustafa Kemal Atatürk offered the country a new opportunity, transforming it into a modern, secular republic. One of the key building blocks of achieving contemporary levels of science and technology is modern medical education (1). The "Kabakçı Rebellion", which resulted in the dethroning of Sultan Selim III, disrupted clinical and surgical education, which had been limited by the "Tersane Tıbbiyesi Nizamnamesi" as part of the "Nizam-ı Cedid" movement, and it completely disappeared after the "Kasımpaşa Fire" in 1822. However, due to social and military needs, higher education institutions were established during Mahmud II's reign, and the first modern medical school, known as "Tıphane-i Âmire" was founded in 1827. Despite the appearance of providing modern medical education in subsequent years, note that the number of Turkish doctors who could practice medicine had decreased significantly because of the French language of instruction (2). With the help of Grand Vizier Fuat Pasha, the Society of Scientific Medicine Translation was founded with the aim of translating medical works in foreign languages into Turkish. The first civilian and completely Turkish-medium medical school was "Mekteb-i Tıbbiye-i Mülkiye", opened in 1867. This school, which merged with the military medical school in Haydarpaşa in 1909, became the Faculty of Medicine under the name "İstanbul Dar'ül Fünunu Tıp Fakültesi" and maintained this structure until the University Reform of 1933. "Dar'ül Fünun", meaning "House of Sciences" or "Gateway to Sciences," was granted scientific, administrative, and financial autonomy by law after the proclamation of the republic. However, due to its persistence as a traditional madrasah and its failure to adapt to the new republican reforms and innovations, there was a need for reform. After the proclamation of the Republic, with the foresight gained from the great leader's historical knowledge and genius, preparations were made for the "university reform" by sending talented students abroad between 1927 and 1930 (3). This reform, aimed at creating a university that would defend the principles of the Turkish revolution and enjoy the support of political power, was based on the examinations and report of Prof. Albert Malche, who worked in the field of pedagogy at the University of Gelf in Switzerland. The noteworthy points in this report are that the education at İstanbul Darülfünun was medieval in nature, lacked room for research, discussion, and critical thinking, and there was no scientific collaboration between faculties.

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Modern medical education is undoubtedly one of the most important building blocks on the road to modern Turkey. Thanks to this education, led by Atatürk, quality and modern healthcare services became easily accessible to every individual. As we proudly celebrate the 100th anniversary of our Republic, a real revolution has been achieved in terms of people's sovereignty, as well as in the fields of economy, culture, technology, and science. In these days when we celebrate the 100th year of our Republic, we should strive even harder for progress in science, education, and the arts. As scientists, we remember with respect and gratitude the great leader Mustafa Kemal Atatürk and his comrades-in-arms, who paved the way for us on this path.

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REVIEW

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Comprehensive Review of Primary Posterior Fossa Tumors in Children

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Abstract

Approximately 50% of central nervous system tumors in children are primary posterior fossa tumors, ranking as the most common solid tumors in childhood. The most frequently encountered types are medulloblastoma, pilocytic astrocytoma, ependymoma, and brainstem gliomas. In addition, less common pathologies such as atypical teratoid/rhabdoid tumors, hemangioblastomas, schwannomas, cerebellar gangliocytomas, and epidermoid tumors are also present. This study comprehensively compiles the epidemiological, histopathological, radiological, and clinical characteristics of pediatric posterior fossa tumors considering current classifications, along with a detailed review of treatment approaches.

Keywords: Pediatric tumor, posterior fossa tumor, medulloblastoma, review

INTRODUCTION

The posterior fossa is a critical area in the human brain, housing vital structures such as the medulla, pons, mesencephalon, and cerebellum (1). Physicians across various specialties encounter posterior fossa lesions. Understanding the clinical presentation, differential diagnosis, investigations, and treatment of these lesions is crucial for all clinicians involved in the care of patients with such medical conditions. Referral of patients suspected or diagnosed with posterior fossa lesions to appropriate specialties is mandatory.

The posterior fossa is bounded anteriorly by the dorsum sella, the posterior part of the sphenoid body, and the clivus; posteriorly by the squamous part of the occipital bone and the petrous and mastoid parts of the temporal bone; and superiorly by a small part of the mastoid angle of the parietal bone. The cerebellum contains parts of the brainstem, including the pons and medulla, and the fourth ventricle (2). Lesions in the posterior fossa can be categorized on the basis of their etiology and classified as vascular, infectious, traumatic, neoplastic, or according to their anatomical location within the posterior fossa. These tumors are differentiated into intra-axial and extra-axial tumors based on their relationship with the pia mater. Intra-axial tumors originate from the brain stem, cerebellum, or fourth ventricle. Tumors that arise from the tissues of the posterior fossa are called primary tumors, whereas those spreading metastatically from another organ are termed secondary posterior fossa tumors. Posterior fossa tumors can occur in both adults and children, with approximately half of pediatric brain tumors developing in this region (3).

This study aims to review the most commonly observed primary pediatric posterior fossa tumors such as medulloblastoma, pilocytic astrocytoma, ependymoma, and brainstem gliomas, as well as less common types such as atypical teratoid/rhabdoid tumors, hemangioblastomas, schwannomas, cerebellar gangliocytomas, and epidermoid tumors, and to describe the treatment methods applied to these tumors.

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The Most Common Primary Posterior Fossa Tumors in Children

Medulloblastoma

Medulloblastoma is the most prevalent primary posterior fossa tumor in the pediatric age group, accounting for 30-40% of such cases. It is also the most common malignant brain tumor in childhood (4). Medulloblastoma occurs more frequently in males, with a bimodal peak incidence at ages 3 and 9. Before the 2016 World Health Organization (WHO) classification, these tumors were divided into histological variants: classic, large cell, anaplastic, desmoplastic/nodular, and extensive nodular types. In the new molecular era, various intracellular mechanisms have been discovered, including the deregulation of Sonic Hedgehog (SHH) and Wingless (WNT) signaling pathways. The recent classification includes groups based on genetic identification of medulloblastomas, namely WNT-activated, SHH-activated TP53 mutant, SHH-activated TP53 wild type, and non-Wnt/non-SHH (subgroups Group 3 and Group 4) (5). Thus, the 2016 WHO classification identifies medulloblastomas by both histological variants and genetic definitions (6). Each molecular subgroup displayed distinct methylation and gene transcription features, epidemiology, recurrence patterns, clinical findings, and prognosis. The 2021 WHO classification consolidates all histological subtypes under the single term "medulloblastoma, histologically defined" (7) (Table 1). This approach, which incorporates genetic changes, emphasizes the importance of molecular biology in determining the prognosis of medulloblastoma, suggesting that molecular changes, rather than histological variants, define tumor behavior (8).

Table 1. WHO 2021 Classification of tumors of the CNS, medulloblastoma classification

Medulloblastomas, molecularly defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated, and wild-type TP53
Medulloblastoma, SHH-activated and TP53-mutant
Medulloblastoma, non-WNT/non-SHH Group 3 Group 4
Medulloblastomas, histologically defined

WHO: World Health Organization, CNS: Central nervous system

Like all posterior fossa tumors, medulloblastomas typically present with symptoms indicative of increased intracranial pressure. Tumors located in the fourth ventricle may cause obstructive hydrocephalus. Early symptoms commonly include headache and vomiting, whereas later stages may present with cerebellar signs such as ataxia, nystagmus, and dysmetria (9). On magnetic resonance imaging (MRI), medulloblastomas typically appear as round lobulated masses with iso-hypointense signals on T1-weighted sequences and heterogeneous iso-hypointense signals on T2-weighted sequences, showing irregular, patchy, or focal contrast enhancement (4).

The crucial part of medulloblastoma treatment is the determination of prognostic factors. Before treatment, these factors are considered to be select appropriate therapy modalities. The most common prognostic classification used is the Chang Staging System, as shown in Table 2 (10) (Table 2). Patients were categorized into standard-risk and high-risk groups before treatment. High risk is considered in patients over 3 years of age with metastases and postoperative residual tumor greater than 1.5 cm^3 (11). During childhood, male gender is a poor prognostic factor. Postoperative radiotherapy (RT) doses and chemotherapy (CT) agents are determined on the basis of these risk groups. Treatment involves maximal surgical resection, craniospinal RT, and CT in children over 3 years. In children under 3, RT is delayed until after the age of 3, and these children receive intensive CT.

Pilocytic Astrocytoma

Pilocytic astrocytoma is the most common low-grade tumor in children and ranks second among primary posterior fossa tumors in childhood, accounting for 25-35% of these tumors (12).

Table 2. Chang's staging system

T1: Tumor <3 cm	M0: No metastasis
T2: Tumor ≥3 cm in diameter	M1: Tumor in the CSF
T3a: Tumor >3 cm in diameter with extension producing hydrocephalus	M2: Intracranial tumor beyond the primary site
T3b: Tumor >3 cm in diameter with unequivocal excision into the brainstem	M3: Gross nodular seeding in the spinal subarachnoid space
T4: Tumor >3 cm in diameter with extension up past the aquaduct and/or down past the foraman magnum	M4: Metastasis outside the cerebrospinal axis

CSF: Cerebrospinal fluid

The average age at diagnosis was between 6 and 8 years, and there was no significant gender predominance. The prognosis of pilocytic astrocytomas is generally favorable because of the tumor's low grade and slow growth rate, with an average 10-year survival rate exceeding 90% (13). However, the rate of tumor recurrence postoperatively is close to 50% (12). In the 2021 WHO classification, pilocytic astrocytomas are placed under the subheading of "circumscribed astrocytic gliomas", separate from diffuse astrocytomas (7). These tumors are often sporadic, arising from translocations or activation of mutations in the *BRAF* gene. BRAF-KIAA fusions are responsible for pilocytic astrocytomas occurring in cerebellar pathways (14).

Pilocytic astrocytomas classically present as a cerebellar mass composed of a large cyst and a solid nodule. On magnetic resonance imaging, the cystic fluid appears slightly hyperintense on T1-weighted sequences and hypointense on T2-weighted sequences. The solid component shows homogeneous contrast enhancement.

As with all low-grade tumors, gross total resection is the primary treatment method, depending on the location of the lesion. If tumor recurrence develops despite total resection, if the tumor has been subtotally removed and residual tumor causes neurological deficits, or if the subtotally resected tumor progresses radiologically, adjuvant therapies such as RT or CT can be considered. Common CT agents used in clinical practice include temozolomide, vemurafenib, and vinblastine (15).

Ependymoma

Ependymomas are the third most common primary posterior fossa tumors in children, accounting for 10-15% of such cases (16). They most often originate from the base of the fourth ventricle. Previously classified on the basis of histological variants, the 2021 WHO classification now divides them into two groups, A and B, on the basis of DNA methylation patterns, as shown in Table 3. Group A ependymoma exhibit significantly increased methylation of CpG islands in promoter regions compared with Group B ependymomas and are associated with worse prognosis (7). Group A ependymomas are characterized by chromosomal balance and are more common in infants and young boys, with an average survival of approximately 65%. Group B ependymomas show chromosomal instability and are more common in girls over 5 years old, with an average survival of 80-90%. Group A typically presents in paramedian and lateral locations, whereas Group B is usually found in the midline (17).

Table 3. Classification of posterior fossa ependymomas

Group A	Group B
Choromosomal balance	Choromosomal instability
Predominantly infants and children	Predominantly >5-year- old children
Male > female	Female > male
A more lateralized location	A more centralized location
Worse prognosis	Better prognosis

In pediatric ependymomas, gene amplifications in chromosomes 1q, 7, and 9 are most frequently reported (18). In addition, approximately three-quarters of cases show deletions in chromosome 22 (19). Other chromosomal deletions include 1p, 3, 6, 6q, 9p, 13q, and 17 (18). Childhood ependymomas may also have translocations involving chromosomes 1, 11, and 22 (19).

Optimal MRI for ependymomas should include spinal MRI to evaluate metastases. These tumors show heterogeneous contrast enhancement and may rarely present with intratumoral hemorrhage. On MRI, the masses can be solid or may have cyst and mural nodule formation. Differential diagnosis should consider tumors such as pilocytic astrocytoma, ganglioglioma, and pleomorphic xanthoastrocytoma. Ependymomas typically appear as iso-hypointense lesions on T1-weighted sequences and as iso-hyperintense lesions on T2-weighted and FLAIR sequences (20).

Surgical intervention followed by RT is the primary treatment for most pediatric posterior fossa ependymomas. The overall survival rate for patients with near-total resection ranges from 67 to 93%. In patients where only subtotal resection is possible, the average survival may drop to 22-52% despite RT (21). Recurrence occurs locally in approximately 80% of cases, with isolated distant recurrence occurring in 3-9% of cases. This usually occurs in higher-grade tumors and is associated with a poor prognosis (22,23).

RT is typically indicated after excision in children over 12 months old, in cases without tumor spread, for WHO grade III tumors, and in non-completely resectable WHO grade II ependymomas. Better local control is achieved when high-dose radiation includes a 1-cm margin around the tumor (22). Delaying RT until the age of 3 years has been reported to increase the rate of recurrence (16). However, in completely resected posterior fossa group B ependymomas, the chance of recurrence is low, and RT may not be necessary. CT may be considered in infants under 1 year of age to prevent or delay radiation toxicity or in high-risk patients before radiation or a second surgical intervention (24). Recurrences are typically treated with re-surgery and CT. Some subgroups that respond to chemotherapeutic agents such as cyclophosphamide, vincristine, cisplatin, and etoposide may not require RT. In particular, in children under 3 years of age

and in cases with metastatic ependymomas, high-dose use of chemotherapeutic agents such as methotrexate, vincristine, cisplatin, cyclophosphamide, and vinblastine is recommended (20).

Brainstem Glioma

Before the 2016 WHO Classification of Central Nervous System Tumors, the most commonly encountered brainstem tumor was known as diffuse infiltrative brainstem glioma. These gliomas usually originate from the pons part of the brainstem and can extend rostrally and caudally, making total resection impossible. Although the average age at diagnosis is 7, they are most commonly observed in children aged 5-10 years, and the average survival time is typically less than one year (25).

Recent molecular biological studies have identified histone H3 alterations in 85% of these gliomas (26). The 2016 WHO classification introduced the term "diffuse midline glioma, H3 K27M-mutant" in reference to the presence of an amino acid mutation in histones 3.3 and 3.1 (27). In the 2021 WHO classification, these tumors have been renamed diffuse midline gliomas, H3 K27-altere, to account for other possible molecular changes (7).

Because of the tumor's infiltrative nature and the delicate structures of the brainstem, diagnostic surgery is not recommended, and diagnosis is made through MRI (28). On T1-weighted MR images, the lesions appear hypointense, whereas on T2-weighted images, they have a heterogeneous hyperintense appearance, with patchy contrast enhancement observed on contrast-enhanced series. Pediatric diffuse infiltrative brainstem gliomas still have an extremely poor prognosis. Focal conventional RT (total dose of 60Gy, 1.5-2 Gy/day, approximately 6 weeks) is administered as the standard treatment (29). Various CT applications and agents, such as adjuvant CT, pre-RT CT, high-dose CT, and concurrent CT-RT, have been attempted without significant improvement in survival duration (30). However, research on monoclonal antibodies, immunotherapy, and various CT protocols ongoing.

Less Common Primary Posterior Fossa Tumors in Children

Atypical Teratoid Rhabdoid Tumor

Atypical teratoid rhabdoid tumor (ATRT) is a rare embryonal tumor, highly vascularized, and aggressive, constituting 1-2% of childhood brain tumors (31). It predominantly affects children under the age of 2 years and is more common in males. The usual location is the posterior fossa. Radiological findings are non-specific; they can mimic the morphological features of choroid plexus papillomas and medulloblastomas. Although some reports indicate better outcomes, the average survival time is less than one year.

In the WHO 2021 classification, ATRTs are categorized under the heading of "Other Embryonal Tumors of the Central Nervous System" (7). ATRTs are currently divided into three subgroups based on gene overexpression: AT/RT-MYC, AT/RT-SHH, and AT/RT-TYR. AT/RT-SHH and AT/RT-TYR commonly occur in the posterior fossa. While AT/RT-TYR is typically seen in infants under 2 years of age, AT/RT-SHH is more prevalent in older children (32).

Radiological findings are non-specific. ATRTs can appear as heterogeneously thick-walled cystic masses with extensive necrosis, hemorrhage, or calcification areas. Immunohistochemistry is valuable for differential diagnosis. Rhabdoid cells, EMA, SMA, and vimentin are positive biomarkers. The absence of INI1 staining is also significant (33). Molecular studies have shown mutations in the rhabdoid tumor suppressor gene (INI1/hSNF5), a member of the SWI/SNF chromatin remodeling complex, on the long arm of chromosome 22q11 in ATRTs. The most definitive diagnosis of ATRTs currently is made through immunohistochemical or fluorescence in situ hybridization demonstration of inactivation or deletion of SMARCB1/INI1, along with loss of expression in tumor cell nuclei, and focal positivity for EMA and smooth muscle actin (34).

Optimal treatment for atypical teratoid rhabdoid tumors remains uncertain. Despite treatment regimens consisting of maximal surgical resection, focal and craniospinal RT, and multiple chemotherapeutic agents, the course of the disease is poor. Most cases show rapid recurrence and progression, leading to a high mortality rate.

Hemangioblastoma

Although hemangioblastomas constitute 1-3% of intracranial masses in all age groups, they are less common in children. Up to 25-40% of cases are associated with Von Hippel-Lindau (VHL) syndrome, in which multiple masses can be present. Cases related to VHL syndrome generally occur in younger patients. Approximately 48% of VHL-associated hemangioblastomas are located in the cerebellum and 12% in the brainstem (35).

VHL disease results from mutations in the VHL gene on chromosome 3p25-26, leading to the loss of function of the pVHL tumor suppressor protein. The main function of this protein is the regulation of vascular endothelial growth factor, and its loss leads to neoplastic formations such as hemangioblastoma (36).

On MRI, the tumor cyst appears isointense to cerebrospinal fluid on T1-weighted sequences and isohyperintense on T2-

weighted sequences. Hemorrhagic findings are common. The tumor nodule stains intensely with the contrast material. Digital subtraction angiography may show tumor staining and varying degrees of arteriovenous shunts (37).

In cases of both sporadic and VHL-associated cerebellar hemangioblastomas, the goal is the total removal of the tumor to prevent residue and recurrence, following general principles. In sporadic cases with a single lesion, surgical treatment is preferred, and most cases do not recur following complete resection (35). Hemangioblastomas are highly vascularized by nature; hence, preoperative embolization may be considered in some cases to facilitate surgery.

For patients with VHL-associated hemangioblastomas who undergo multiple surgeries throughout their lives, craniospinal and infratentorial RT is considered an important potential treatment option. It is believed to reduce the tumor growth rate compared with its natural course, decrease the number of surgical interventions, and improve overall management (38).

Schwannoma

Schwannomas comprise 6-8% of intracranial primary tumors. Approximately 80-90% of all cerebellopontine angle tumors originate from the 8th cranial nerve and are known as acoustic schwannomas, whereas approximately 8% originate from the 5th cranial nerve and are called trigeminal schwannomas (39). In the pediatric age group, schwannomas constitute approximately 2% of posterior fossa tumors and are much less common compared with the adult population. In children, they can occur sporadically but are often associated with neurofibromatosis type 2 (NF2).

Diagnosis is made earlier in patients with NF2 than in sporadic cases because of characteristic symptoms of NF2 or the mass effect of bilateral vestibular schwannomas (39). The most significant indicators of disease severity are the age of symptom onset and the age at diagnosis. The majority of NF2 patients have vestibular schwannomas (40). NF2 diagnosis criteria include 1) bilateral vestibular schwannomas or a family history of NF2 and 2) the presence of unilateral vestibular schwannomas at a young age or any two of meningiomas, gliomas, schwannomas, juvenile posterior subcapsular lenticular opacities/juvenile cataracts (39,41). Developments in molecular biology have shown that defects on chromosome 22q12 are involved in the development of both sporadic and NF2-associated vestibular schwannomas.

On MRI, schwannomas appear as well-circumscribed, isointense or hypointense on T1-weighted images and hyperintense on T2. They show homogeneous contrast enhancement. Large tumors may show heterogeneous enhancement in the presence of intratumoral hemorrhage or cystic components (42). Histopathological examination is essential for a definitive diagnosis.

Asymptomatic vestibular schwannoma cases in NF2 patients or those with normal hearing on the lesion side can be managed conservatively regardless of mass size, as schwanomas are very slow-growing tumors. However, if there is hearing deterioration or other neurological symptoms, other treatment options should be considered. These include surgery and stereotactic radiosurgery (SRS). Surgery is preferred if the tumor size exceeds 1.5 cm, shows rapid progression even if smaller than 1.5 cm, or causes brainstem compression or hydrocephalus (43). The goal of surgery is total tumor resection although subtotal resection may be necessary to preserve the facial and vestibular nerves. Patients who benefit most from surgery are those with a small tumor diameter, better hearing function, younger age, and no family history or symptoms of NF2 (43).

The effectiveness of SRS in treating vestibular schwannomas is indisputable, and research in this area is increasing, especially as the main principles in NF2 treatment are function preservation, symptom relief, and quality of life improvement. Studies suggest that outcomes are better when diagnosed early (44). However, debates continue regarding SRS treatment in children because of the unexplored risks of radiation therapy at a young age.

Cerebellar Gangliocytoma (Lhermitte-Duclos Disease)

Dysplastic cerebellar gangliocytoma, also known as Lhermitte-Duclos disease (LDD), is a disorder characterized by abnormal development and hamartomatous features of the cerebellum. Although histologically overlapping with gangliocytoma, it is more of a hamartomatous malformation with enlarged dysplastic cells than a true neoplasm (45). In the 2016 WHO classification, it is listed under "glioneuronal and neuronal tumors" as "Dysplastic Gangliocytoma of the Cerebellum, Lhermitte-Duclos disease" and is considered a benign (WHO Grade I) tumor (6).

This rare pathology, which can occur at any age but more frequently in late childhood and adolescence, has recently been associated with phacomatosis and Cowden syndrome (CS) (45). CS is a very rare, autosomal dominant condition closely associated with malignant tumors (46). Approximately 40% of LDD cases are proposed to be associated with CS. In addition, there are sporadic cases of LDD that occur in childhood.

Histopathologically, there is diffuse hypertrophy in the granular layer and mature ganglion cells with dysplastic features.

The presence of perivascular lymphocytic infiltration and the absence of glial neoplastic characteristics are important for diagnosis. Immunohistochemically, loss of PTEN protein production is frequently observed, with most mutations reported in the germline. Staining of neurofilaments, MAP2 protein, synaptophysin, chromogranin A, and S-100 proteins has also been demonstrated (47).

In LDD, the lesion is located in the cerebellar hemispheres and vermis. Bilateral LDD involving both cerebellar hemispheres has been reported. On MRI, T1-weighted sequences showed linear hypointense structures and T2-weighted sequences showed typical tiger-stripe-like hypertrophy of the cerebellar folia. Concomitant white matter atrophy is also present.

In LDD patients with CS, conservative treatment may be an option if there are no neurological signs or symptoms of cerebellar gangliocytoma and the tumor progresses slowly. However, the possibility of tumor progression should be considered during follow-up. There are two surgical options. If symptoms related to hydrocephalus develop, a shunt can be placed. The other option is surgical resection. There is no capsule formation at the margins of LDD, and it is a diffuse tumor, making it difficult to distinguish from normal cerebellar tissue. Therefore, surgical resection can be challenging and carries a risk of morbidity.

Epidermoid Tumors

Epidermoid tumors are rare benign tumors that arise from intracranial remnants due to incomplete separation of the neuroectoderm from the cutaneous ectoderm during neural tube closure. They contain cholesterol and desquamated keratin. These tumors constitute less than 1% of all intracranial tumors, with approximately half occurring in the cerebellopontine area (48).

Depending on their location, they are closely associated with cranial nerves and vascular structures and tend to grow slowly. On MRI, they appear hypointense on T1-weighted images and hypohyperintense on T2-weighted images, with signal intensities similar to those of cerebrospinal fluid. They typically show diffusion restriction on diffusion-weighted imaging, which helps distinguish them from arachnoid cysts (49).

Total resection is recommended to minimize the risk of postoperative aseptic meningitis, hydrocephalus, and tumor recurrence. However, aggressive resection can often lead to cranial nerve damage or ischemic deficits. Therefore, some sources report that total resection is only achievable in 50-80% of epidermoid tumor cases (50). There is limited information in the literature regarding the effectiveness of RT. A successful small case series treated with Gamma Knife Radiosurgery and external-beam RT as treatment options has been reported.

CONCLUSION

Recent studies aimed at understanding tumor biology and new imaging techniques are striving for a more accurate understanding of pediatric posterior fossa tumors. Thus, the application of accurate diagnosis and treatments can lead to a better quality of life and improved survival. All these approaches are possible with the multidisciplinary work of clinics such as neurosurgery, pediatrics, radiology, and medical and radiation oncology.

Ethics

Peer-review: Internally peer reviewed.

Authorship Contributions

Concept: S.A., K.O.Y., Design: S.A., R.B., Analysis or Interpretation: S.A., G.P., Literature Search: S.A., K.O.Y., R.B., Writing: S.A., G.P.

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ORIGINAL ARTICLE

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Investigation of the Effectiveness of Misoprostol and Foley Catheter Use Alone or Together in Second Trimester Pregnancy Terminations

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Abstract

Objective: To compare the effectiveness of misoprostol only, Foley's catheter only, and combined misoprostol plus Foley's catheter for second-trimester pregnancy terminations.

Methods: This retrospective study comprised 146 patients who underwent second-trimester pregnancy termination. Patients were divided into three groups: group 1 (n=62), misoprostol alone; group 2 (n=35), Foley catheter alone; and group 3 (n=49), combined group (Misoprostol plus Foley's catheter). The primary outcome in our study was determined by comparing the induction-abortion interval between methods. Secondary outcomes were termination in the first 24 h, complications including surgical removal of the placenta, and uterine rupture.

Results: According to the termination methods, the total termination time of the cases, the duration of hospital stays, and the termination rates in the first 24 h did not show statistically significant differences according to the procedures performed (p>0.05). The doses of misoprostol in nullipara and multiparous cases were statistically significantly higher in those who received misoprostol alone than those who received Foley + Misoprostol (respectively p=0.029; p=0.002). It was found that misoprostol dose was statistically significantly lower in those with a history of cesarean delivery (p=0.004).

Conclusion: Although the methods used in second trimester pregnancy terminations are not superior to each other in terms of efficiency, the combined method may be preferred in reducing the side effects associated with misoprostol, including a severe condition such as uterine rupture, in those with a history of cesarean section.

Keywords: Cervical ripening, foley catheter, misoprostol, pregnancy termination, second trimester

INTRODUCTION

Second-trimester termination of pregnancy is a common obstetric procedure that constitutes 10-15% of all terminations (1). Cervical ripening is essential for the smooth termination. Various pharmacological and mechanical methods have been used for cervical ripening (2-5). Misoprostol is one of the most frequently used pharmacological methods in second trimester pregnancy termination because it is safe, effective, and easy to use (2,3,6). Although a dose of 400 mcg every 4-6 h misoprostol is effective in the second trimester pregnancy termination, it lacks safety in women with previous uterine surgery and has a risk of uterine rupture (7). The recommended dose of misoprostol in patients who have undergone uterine surgery is 100 mcg or less to reduce the risk of uterine rupture. However, this reduction in drug dose causes a prolonged induction-expulsion time (8). Foley catheter, which is one of the cervical ripening methods, is cheap, effective, and safe. In addition to its mechanical effect, it also increases prostaglandin release

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by causing separation of membranes, particularly on the cervix (9).

We designed this study to compare the effectiveness, safety, and acceptability of misoprostol only, Foley's catheter only, and combined misoprostol plus Foley's catheter in second trimester pregnancy termination.

METHODS

In this retrospective study, second trimester pregnancy terminations at the Sakarya University Training and Research Hospital Department of Obstetrics and Gynecology between December 2016 and September 2020 were evaluated. Because the data were collected retrospectively, informed consent was not required. This study was approved by the local ethics committee according to the principles outlined in the Declaration of Helsinki (71522473/050.01.04/562). Inclusion criteria in the study: second-trimester single pregnancy between 14 and 28 weeks of gestation. Patients with a pregnancy less than 14 weeks and greater than 28 weeks, multiple pregnancies, low-lying placenta (lower located placenta) or placenta previa, patients with chorioamnionitis findings, maternal systemic diseases, coagulation disorders, misoprostol, or latex allergy were excluded from the study. One hundred and 46 patients were included in our study. The hospitalization files of these patients between the specified dates were reviewed. The official termination decisions of the cases in our study were confirmed in the registry book of our hospital, where terminations were recorded.

In our study, patients were divided into 3 groups. Group 1 (n=62); misoprostol alone with a standard regimen of moistened misoprostol (400 mcg) 4 h intravaginally was used until abortion, group 2 (n=35); Foley catheter alone, intracervical Foley catheter no. 14-16 Fr inserted, inflated with 30 mL of normal saline and strapped to the thigh and kept in place until it was expelled spontaneously. Group 3 (n=49); Combined group intracervical Foley catheter inserted with a standard regimen of moistened misoprostol (400 mcg) 4 h intravaginally was used.

In both groups, age, gestational age, body mass index (BMI), parity, previous birth history, number of previous cesarean sections, termination indications, methods applied, and results obtained depending on the method values before and after termination and indication for termination were retrieved from medical records.

The primary outcome in our study was determined as the comparison of induction - abortion time between methods. In addition, as secondary outcomes, termination in the first 24 h and complications including surgical removal of the placenta and uterine rupture were analyzed from the medical records.

Statistical Analysis

The Number Cruncher Statistical System 2007 (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 to normal distribution was tested by Kolmogorov-Smirnov, Shapiro-Wilk test, and graphical evaluations. Student's t-test was used for 2 group comparison of variables showing normal distribution, and Mann-Whitney U test was used for those not showing normal distribution. A one-way ANOVA test was used to compare three or more customarily distributed groups, and the Bonferroni test was used for paired comparisons. The Kruskal-Wallis test was used to compare three or more groups that did not show normal distribution. In comparing qualitative data, the Pearson chi-square test, Fisher's Exact test, and Fisher-Freeman-Halton exact test were used. Significance was assessed at least at the $p<0.05$ level.

RESULTS

In this study, 146 cases who underwent second trimester pregnancy termination were evaluated. The ages of the patients ranged from 17 to 44 years, with a mean of 30.01±6.39 years. The distribution of demographic and obstetric characteristics of all patients is shown in Table 1. The age, parity, and BMI measurements of the patients did not significantly differ between the groups ($p>0.05$) (Table 1).

A statistically significant difference was found in terms of the gestational weeks of the cases according to the termination methods applied ($p=0.001$; $p<0.01$) (Table 1). According to the paired comparisons made, the gestational weeks of the misoprostol applied cases were significantly lower than those of the Foley and Foley + misoprostol applied cases ($p=0.001$; $p=0.001$; $p<0.01$, respectively). There was no statistically significant difference between the gestational weeks of the Foley and Foley + Misoprostol cases ($p>0.05$). As indicated in Table 1, the termination indications of the cases according to the methods did not show a statistically significant difference ($p>0.05$).

According to the termination methods, the induction to abortion interval of the cases, the duration of hospital stays, and the termination rates in the first 24 h did not show a statistically significant difference according to the procedures performed ($p>0.05$) (Table 2).

Table 1. Demographic characteristics of the participants

		Misoprostol (n=62)	Foley (n=35)	Foley + misoprostol (n=49)	p value
Age (years)	Min-max (median)	20-44 (28.5)	18-43 (30)	17-43 (31)	[a]0.722
	Mean ± SD	30.08±6.25	30.63±7.01	29.49±6.18	
Body mass index (kg/m²)	Min-max (median)	18.6-31.2 (23.4)	18.6-31.2 (23.4)	18.6-30.5 (26)	[a]0.129
	Mean ± SD	23.87±3.89	24.35±4.26	25.35±3.41	
Parity	Nulliparity	22 (35.5%)	13 (37.1%)	12 (24.5%)	[b]0.362
	Multiparity	40 (64.5%)	22 (62.9%)	37 (75.5%)	
Gestational age (weeks)	Min-max (median)	14-25 (17)	14.4-28 (20)	15-28 (20)	**[a]0.001****
	Mean ± SD	17.53±2.73	20.03±3.37	20.19±3.24	
Previous birth history	Nulliparous	22 (35.5%)	13 (37.1%)	12 (24.5%)	**[c]0.009****
	History of vaginal delivery	29 (46.8)	13 (37.1%)	13 (26.5%)	
	History of cesarean section	11 (17.7%)	9 (25.8%)	24 (49.0%)	
Number of previous cesarean sections	0	51 (82.2%)	26 (74.3%)	25 (51.0%)	**[c]0.004****
	1	7 (11.3%)	4 (11.4%)	15 (30.6%)	
	2	4 (6.5%)	2 (5.7%)	7 (14.3%)	
	≥3	0	3 (8.6%)	2 (4.1%)	
Indications for pregnancy termination	Fetal anomalies	34 (54.8%)	25 (71.4%)	30 (61.2%)	[c]0.609
	Intrauterine fetal demise	7 (11.3%)	2 (5.7%)	7 (14.3%)	
	Amnion fluid abnormalities (PPROM. anhydroamnios)	20 (32.3%)	7 (20.0%)	11 (22.4%)	
	Others (maternal teratogen exposure)	1 (1.6%)	1 (2.9%)	1 (2.0%)	

[a]One-way ANOVA test, [b]Pearson chi-square test, [c]Fisher Freeman Halton Exact test, **p<0.01. PPROM: Preterm premature rupture of membranes, SD: Standard deviation

Table 2. Clinical outcomes of the groups

		Misoprostol (n=62)	Foley (n=35)	Foley + misoprostol (n=49)	p value
Induction to abortion interval (hours)	Min-max (median)	1.5-76 (12)	2-75 (13)	3.5-76 (15)	[d]0.279
	Mean ± standard deviation	16.1±14.13	18.43±14.89	19.92±15.57	
Completed termination in 24 hours	Yes	49 (79%)	27 (77.1%)	34 (69.4%)	[b]0.484
	No	13 (21%)	8 (22.9%)	15 (30.6%)	
Duration of hospital stay (hours)	Min-max (median)	7.5-85 (20)	9-86 (20)	8-82 (21.4)	[d]0.322
	Mean ± standard deviation	23.47±14.24	25.02±15.56	26.85±15.4	
Fever	Yes	1 (1.6%)	0	4 (8.2%)	[c]0.130
	No	61 (98.4%)	35 (100%)	45 (91.8%)	
Tachycardia	Yes	7 (11.3%)	2 (5.7%)	5 (10.2%)	[c]0.718
	No	55 (88.7%)	33 (94.3%)	44 (89.8%)	
Bleeding	Yes	4 (6.5%)	0	2 (4.1%)	[c]0.382
	No	58 (93.5%)	35 (100%)	47 (95.9%)	
Surgical removal of the placenta	Yes	8 (12.9%)	3 (8.6%)	3 (6.1%)	[c]0.486
	No	54(87.1%)	32 (91.4%)	46 (93.9%)	
Blood transfusion	Yes	1 (1.6%)	0	2 (4.1%)	[c]0.602
	No	61 (98.4%)	35 (100%)	47 (95.9%)	
Uterine rupture		0	0	0	

[b]Pearson chi-square test, [c]Fisher Freeman Halton Exact test, [d]Kruskal-Wallis test

In terms of the induction to abortion interval, it was found that there was no statistically significant difference between the methods when nulliparous, multiparous, those with a history of vaginal delivery, and those with a history of cesarean section were evaluated among themselves, and these groups were compared with each other.

According to the methods, the rates of fever, tachycardia, bleeding, curettage (surgical removal of the placenta), and need for blood transfusion did not show statistically significant differences (p>0.05) (Table 2). Uterine rupture was not observed in any case (Table 2). The doses of misoprostol in nulliparous and multiparous cases were significantly higher in those who received misoprostol alone than those who received Foley + Misoprostol (respectively p=0.029; p=0.002) (Table 3). The misoprostol dose was statistically significantly lower in those with a history of cesarean delivery (p=0.004) (Table 4). The induction to abortion interval did not differ statistically significantly according to the methods in those with a cesarean delivery history (p>0.05) (Table 5).

DISCUSSION

Misoprostol is a widely used pharmacological agent that stimulates uterine contractility and cervical ripening (10). Despite this frequent usage, there is no consensus on the administration route and interval. Uterine rupture is a life-threatening complication of misoprostol administration for second-trimester pregnancy termination, and it can occur with a scarred and unscarred uterus (11). Ho et al. (12) stated that care should be taken when using misoprostol because of the increased uterine sensitivity to prostaglandins and the risk of uterine rupture as the gestational week progresses, and it would be wise to have a lower dose of misoprostol and less frequency of administration in advanced weeks of gestation. However, no rupture was reported in a study conducted by Dickinson (13) in 720 women with one or more previous cesarean section histories in which pregnancies between 14 and 28 weeks were terminated with misoprostol. In our study, in accordance with the literature, no rupture was found in all patient groups, including nulliparous, multiparous, and those with a previous cesarean section history.

Table 3. Evaluation of misoprostol dose according to parity and previous delivery history when used alone or in combination

Parity/previous delivery history	Dose of misoprostol (mcg)	Misoprostol	Foley + misoprostol	p value
Nulliparous	N	22	12	[c]**0.029***
	Min-max (median)	200-3,200 (1,000)	200-3,200 (400)	
	Mean ± SD	1236.36±834.12	783.33±811.10	
Multiparous	N	40	37	[c]**0.002****
	Min-max (median)	200-2,800 (1,000)	50-3,200 (600)	
	Mean ± SD	1,115±624.10	744.59±679.03	
History of vaginal delivery	N	29	13	[c]0.174
	Min-max (median)	400-2,800 (1,200)	200-3,000 (600)	
	Mean ± SD	1165.52±611.95	1053.85±959.70	
History of cesarean section	N	11	24	[c]0.080
	Min-max (median)	200-2,400 (1,000)	50-1,400 (400)	
	Mean ± SD	981.82±666.06	577.08±397.27	

[c]Mann-Whitney U test, *p<0.05, **p<0,01, SD: Standard deviation

Table 4. Comparison of misoprostol dose by parity and previous cesarean delivery history

Dose of misoprostol (mcg)					
	N	**Mean ± standard deviation**	**Min-max**	**Median**	**p value**
Nulliparous	34	1076.47±842.82	200-3,200	800	[c]0.563
Multiparous	77	937.01±673.04	50-3,000	800	
Patients with no prior cesarean section	76	1106.57±775.85	200-3,200	1,000	[c]**0.004****
Patients with prior cesarean section	35	704.29±523.05	50-2,400	600	

[c]Mann-Whitney U test, **p<0.01, min: Minimum, max: Maximum

Table 5. Comparison of methods in those with previous cesarean delivery history					
		Misoprostol (n=11)	Foley (n=9)	Foley + Misoprostol (n=24)	p value
Induction to termination interval (hours)	Min-max (median)	2-51.5 (13.4)	2-75 (16.5)	3.5-76 (13.7)	[d]0.878
	Mean ± SD	18.3±14.33	23.22±22.94	18.05±15.29	
[d]Kruskal-Wallis test, SD: Standard deviation, min: Minimum, max: Maximum					

Foley catheter is a mechanical method commonly used in labor induction. Few side effects, simple applicability, and cost-effectiveness are the factors that make this method attractive. Although there are studies on using Foley catheters in labor induction in third-trimester pregnancies, data on its use in second-trimester pregnancy termination are limited (14-16). Rab et al. (17) compared the Foley catheter and double-balloon catheter in patients with a previous cesarean section history of 20 weeks and whose pregnancy was planned to be terminated due to fetal death and found that the time from balloon placement to delivery was shorter in the Foley catheter group. In our study, in which only 14-28 weeks of gestation were examined, the mean induction to abortion interval was 23.22±22.94 hours in the Foley catheter group in 44 patients with a history of cesarean section during these weeks. This difference can be explained by the fact that the patient group in our study was at lower gestational weeks, and consequently, cervical maturity was lower. In a study by Demirezen et al. (18) comparing foley catheter and double-balloon catheter in 91 pregnant women scheduled for termination between 14 and 28 weeks of gestation, the time between induction and delivery was shorter in the foley catheter group. In our study, it is noteworthy that the induction to abortion interval and the duration of hospital stay were shorter from this study.

In a study investigating the effectiveness of Foley catheter traction in mid-trimester delayed abortions, termination occurred in a shorter time in the traction group than in the non-traction group (19). In this study, the mean week of gestation was lower than that in our study, and more patients were evaluated. Based on the time between induction and termination as the method's success, the termination time in this study was similar to that in our study (19).

Toptas et al. (20) involving 91 patients between 13 and 26 weeks of gestation, only misoprostol was used in one group and misoprostol and Foley were used in the other group, and they showed that the combined method did not provide an additional benefit in terms of efficacy, similar to our study. In the study conducted by Rezk et al. (21), which excluded pregnant women with a history of uterine scarring, unlike our study, the time between induction and abortion was shorter in the combined group than in the other groups.

Ercan et al. (14) stated that combining misoprostol and Foley in second-trimester pregnancy terminations resulted in shorter induction termination intervals and less need for misoprostol compared with misoprostol alone, especially in women with 2 or more cesarean sections with high rupture risk. El Sharkwy et al. (15) compared the use of low-dose misoprostol alone with misoprostol and Foley catheter in late second-trimester pregnancy terminations in patients with a previous history of multiple cesarean sections. They found that the combined method had a shorter induction-termination time and required less misoprostol (15). In our study, we found that the dose of misoprostol was lower with combined use. However, this method shortened the induction to abortion interval only in the cesarean section group compared with misoprostol alone although it was not statistically significant. The combined methods can be used in women with a history of cesarean section to reduce the risk of severe conditions such as uterine rupture and the side effects associated with misoprostol. In addition, in our study, although the combined method was not statistically significant in the group with a history of cesarean section, it was found that it was associated with less dose requirement and shorter induction to abortion interval.

Study Limitations

The limitations of our study are that it is a retrospective study and Bishop scores were not recorded.

CONCLUSION

Although the methods used in second trimester pregnancy terminations are not superior to each other in terms of efficiency, the combined method may be preferred in reducing the side effects associated with misoprostol, including a severe condition such as uterine rupture, in those with a history of cesarean section. Further prospective studies are required to verify these results.

Ethics

Ethics Committee Approval: This study was approved by the local ethics committee according to the principles outlined in the Declaration of Helsinki (71522473/050.01.04/562).

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ş.K., S.Ö., Design: Ş.K., S.Ö., Data Collection or Processing: Ş.K., O.K., K.G., Analysis or Interpretation: Ş.K., O.K., K.G., Literature Search: Ş.K., O.K., K.G., M.S.B, S.Ö. Writing: Ş.K., K.G., M.S.B., S.Ö.

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ORIGINAL ARTICLE

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The Effect of Serum Laminin Level on Obstetric Outcomes in Pregnants with Preeclampsia

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Abstract

Objective: To evaluate maternal serum laminin level in cases with preeclampsia, and to investigate the relationship of laminin with clinical parameters and perinatal outcomes in this case group.

Methods: In this prospective observational study, 62 pregnant women with preeclampsia and 76 healthy normotensive pregnant women, matched for maternal age and body mass index, were evaluated. Maternal serum laminin levels were measured by ELISA and compared between groups.

Results: Maternal serum laminin levels were significantly higher in the preeclampsia group (p=0.001). Laminin was significantly positively correlated with mean arterial pressure and amount of proteinuria (p=0.005, p=0.000; respectively), while significantly negatively correlated with umbilical cord pH and week of delivery (p=0.000, p=0.001; respectively). ROC curve analysis and Youden's index showed that the optimal threshold for laminin was 53.95 ng/mL when it comes to distinguishing pregnancies with preeclampsia from controls, with 65% sensitivity and 59% specificity.

Conclusion: In conclusion, this study showed that serum laminin levels in pregnant women with preeclampsia were significantly higher than in the healthy normotensive control group. It was also reported that laminin levels were positively correlated with mean arterial pressure and proteinuria. We think that these findings point to the role of laminin in the pathogenesis of preeclampsia.

Keywords: Preeclampsia, laminin, mean arterial pressure, proteinuria, pregnancy

INTRODUCTION

Pre-eclampsia is an important disease that develops in 2-8% of all pregnancies and progresses with maternal, fetal, and neonatal morbidity and mortality (1,2). The pathophysiology of pre-eclampsia has not yet been attributed to a definite cause so far. Inappropriate remodelling of spiral arteries, insufficient cytotrophoblastic invasion associated with uteroplacental hypoperfusion, and endothelial damage caused by antiangiogenic factors released from the is chemic placenta into the maternal circulation are thought to play a role in the pathophysiology of pre-eclampsia. Additionally, an increase in inflammatory cytokines is observed as a result of endothelial damage. Chronic uteroplacental ischemia, immune maladaptation, genetic factors, increased trophoblast apoptosis or necrosis, and an increased inflammatory response against trophoblasts play an important role in the pathophysiology of pre-eclampsia (1,2).

Laminins are a family of glycoproteins that comprise the basement membrane (3). Cell surfaces provide the integrity of the basement membrane by adhering to collagen type IV, heparan sulfate. Laminins trigger intracellular signals by interacting with cell surface receptors to regulate implantation and placentation (3,4). Laminin is required for trophoblast invasion of the uterine decidua and maternal vascular system and for successful embryo implantation (3,4).

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The placenta is an organ rich in the basement membrane (5,6). In some studies, it has been observed that serum laminin values increase during pregnancy with increasing placental volume, remain at high levels after reaching a plateau in the third trimester, and decrease with delivery (7). This relationship between the placenta and laminin may shed light on the pathogenesis of preeclampsia, which develops because of defective placentation.

The aim of our study is to evaluate maternal serum laminin levels in cases with preeclampsia and to investigate the relationship of laminin with clinical parameters and perinatal outcomes in this case group.

METHODS

Our study is a prospective observational study conducted between June 2021 and June 2022 at the University of Health Sciences Turkey Prof. Dr. Cemil Taşcıoğlu City Hospital, Obstetrics and Gynecology Clinic. This included 62 pregnant women with pre-eclampsia and 76 healthy normotensive pregnant women, matched for maternal age and body mass index (BMI), and who presented continuously to the clinic. Women younger than 18 years old and older than 45 years those with multiple pregnancies, presence of fetal anomaly, diabetes, renal or autoimmune disease were excluded from our study.

The diagnosis of preeclampsia was defined as hypertension (systolic and/or diastolic blood pressure of 140 and/or 90 mmHg measured at least 4 hours apart) and proteinuria (≥300 mg in 24 h urine or urine protein/creatinine ratio ≥0.3) beginning after 20 weeks of gestation in a previously normotensive woman. Cases with new-onset hypertension but not accompanied by proteinuria were included in the preeclampsia group if they had the following signs and symptoms, which show end organ tissue damage: headache unresponsive to medical therapy, visual impairment, pulmonary edema, platelet count $<100x10^9$/L, serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease, elevated blood concentrations of liver transaminases to twice normal concentration (1). The case group was divided into subgroups. During this process, pregnant women diagnosed with preeclampsia before 34 weeks of gestation were included in the early-onset preeclampsia (EOPE) group (n=35), whereas pregnant women diagnosed after 34 weeks of gestation were considered to have late-onset pre-eclampsia (LOPE) (n=27) (8).

Five milliliters of venous blood samples were collected from all participants after 12 h of fasting and placed in vacuum tubes without anticoagulant. These tubes were centrifuged at 2,000 rpm for 20 minutes, and the serum samples obtained were placed in an Eppendorf tube and frozen at -40 °C until analysis. The samples were brought to room temperature at the time of analysis. Collected serum samples were measured with Microplate Reader RT 2,100 C and Microplate Washer RT 2,600 C instruments with Human Laminin ELISA kits (Bioassay Technology Laboratory, Shanghai, China, catalog no. E4996Hu). Serum laminin values were measured in pg/mL and the reference range was determined as 6.5-400. This study was approved by the Medical Ethical Committee of the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (no: 236, E-48670771- 514.10; date: 21.06.2021). In our study, which was conducted in accordance with the Declaration of Helsinki, informed consent was obtained from all patients.

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences software version 25.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate the normality of the distribution of the variables. Data were presented as mean ± standard deviation. The Mann-Whitney U test and Kruskal-Wallis test were used for statistical comparisons between groups, and Dunnett's T3 post-hoc test was preferred for multiple comparisons. Categorical variables were expressed as a percentage of the total. Pearson's chi-square independence test was used to examine the interdependence between categorical variables. Pearson correlation analysis was performed to evaluate the correlations between parametric variables. A receiver operating characteristic curve and Youden index were used to determine an optimal laminin cut-off point for the diagnosis of pre-eclampsia. $P<0.005$ value was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the study groups are shown in Table 1. There was no significant difference between the groups in terms of age, gravidity, parity, BMI, and blood collection time. Week of birth, birth weight, umbilical cord pH, and 5th minute APGAR score were found to be significantly lower in the preeclampsia group than in the control group ($p<0.001$, $p<0.001$, $p=0.021$, and $p=0.004$; respectively). Mean arterial pressure (MAP), neonatal intensive care unit requirement, and maternal serum laminin levels were higher in the pre-eclampsia group ($p<0.001$, $p<0.001$, $p=0.001$; respectively).

The comparison of the laminin levels of the pre-eclampsia subgroups is presented in Table 2, 3. Maternal serum laminin

levels were found to be significantly higher in the EOPE group than in the LOPE group (p=0.105).

When the correlation of maternal serum laminin levels with demographic and clinical parameters was examined, laminin showed a significant positive correlation with mean arterial pressure and amount of proteinuria (p=0.005, p<0.001; respectively) and a significant negative correlation with umbilical cord pH and week of delivery (p<0.001 and p=0.004; respectively).

Receiver operating characteristic curve analysis and Youden's index showed that the optimal cut-off of laminin was 53.95 ng/mL to distinguish pre-eclamptic pregnancies from controls, with 65% sensitivity and 59% specificity (area under the curve: 0.664; 95% confidence interval, 0.574-0.753, p=0.001) (Figure 1).

Table 1. Comparison of demographic and clinical features of the cases

	Preeclampsia group (n=62)	**Control group (n=76)**	**p**
Age	32.4±5.5	30.8±5.3	0.054
Gravidity	2.7±1.6	2.5±1.6	0.575
Parity	1.4±1.3	1.2±1.3	0.444
BMI (kg/m²)	31.9±5.2	30.8±4.7	0.174
MAP	111.9±9.3	81.8±5.5	**0.000**
Proteinuria	755.5±1610.4	-	-
Blood collection time	32.3±2.8	32.1±1.7	0.691
Birth week	33.9±5.7	38.3±1.8	**0.000**
Birth weight (g)	2397±993	3176±549	**0.000**
Cord pH	7.31±0.07	7.34±0.04	**0.021**
5' APGAR	8.42±1.4	8.87±0.5	**0.004**
NICU	31/62 (50%)	14/76 (18.4%)	**0.000**
Laminin (pg/mL)	83.9±72.2	50.9±20.1	**0.001**

BMI: Body mass index, MAP: Mean arterial pressure, NICU: Neonatal intensive care unit

Table 2. Comparison of laminin levels between preeclampsia subgroups and the control group

	Laminin (pg/mL)	**p**
EOPE group (n=35)	99.5±86.4	0.105
LOPE group (n=27)	63.8±41.5	**0.007**
Control group (n=76)	50.9±20.1	0.336

EOPE: Early onset pre-eclampsia, LOPE: Late onset pre-eclampsia

Table 3. Correlation of laminin with demographic and clinical parameters

	Laminin	
	R	**p**
Age	-0.089	0.296
BMI	-0.003	0.969
MAP	0.237	**0.005**
Proteinuria	0.566	**0.000**
Cord pH	-0.500	**0.000**
Week of birth	-0.241	**0.004**
Birth weight	0.060	0.481
5' APGAR	0.065	0.448

BMI: Body mass index, MAP: Mean arterial pressure, APGAR: Appearance, pulse, grimace, activity, respiratory

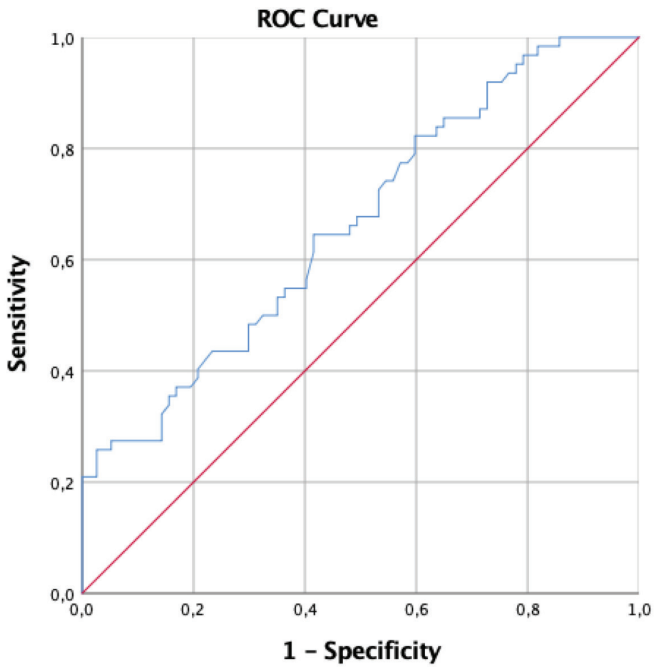

Figure 1. ROC curve for laminin levels

DISCUSSION

In our study, we planned to investigate maternal serum laminin values in pre-eclamptic pregnant women and to evaluate the relationship between laminin levels and laboratory parameters and perinatal outcomes in this case group. We found that maternal serum laminin levels were significantly higher in pregnant women with pre-eclampsia than in the control group in our study. Maternal serum laminin level was especially higher in cases with early-onset pre-eclampsia. In addition, while maternal serum laminin levels showed a significant positive correlation with MAP and the amount of proteinuria, it showed a significant negative correlation with cord pH and week of delivery.

Laminin plays an important role in cell proliferation, migration, and invasion for trophoblast cells and probably contributes to the development of pre-eclampsia by regulating the PI3K/Akt/mTOR signaling pathway in trophoblasts (9). Insufficient adhesion between extravillous trophoblasts and the extracellular matrix during placental formation is a basic element of the pathogenesis of early-onset pre-eclampsia (10,11). In late-onset preeclampsia, although placentation is normal, a widespread inflammatory response triggered by maternal microvascular diseases and hypoxia is observed (11,12). In our study, the reason for the higher maternal serum laminin values in cases with early-onset pre-eclampsia may be the initiation of the destruction of the laminin molecule during the placentation stage. In our study, patients with late-onset preeclampsia had higher serum laminin values than the control group, and we believe that this is related to the widespread systemic inflammatory response involved in the pathophysiology of late-onset pre-eclampsia. Koutroubakis et al. (13) reported that serum laminin levels were higher in the active period in individuals diagnosed with inflammatory bowel disease, in their study in which they compared the cases diagnosed with inflammatory bowel disease, another inflammation-based disease, and the healthy control group. This result is compatible with our study.

Furuhashi et al. (7), in their study in which they compared 19 healthy pregnant women, 21 pregnant women diagnosed with preeclampsia, and 22 healthy women who were not pregnant, found that serum laminin levels increased during pregnancy. This increase in laminin level has been attributed to the increased volume of the basal lamina-rich placenta during pregnancy. In the pre-eclamptic group, serum laminin levels were found to be significantly higher not only during pregnancy but also in the postpartum period compared to the healthy pregnant group (7). These findings point to changes and damage in the composition of the basement membrane. In addition, the same study argued that increased laminin levels may also occur due to glomerular damage, but stated that serum laminin levels did not correlate with the amount of proteinuria, urea, and creatinine values (7). Laminin is a glycoprotein that occupies an important place in the glomerular basement membrane structure, and changes in laminin level may affect villus permeability (14,15). In our study, there was a significant positive correlation between maternal serum laminin levels and proteinuria. The reason for this difference may be the higher number of cases in our study and the fact that we included cases with early-onset and severe pre-eclampsia.

Study Limitations

The main limitations of our study are that it was conducted in a single center and the relatively small sample size. Additionally, investigating laminin levels only in maternal serum and not investigating placental expression of the molecule is another important limitation. The strengths of our study are its prospective design, investigation of the laminin level in pre-eclampsia subgroups, and determination of an optimal threshold value for laminin in the prediction of the disease.

CONCLUSION

In conclusion, this study showed that serum laminin levels in pregnant women with pre-eclampsia were significantly higher

than in the healthy normotensive control group. It was also reported that laminin levels were positively correlated with MAP and proteinuria. We believe that these findings point to the role of laminin in the pathogenesis of pre-eclampsia.

Ethics

Ethics Committee Approval: This study was approved by the Medical Ethical Committee of the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (no: 236, E-48670771- 514.10; date: 21.06.2021).

Informed Consent: Consent was received from the patients who participated in this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ö., N.Ç.Ç., S.G., Concept: H.Ö.Ç., B.Ç., V.M., Design: H.Ö., M.Ö., B.Ç., V.M., Data Collection or Processing: H.Ö., N.Ç.Ç., S.G., Analysis or Interpretation: H.Ö., N.Ç.Ç., M.Ö., Literature Search: H.Ö., S.G., V.M., Writing: H.Ö.Ç., M.Ö., B.Ç.

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ORIGINAL ARTICLE

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The Value of Shear-wave Ultrasonography in Calculating Elastographic Values in Liver Pathologies

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Abstract

Objective: Liver pathologies consist of multiple benign and malignant diseases; shear-wave elastography values vary according to the lesions. In our study, we tried to figure out how to measure the mean shear-wave elastography values in different liver lesions.

Methods: Seventeen focal nodular hyperplasia (FNH), 41 hemangiomas, 25 cysts, and 45 malignant lesions were evaluated in 112 patients who had liver pathology. Twenty patients had hepatosteatosis, and fibrosis was present in 26 patients. B-mode and shear wave ultrasonography examinations were performed on defined pathologies. Malignant lesions were histopathologically diagnosed and benign lesions were evaluated according to cross-sectional examination (computerized tomography and magnetic resonance imaging) methods.

Results: In our study, the average elastography values were determined as 50.38 kilopascals (kPa) and 3.69 meters per second (m/s) in FNH; 12.54 kPa and 1.97 m/s in hemangiomas; 116.47 kPa and 6.34 m/s in malignant lesions; 8.97 kPa and 1.57 m/s in cysts; 16.54 kPa and 2.30 m/s in cases with hepatosteatosis; and 90.98 kPa and 5.44 m/s in cases with liver fibrosis. Mean values in cysts, hepatosteatosis, and hemangiomas were close to normal; in liver fibrosis, malignant lesions, and FNH, they were higher than normal.

Conclusion: We think that shear wave elastography is a promising method for distinguishing benign from malign liver lesions by calculating quantitative values where a biopsy-free diagnosis is preferred in the present day.

Keywords: Diffuse liver diseases, FNH, hemangioma, shear wave ultrasound

INTRODUCTION

Every year, many patients are referred to radiology clinics with the diagnosis of a liver mass. The majority of malignant masses are metastases. But benign lesions of the liver are also frequently observed. Using radiological diagnostic methods correctly is crucial for detecting carcinoma early, determining the most effective treatment, and reducing disease-related fatalities.

Elastography is a new technique that contributes to ultrasonography in the characterization of liver lesions (1,2). This technique gives information about the stiffness of the lesion, as in clinical palpation. There are two methods, strain elastography and shear-wave elastography, in clinical use (1-4). Shear-wave elastography provides quantitative measurement of lesion stiffness (in kPa).

Liver pathologies consist of many benign and malignant diseases; shear-wave elastography values vary according to lesions. In our study, we determined the mean shear-wave elastography values in different liver lesions. In clinical use, we believe that these values may be helpful in the diagnosis of lesions that are unidentified with imaging modalities without a biopsy.

METHODS

The study received the approval of the Human Subjects Ethics Committee, and informed written consent was obtained from

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all subjects. We evaluated 17 focal nodular hyperplasias (FNH), 41 hemangiomas, 25 cysts, and 45 malignant lesions in 112 patients aged between 22 and 76 years who had liver pathology and were referred to our clinic for an abdominal examination, and mean kilopascals (kPa) and meter per second (m/s) values were calculated. Hepatosteatosis was present in 20 patients and fibrosis was present in 26 patients.

The Toshiba Aplio 500 Premium (Tokyo, Japan) device was subjected to a B-mode and shear wave ultrasonography examination for defined pathologies. All individuals were lying in a supine position. Pathologies were evaluated using a 10-megahertz linear probe while patients were holding their breath with shear wave elastography. The region of interest (ROI) was at its minimum size in our study. After elastographic mapping, at least 4-5 measurements were taken from the hardest sections of each pathology, and average values were obtained. Malignant lesions were histopathologically diagnosed, and benign lesions were evaluated according to cross-sectional examination (computerized tomography and magnetic resonance imaging) methods. Patients with indeterminate lesions were not included in the study.

Statistical Analysis

The IBM Statistical Package for the Social Sciences (SPSS) Statistics 20 program was used for statistical analysis. The Independent Samples t-test and F-test (ANOVA) were used, as well as descriptive statistical methods (mean, standard deviation, median, frequency, minimum, and maximum), to determine whether the difference between two groups of variables with normal distribution compared to quantitative data is coincidental or statistically significant. Significance was evaluated at $p<0.05$. Matrix Laboratory R2007b program was used to plot the data. A column graph was drawn using the IBM SPSS Statistics 20 program.

RESULTS

The average elastography values in FNH lesions were 50.38 kPa and 3.69 m/s; 12.54 kPa and 1.97 m/s in hemangiomas (Figure 1); 116.47 kPa and 6.34 m/s in malignant lesions (Figure 2); 8.97 kPa and 1.57 m/s in cysts; 16.54 kPa and 2.30 m/s in cases of hepatosteatosis; and 90.98 kPa and 5.44 m/s in liver fibrosis (Tables 1 and 2).

In our clinic, we found a mean elastography value of 10.49 in the shear wave elastography measurements in healthy subjects with normal laboratory and liver USG findings (Table 3).

In our study, we found that the elastography values were low in lesions with lower stiffness. The mean values in cysts, hepatosteatosis, and hemangiomas were close to those in normal liver parenchyma (slightly lower in cysts, slightly higher in hemangiomas, and hepatosteatosis) (Figure 3). The values were higher in liver fibrosis and FNH lesions and were significantly higher in malignant lesions than in normal lesions (Figure 4).

DISCUSSION

Liver diseases are an important global health problem. Diseases like fatty liver disease, autoimmune and chronic viral hepatitis, and primary biliary cirrhosis cause fibrosis that leads to portal hypertension, liver failure, and hepatocellular carcinoma development.

Correct classification of the degree of fibrosis is critical for treatment planning and for predicting response to treatment and the likelihood of malignancy. Liver biopsy is an invasive

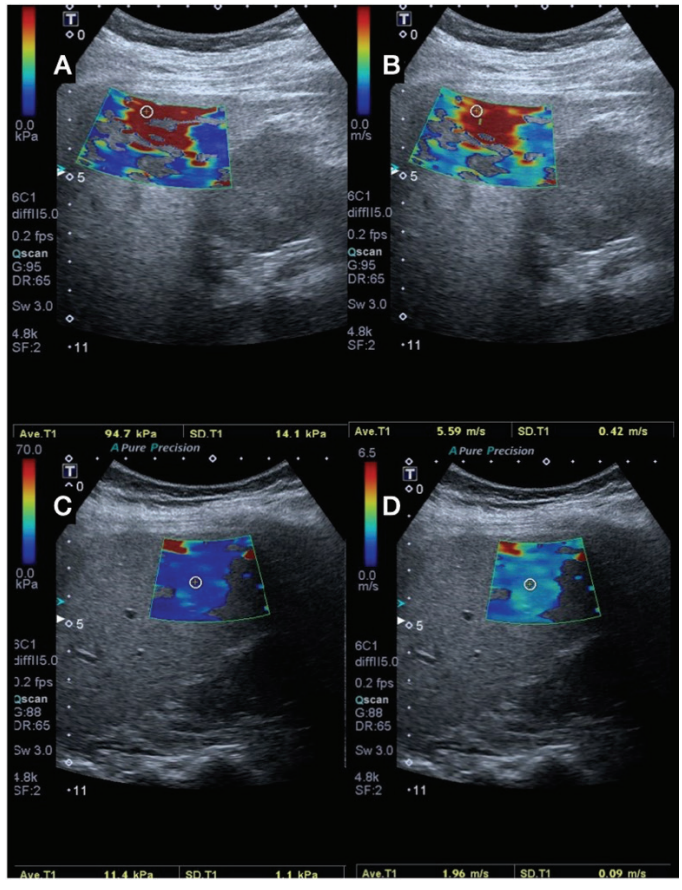


Figure 1. A 48-year-old female patient with focal nodular hyperplasia. Shear wave images are noticeable in kPa (a) and in m/s (b). Another example is a 44-year-old female patient with hemangioma. We can see hyperechoic solid lesion and elastography values in kPa (c) and in m/s (d). Circles depict the area of interest where the measurement is calculated

procedure that includes complications like severe pain and bleeding, despite having been the gold standard method for diagnosis (5,6). However, because of the small sample size from a heterogeneous organ, sampling error is an inherent problem (7), and diagnostic consistency can be affected by interobserver variability (8-10). Therefore, non-invasive techniques to evaluate liver fibrosis have attracted great attention. There are many studies in the literature on the use of serum markers such as the transaminase/platelet ratio index, hyaluronic acid, platelets, and collagen type IV (11). However, they may also be affected by non-hepatic causes.

Elastography can be used to noninvasively assess liver stiffness. Magnetic resonance imaging or ultrasound that applies mechanical stress evaluates tissue response. The optimal conditions in the examination include the patient being hungry, the decubitus position where the right hand is above the head to provide an optimum intercostal approach, resting breathing, placing ROI approximately 1.5-2.0 cm underneath the Glisson capsule to prevent increased subcapsular stiffness and reverberation artifacts, and taking at least 4 measurements.

Point shear wave velocity measurement and slip wave velocity (SWSI) are the two major shear wave methods. The two basic methods used in the PSWSM method are the Virtual Touch Tissue Quantification (VTTQ) method, which shows the results in m/s, and the ElastPQ technique, which shows the results in m/s or kPa. There are countless studies using the VTTQ technique available, but there are very few studies using ElastPQ. The repeatability of the VTTQ method is high, with correlation coefficients ranging from 0.84 to 0.87 (12-15). Training the operator is not required (13). Similarly, the interobserver values

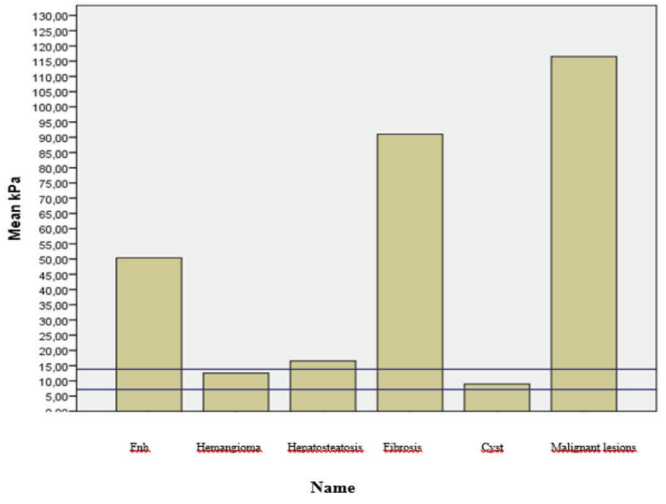
Table 1. Mean elastography values of liver lesions

	kPa	m/s
FNH	50.3765	3.6947
Hemangioma	12.5439	1.9685
Hepatosteatosis	16.545	2.306
Liver fibrosis	90.9808	5.4431
Cyst	8.9708	1.5744
Malignant lesions	116.4756	6.3398

Table 2. Comparison of mean elastography values

Liver right lobe					
ave t1(m/s)	31	2.20	1.75	1.36	11.48
SD t1(m/s)	31	0.27	0.51	0.08	3.00
kPa	34	10.49	3.30	5.40	17.70
SD t1 kPa	34	2.01	1.05	0.50	5.00

Table 3. Normal liver elastography values



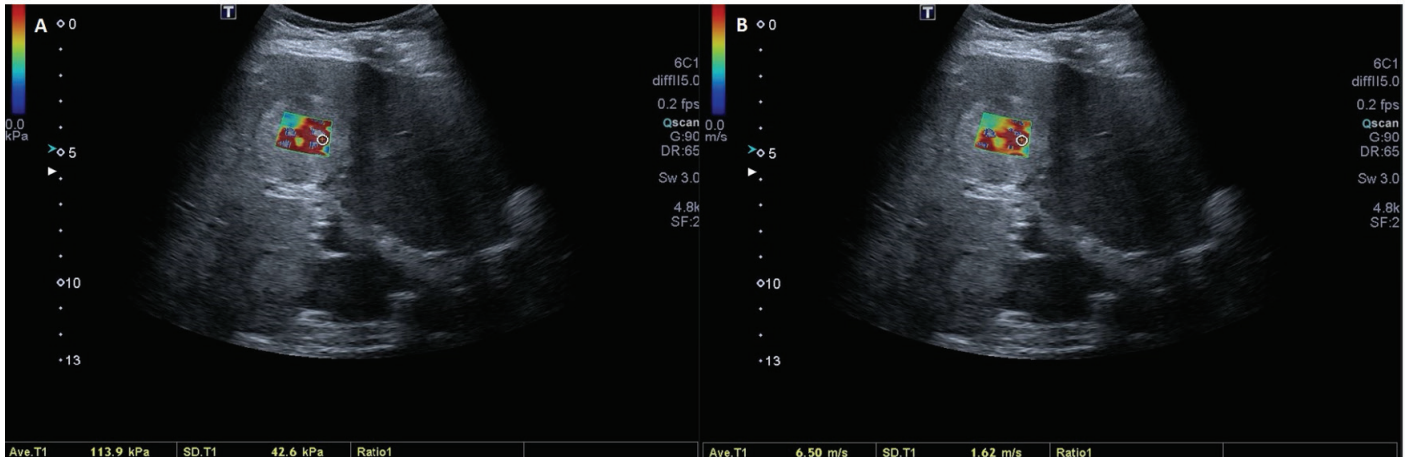


Figure 2. A 62-year-old male patient with hepatocellular carcinoma. Heterogeneous hyperechoic solid lesion and elastography values can be seen in kPa (a) and in m/s (b). The area of interest where the measurement is calculated is represented by circles

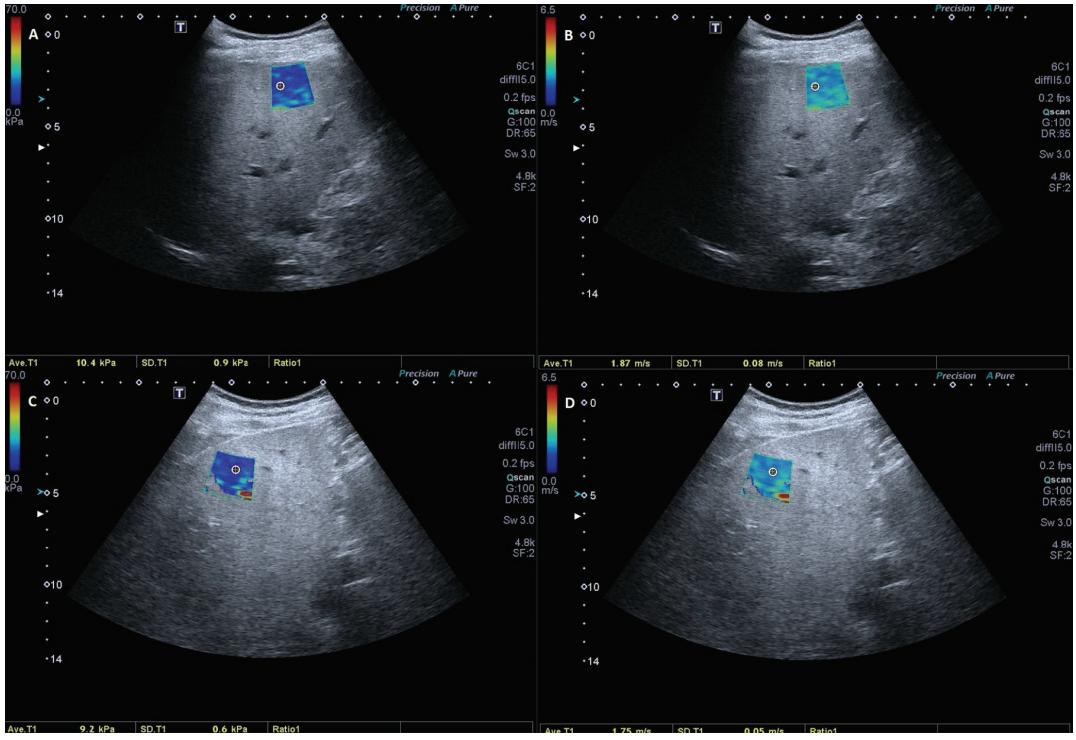


Figure 3. A pure cyst in a 52-year-old male patient; shear wave images are shown in kPA (a) and m/s (b). 36-year-old female patient with hepatosteatosis. Shear wave images are displayed in kPA (c) and m/s (d). Circles depict the area of interest where the measurement is calculated

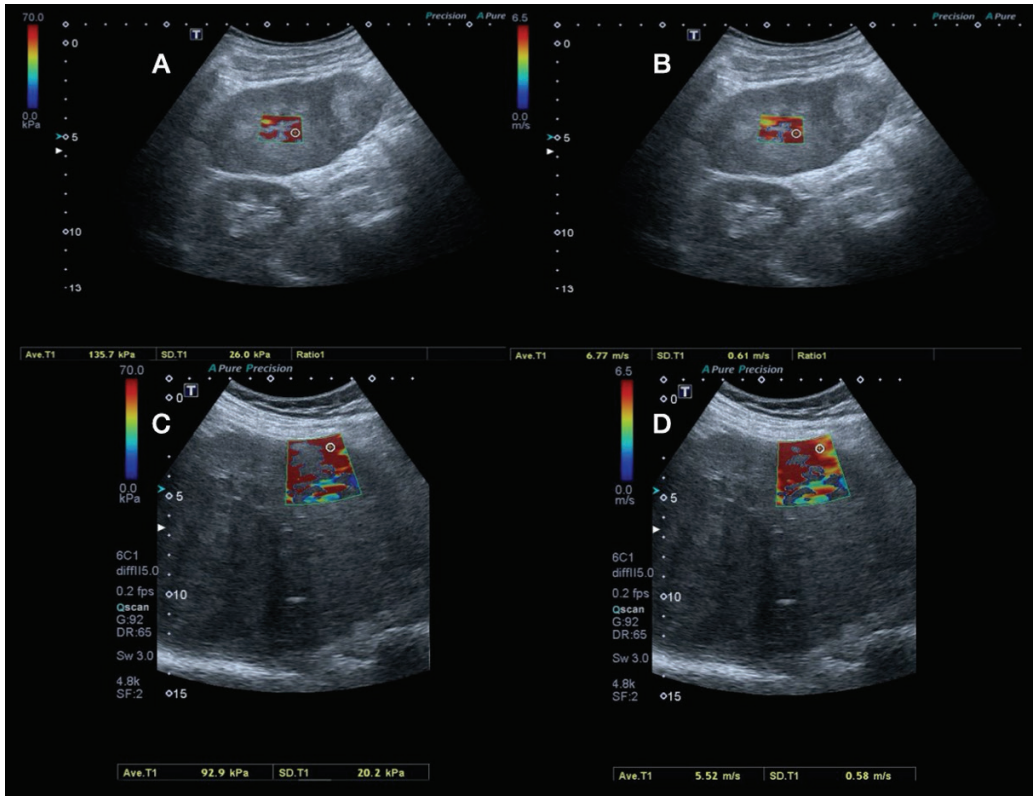


Figure 4. Multiple liver metastases in a 72-year-old male patient; shear wave images can be seen in kPA (a) and m/s (b). 62-year-old male patient with liver fibrosis. Shear wave images are shown in kPA (c) and m/s (d). The area of interest where the measurement is calculated is represented by circles

for the ElastPQ technique range from 0.83 to 0.93 (16), which shows that it is easy to repeat.

In healthy volunteers, PSWSM values with VTTQ can be found in various publications (17-19). In all of these studies, the values were lower than those of chronic hepatitis patients (<1.2 m/s). Liver stiffness increases significantly with food intake (20). The average PSWSM value obtained with ElastPQ is 3.5 kPa in healthy volunteers (21).

The cutoff range for each fibrosis stage is quite wide. The values of early-stage fibrosis ranged from 1.13 to 1.55 m/s, whereas they were 1.36-2.13 at the advanced stage (21). The largest series included more than 600 patients with chronic liver disease of various etiologies; the cut-off values for fibrosis, severe fibrosis, and cirrhosis in patients with chronic liver disease due to different causes were 1.34, 1.55, and 1.80 m/s, respectively. According to the PSWSM method, TE showed higher diagnostic accuracy for fibrosis and liver cirrhosis, whereas PSWSM and TE sensitivity were similar for the diagnosis of severe fibrosis (22).

In a meta-analysis (12), Bota et al. (12) showed that the PSWSM method had a similar predictive value for liver fibrosis and cirrhosis. In our study, the mean elastography values were found to be 90.98 kPa and 5.44 m/s in patients with liver fibrosis. In an international multicenter study with 181 patients with chronic hepatitis B and 914 patients with chronic hepatitis C, the correlation of PSWSM with histological fibrosis was found to be significantly higher in patients with chronic hepatitis C than in patients with chronic hepatitis B (r=0.653 vs. r=0.511, p=0.007). Similar PSWSM values were determined for each fibrosis stage in both groups (23).

Rizzo et al. (24) showed that PSWSM cut-off values were 1.3 m/s for fibrosis, 1.7 m/s for severe fibrosis, and 2.0 m/s for cirrhosis. In patients with severe hepatic inflammation, TE may exaggerate fibrosis (25). The same limitations were observed in several studies using PSWSM. It was observed that the degree of hepatosteatosis did not affect PSWSM values (24). Likewise, we found similar values for hepatosteatosis in normal liver parenchyma in our study. SWSI shows results in m/s and kPa. Ferraioli et al. (26) determined that the correlation between the expert and novice operators was to be 0.95 and 0.93 on the same day and 0.84 and 0.65 on different days by comparing the measurements. These results were confirmed by Hudson et al. (27) in the study they published.

Poynard et al. (28) found that the feasibility of SWSI was lower than that of TE in a cohort study of 442 patients in whom liver fibrosis was evaluated, in which no gold standard method was used, although the performance of the two methods is similar. Stiffness values were reported not to be associated with hepatosteatosis or necroinflammation (29). In our study, we evaluated the mean elastography values in patients with hepatosteatosis as 16.54 kPa and 2.30 m/s

PSWSM and SWSI can be used to evaluate the severity of liver fibrosis in patients with chronic viral hepatitis, best demonstrated in patients with hepatitis C. However, the available studies are limited to SWSI. In PSWSM and SWSI as TE, the results are accurate when figuring out if someone has mild fibrosis or cirrhosis.

The mean shear wave values were evaluated as 57.91 kPa for malignant tumors and 23.87 kPa for hemangiomas, and the cut-off value was 23.62 kPa in a study on the stiffness of malignant masses and hemangiomas in 20 patients (30). Similarly, in our study, we found that the elastography values of malignant tumors were significantly higher than those of hemangiomas.

Average values were found to be 1.80±0.57 m/s for hemangiomas, 2.66±0.94 m/s for hepatocellular carcinomas, 3.27±0.64 m/s for cholangiocarcinomas, 3.70±0.61 m/s for colon cancer metastases, and 2.82±0.96 m/s for other metastases with the analysis using the ARFI method in the study on 74 patients with 101 benign and malignant tumors (31). According to these results, the mean SW values were significantly higher in hepatic tumor groups than in the hemangiomas.

Brunel et al. (32) determined the mean elastography values as 46.99±31.15 kPa for FNH and 12.08±10.68 kPa for adenomas in a study of 76 liver lesions of FNH and adenomas, which were confirmed by MRI imaging, contrast-enhanced USG, or histologically in 56 patients. In this study, a cut-off value of 18.8 kPa was determined for the differentiation of FNH and adenoma.

Benign liver tumors that develop in healthy livers continue to be important problems in diagnosis and treatment. Conservative treatment is performed most often in patients with FNH. In contrast, treatment of hepatic adenomas is more invasive because of the risk of bleeding and malignant transformation.

There are studies using the ARFI or SWE method in a variety of malignant and benign multiple liver lesions, and some have reported differences between the degrees of hardness of FNH and hepatic adenomas.

Gallotti et al. (33) did not find a significant difference between the elasticity values measured in the adenoma and surrounding healthy liver tissue using the ARFI method. They also reported that FNH was the second most severe lesion after metastases, irrespective of the presence or extent of the central scar. Frulio et al. (34) found that FNHs were the stiffest lesions in benign liver

lesions. In their study with SWE on FNH and adenomas, Guibal et al. (35) found similar results. In our study, we determined that the elastography values in FNH were higher than those in other benign lesions.

Using point shear-wave elastography, Qiu et al. (36) compared the focal fatty change group with the liver mass group. They evaluated the lesion stiffness value, absolute stiffness difference, and stiffness ratio of lesions and found that the liver mass groups' shear wave values were significantly higher than those of the focal fatty change group. They concluded that this technique could reduce the need for additional contrast-enhanced imaging or biopsies when diagnosing mass-like focal fatty changes (36). Wang et al. (37) compared the diagnostic accuracy of SWE and shear wave dispersion (SWD) in the evaluation of hepatic parenchyma in patients with liver malignancies. They found that the optimal SWE cut-off values for S ≥1, S ≥2, S ≥3, and S =4 were 6.9, 7.9, 8.7, and 10.6 kPa, respectively, and determined that SWE was a more accurate predictor of severe fibrosis (S ≥3) and cirrhosis (S =4) than SWD (37).

Although the SWE and ARFI methods are based on the principle of measuring local shear wave velocities from the liver, the former has the advantage of providing real-time imaging and adding mapping of lesion stiffness to B-mode images. This mapping method can help you see the differences in elasticity between the lesion and the surrounding tissue and determine how different the tumoral parenchyma is.

To our knowledge, there is no study that evaluated liver masses with kPa and m/s at the same time. There are some limitations in studies, as in ours. SWSI accuracy was evaluated only on the right lobe at the intercostal space. Interlobar variations were reported with PSWSM at liver stiffness levels. Body structures such as obesity and a narrow intercostal space may hinder the results from being obtained. Because the elastic properties of the tissue show frequency dependance techniques should be used with care and caution when comparing the quantitative results obtained from these techniques. The results determined in kPa are not comparable between TE, PSWSM, and SWSI. Since most studies were conducted in patients with chronic hepatitis C, cut-off values may not apply to non-alcoholic fatty liver disease and other viral etiologies. Non-alcoholic fatty liver diseases were examined in only a small series of patients, and the cut-off values in these patients require further studies. Values may be higher in patients whose hepatic enzyme levels are 5 times the upper limit. Therefore, the influence of inflammation should be considered, and results should always be assessed in the presence of clinical information. Similar to TE, congestive heart failure is probably associated with more severe liver tissue.

Error rates have increased in the elastographic evaluation, especially in the left lobe lesions, depending on the localization and depth of the tumor, the patient's breathlessness, and the heart rate. These conditions make elastography examinations difficult for patients. Although we did not have and could not include enough patients with hepatic adenomas diagnosed histopathologically, the average elastography values we found for FNH were high, and compared with the studies in the literature about hepatic adenomas with relatively low stiffness, this suggests that shear wave elastography may be helpful in differentiating these 2 benign liver lesions (38).

CONCLUSION

We found that shear wave elastography could be helpful in the differential diagnosis of liver lesions by calculating quantitative values in accordance with previous studies. We observed that it could be useful in the differentiation of malignant hepatic tumors from hemangiomas because of their high elastography values. In patients with liver fibrosis, we found that the elastography values increased in parallel with the increased stiffness of the tissue secondary to fibrosis. We calculated lower shear wave values in the cystic lesions of the liver because of the liquid content. In conclusion, shear wave elastography is a promising method for the differentiation of benign and malignant lesions in our study as well as in the literature, where a biopsy-free diagnosis is preferred.

Ethics

Ethics Committee Approval: The study received the approval of the Human Subjects Ethics Committee.

Informed Consent: Informed written consent was obtained from all subjects.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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Diagnostic and Prognostic Value of Blood Lactate Level in Adult Acute Gastrointestinal Bleeding Patients Admitted to the Emergency Department

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Abstract

Objective: In our study, it was aimed to determine the diagnostic and prognostic value of lactate level in patients with gastrointestinal bleeding.

Methods: This study was performed by retrospective screening of the information of patients who applied to the tertiary education and research hospital with acute gastrointestinal bleeding. Data such as lactate level, age, gender, application complaint, known diseases, medications used, physical examination symptoms and findings, laboratory results, endoscopy and/or colonoscopy reports, treatment were collected and their effects on prognosis and mortality were evaluated.

Results: The median age of 506 patients included in the study was 67 (IQR: 53-80) and 61.3% of the patients were male. 87.5% of the patients were upper and 12.5% lower gastrointestinal bleeding. No relation was found between bleeding region and lactate level ($p=0.759$). The lactate level of patients who needed erythrocyte suspension, who underwent intensive care and died, was found to be high ($p<0.001$, $p=0.009$, $p<0.001$, respectively). When the test performance of lactate in predicting mortality was evaluated, the AUC value was calculated as 0.714 cm^2 according to the ROC curve ($p<0.001$). When the cut-off value was taken as 4 mmol/L, the sensitivity of lactate in predicting mortality was 29%, specificity was 91%, positive predictive value was 31%, negative predictive value was 90%, positive likelihood ratio was 3.22 and negative likelihood ratio was 0.78.

Conclusion: Lactate level is a test that can be used as a follow-up parameter in both upper and lower gastrointestinal system hemorrhage cases to confirm diagnosis and predict prognosis. In the cases with high lactate value, more hospitalization time, more erythrocyte suspension supplement requirement, increased risk of hospitalization and death were determined.

Keywords: Gastrointestinal bleeding, lactate, prognosis, mortality

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INTRODUCTION

Gastrointestinal system (GIS) bleeding has an important place among patients who applied to the emergency department (1,2). Its frequency is between 36 and 172 per 100,000 people (3). GIS hemorrhages are pathologies that develop suddenly and result in death if proper intervention is not performed. The mortality rate can go up to 30-40% (4).

Bleeding that originates above the ligament of Treitz is defined as upper GIS bleeding, and 80% of bleeding occurs in this area. In 80% of GIS bleeding cases, bleeding stops spontaneously and 20% require intervention. 20% of all GIS bleeding patients, apply to the hospital with recurrent attacks and surgical intervention is planned in 15-30% of these recurrent bleeding (4-7).

Lactate is a biomarker of hypoperfusion that can be measured from arterial blood as well as from venous blood. It has focused on the relationship of morbidity as well as mortality in emergency and intensive care patients and has been a useful biomarker in predicting the risk of death (8,9).

Foreseeing the prognosis in these patients will contribute to clinicians in terms of treatment efficacy. In our study, we determined the diagnostic and prognostic value of lactate level in patients with GIS bleeding.

METHODS

The study was conducted by retrospectively scanning the information of patients in the tertiary education and research hospital emergency department for 2 years, after the approval of the local ethics committee (B.10.1.TKH.4.34.H.GP.0.01/66). Patient data were obtained from the hospital automation system.

Patients' sex, age, application complaint, known heart and liver diseases, known malignancy, antiaggregant, anticoagulant, and nonsteroidal anti-inflammatory drugs used, arrival arterial blood pressure and pulse rate per minute, pre-existing GIS bleeding presence, blood gas lactate value, the amount of hemoglobin (Hgb) and hematocrit (Hct) in the first hemogram taken, urea and creatinine values, endoscopy and colonoscopy findings, the amount of erythrocyte suspension (ES) need during the patient's stay in hospital, and mortality were evaluated.

According to the results of the screening of the hospital data processing system, patients who were over 18 years of age who had melena, hematemesis, or hematoquesia on physical examination were determined to have no bleeding other than GI bleeding or were diagnosed with gastrointestinal bleeding by endoscopy and colonoscopy. Patients under the age of 18 years, pregnant patients, and patients with missing physical examination, history, and laboratory data were excluded from the study.

Statistical Analysis

After all the data was collected, the program called SPSS for Windows® 16.0 was used. The conformity of the data to normal distribution was tested with the Kolmogorov-Smirnov test. Continuous data that did not conform to the normal distribution were expressed as median and percentile slices, and those that did not conform were expressed as mean and standard deviation. Student's t-test was used to compare the data that fit the normal distribution, and the Mann-Whitney U test was used to compare those that did not. The chi-square test was used to compare categorical data, and Fisher's Exact test was performed where appropriate. The diagnostic value of lactate level for predicting mortality was evaluated by ROC analysis. In the analyses, $p<0.05$ value was accepted as statistically significant.

RESULTS

In the study 866 patients were evaluated as all GIS bleeding cases without discriminating between upper and lower GIS bleeding. Of these, 294 were excluded because of the lack of blood lactate level at the time of application, and 66 were excluded because of insufficiency in various other data, especially endoscopy and colonoscopy. As a result, 506 patients were included in the study.

In our study, the median age of the patients was 67 (IQR: 53-80) years and 310 (61.3%) were male. Of the patients, 443 (87.5%) had upper GIS bleeding and 63 (12.5%) had lower GIS bleeding. Other demographic data of the patients are shown in Table 1.

The median lactate level in our study was 1.8 mmol/L (IQR: 1.3-2.7); the lactate level of 311 (61.5%) of the cases was above the reference (minimum: 0.5-maximum: 1.6) values. The median lactate level in upper GIS bleeding was 1.8 mmol/L (1.3-2.7), and the median lactate level in lower GIS bleeding was 1.8 mmol/L (1.3-2.4). There was no statistical difference between the groups ($p=0.759$) (Figure 1).

Three hundred eighty six (76.3%) of the patients needed ES. The median lactate level in patients who required ES was 1.9 mmol/L (IQR: 1.3-2.88), and the median lactate level in patients without ES requirement was 1.6 mmol/L (IQR: 1.1-2.2). The lactate level of patients who were given ES was found to be significantly higher ($p<0.001$).

Nine of the patients (1.8%) were discharged from the emergency service, while 475 (93.8%) were hospitalized. Twenty-two

patients (4.4%) were admitted to the intensive care unit or died in the emergency service. The lactate median level of patients discharged was 1.3 mmol/L (IQR: 1.1-1.7), the lactate median level of patients hospitalized in the service was 1.8 mmol/L (IQR: 1.3-2.7), and the lactate median level of patients hospitalized in intensive care was 2.55 mmol/L (1.7-4.77). There was a statistically significant difference between these 3 groups in terms of lactate levels (Kruskal-Wallis, p=0.008), and in the post hoc evaluation,

Table 1. Basic descriptive data of patients

			Upper GIS bleeding (n=443) median (IQR)/n (%)	Lower GIS bleeding median (IQR)/n (%)
Age			66 (50-80)	72 (63-80.5)
Sex	Male		277 (62.5)	33 (52.4)
	Female		166 (37.5)	30 (47.6)
Symptoms	Melena		258 (58.2)	2 (3.2)
	Hemathemesis		236 (53.3)	0
	Hematoquesia		28 (6.3)	59 (93.7)
	Dizziness		54 (12.2)	1 (1.6)
	Shortness of breath		15 (3.4)	1 (1.6)
	Syncope		54 (12.2)	5 (7.9)
	Chest pain		3 (0.7)	0
Additional disease and drug use	Liver disease		68(15.3)	6 (9.5)
	Heart disease		125(28.2)	25 (39.7)
	A history of malignancy		72(16.3)	13(20.6)
	Previous GI bleeding		122(27.5)	10(15.9)
	Antiagregan use		108 (24.4)	15 (23.8)
	Anticoagulant use		52 (11.7)	12 (19)
	NSAID use		(24.4)	4 (6.3)
Endoscopy (n=473)	Ulcer		246 (52.0)	
	Forrest classification	1a	22 (9)	
		1b	21 (8.5)	
		2a	22 (9)	
		2b	20 (8.1)	
		2c	25 (10.1)	
		3	136 (55.3)	
	Gastritis		281 (59.4)	
	Varicosis		66 (14.0)	
	Mallory weiss		10 (2.1)	
	Mass in the upper GIS		54 (11.4)	
	Erosion		75 (15.9)	
	Esophagitis		60 (12.7)	
Colonoscopy (n=87)	Normal			6 (9.5)
	Mass			12 (19)
	Hemoroid			15 (23.8)
	Diverticulum			17 (27)
	Polyp			7 (11.1)
	Ulcer			14 (22.2)
	Angiodysplasia			2 (3.2)

GIS: Gastrointestinal system

the number of patients who were admitted to intensive care were significantly higher than that in the other groups.

There was no correlation between lactate level and creatinine, platelet count and forrest classification (p=0.094, p=0.243, p=0.148, respectively). Lactate level was found to have a weak negative correlation with systolic blood pressure, diastolic blood pressure, Hgb, and Htc value (r=-0.174, r=-0.114, r=-0.123, r=-0.124, respectively) ; and a weak positive correlation with pulse rate, urea, amount of ES given, and duration of hospitalization (r=0.185, r=0.172, r=0.201, r=0.093, respectively) (Table 2).

It was determined that 62 (0.3) of the patients died. The lactate median value of patients who died was 2.7 mmol/L (IQR: 1.7-4.2), and the lactate median value of those living was 1.7 mmol/L (IQR: 1.2-2.5). The lactate level of the patients who died was found to be significantly high (p<0.001).

In our study, the area under the curve was found to be 0.714 cm^2 (Figure 2). When the cut-off value of lactate is taken as 4 mmol /L, the test performance results in predicting mortality are as follows: sensitivity, 29%; specificity, 91%; positive predictive value, 31%; negative predictive value, 90%; positive likelihood ratio, 3.22; and negative likelihood ratio, 0.78. The sensitivity and specificity values of lactate for different cut-off values are given in Table 3.

Table 2. Relationship of lactate level with vital signs, laboratory parameters, ES requirement, forrest stage and number of days of hospitalization in all GIS bleeding

Groups	R	p
Systolic blood pressure	-0.174	<0.001
Diastolic blood pressure	-0.114	<0.001
Pulse (beats/min)	0.185	<0.001
Creatinine	0.074	0.094
Urea	0.172	<0.001
Hemoglobin	-0.123	0.006
Hematocrit	-0.124	0.005
Platelet	-0.052	0.243
Erythrocyte need	0.201	<0.001
Forrest stage	-0.069	0.148
Duration of hospitalization	0.093	0.037

Min: Minimum, GIS: Gastrointestinal system

DISCUSSION

In our study, the median value of the lactate level was 1.8 mmol/L in accordance with the literature, and in 61.5% of the cases, the lactate level exceeded the reference level. In studies in the literature, similar to our study, it was stated that lactate level increased in patients with GIS bleeding, and this situation developed due to hypoperfusion and hypoxia (10-12). Shrestha et al. (13) stated that a single venous lactate level provides clinically useful information in patients with acute

Table 3. Sensitivity and specificity of lactate in predicting mortality at different cut-off values

Cut-off values for lactate	Sensitivity (%)	Specificity (%)
2 mmol/L	71	64
4 mmol/L	29	91
6 mmol/L	19	97

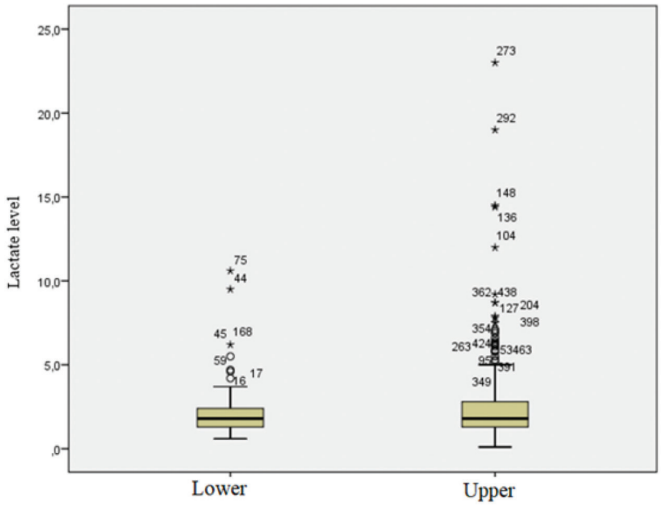

Figure 1. Comparison of lactate levels in upper and lower GIS bleeding
GIS: Gastrointestinal system

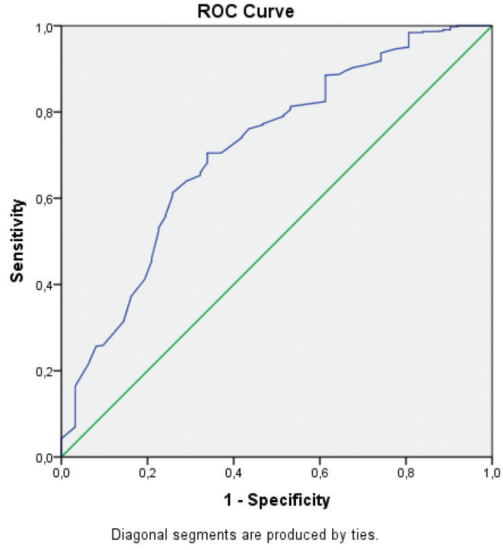

Figure 2. ROC curve of lactate for mortality in all GIS bleeding patients
GIS: Gastrointestinal system

GIS bleeding and is an important parameter in the planning of treatment.

In our study, the mortality rate was found to be 12.3% in line with the literature, and it was shown that this rate increased to 23% according to some study results (14,15). The lactate levels of patients who died were found to be higher, and when the lactate threshold value of 4 mmol/L for mortality was taken, it was observed that they had similar specificity and sensitivity with other studies (15-18). In other studies, they concluded that serum lactate levels are better than prognostic indicators, such as the Rockall or Glasgow-Blatchford systems, physiological triage criteria, such as heart rate, blood pressure, Glasgow coma scale, and respiratory rate (19,20). Although it was determined in our study that high lactate levels contributed significantly to predicting mortality, we believe that it is not reliable to estimate prognosis with lactate level alone because the test performance results are not strong enough. However, when used with other prognosis indicators, we believe that lactate levels is a very useful marker in the follow-up of patients with GI bleeding.

In our study, no difference was found between the upper and lower GIS bleeding lactate levels. Similarly, Kollef et al. (10) also stated that lactate levels increased in all GIS bleeding cases,and lactate levels were similar in upper and lower GIS bleeding. We believe that the lactate level in GIS bleeding is related to hypoxia caused by the amount of bleeding rather than the bleeding focus.

Some studies in the literature have stated that the lactate level is correlated with the severity of the lesion and may indicate rebleeding (11,12). However, in our study, no significant relationship was found between Forrest classification and lactate level. The data to explain the reason of this condition have not been determined in our study, and we believe that factors such as mild and chronic losses in the cases do not give symptoms unless they reach serious rates, and rapid intervention to serious lesions may have led to this result.

Shah et al. (16) reported that there was no relationship between lactate, pulse rate, and Htc in their study in patients with GIS bleeding. Ko et al. (21) stated that high serum lactate level can predict hypotension in patients with GIS bleeding. In their study in GIS bleeding cases, Shrestha et al. (13) stated that patients with high and normal lactate levels had similar heart rate and blood pressures, and patients with high lactate levels had low Hgb. In our study, it was determined that lactate level had negative and weak correlations with blood pressure, Hgb, and Hct, and positive and weak correlations with pulse rate and urea.

Previous studies have shown a relationship between blood transfusion and mortality and length of hospital stay (13,19,22,23). Although Kollef et al. (10) reported in their study that there is a similarity between the lactate level and the need for ES, Ayık et al. (10,24) reported that they did not find a significant relationship between the two in their studies. In our study, it was determined that 76.3% of the patients needed ES, the median value of ES requirement was 3 units, the lactate level of patients with ES requirement was high, and there was a positive correlation between the amount of ES delivered and the lactate level. This may be related to the amount of blood lost from the body, leading to a decrease in the amount of blood flowing to the tissues and thus to hypoxia.

Study Limitations

The main limitation of this study is that it was designed retrospectively. The second important limitation is the deficiencies in patient anamnesis and the fact that the lactate intake time of the patients is unknown. Again, we believe that the fact that the study was single-centered reduces the generalizability, while the relatively high number of patients increases the reliability of the study results.

CONCLUSION

As a result, lactate level is a parameter that can be used in conjunction with other clinical and laboratory markers and is effective in determining prognosis in patients with GIS bleeding. In the cases with high lactate value, more hospitalization time, more ES supplement requirement, and increased risk of hospitalization and death were determined.

Ethics

Ethics Committee Approval: The study was conducted by retrospectively scanning the information of patients in the tertiary education and research hospital emergency department for 2 years, after the approval of the local ethics committee (B.10.1.TKH.4.34.H.GP.0.01/66). Patient data were obtained from the hospital automation system.

Informed Consent: A retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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Evaluation of Dynamic Contrast Breast Magnetic Resonance Imaging Findings in Molecular Subtypses of Breast Cancer According to Birads Descriptions

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Abstract

Objective: Our aim is to reveal the correlation between the molecular subtypes of breast cancer (BC) and contrast-enhanced breast magnetic resonance imaging (MRI) findings and to determine the possible molecular subtype and prognosis of the breast mass before the operation according to the MRI findings. In this way, it is aimed to ensure that contrast-enhanced breast MRI guides diagnosis and treatment.

Methods: This study was conducted retrospectively between June 2015 and October 2020 including 265 patients who underwent dynamic contrast-enhanced breast MRI in our hospital and whose pathology results were consistent with invasive breast carcinoma. As a result of histopathological studies, patients were divided into molecular subtypes according to hormone receptor status (estrogen, progesterone, human epidermal growth factor receptor-2), and Ki-67 level, and MRI findings were evaluated for these subtypes according to the "Breast Imaging Reporting and Data System" updated in 2014 by the American College of Radiology.

Results: A total of 265 cases of invasive BC were included. In these cases, the most common subtype was luminal A in 93 cases (35%), 79 luminal B tumor cases (29.8%), 51 triple-negative tumors (19.3%), and 42 HER2 tumor cases (6.7%). There was a statistically significant difference between molecular subtypes in terms of MRI findings and lesion presentation ($p<0.0001$). In addition, statistical analyses showed that there was a significant difference between the subgroups of mass shape and contour. In our study, no significant difference was found between the contrast enhancement pattern and contrast enhancement kinetic curves between molecular subtypes.

Conclusion: There is a correlation between molecular subtypes and some MRI findings, and molecular subtypes can be determined early before the operation and prognostic markers can be revealed earlier.

Keywords: Breast cancer, hormone receptors, breast magnetic resonance imaging

INTRODUCTION

Invasive breast cancer (BC) is the most common type of cancer in the female population and is the second leading cause of death after lung cancer. BC accounts for approximately 30% of all cancers diagnosed in women and approximately 17-18% of cancer-related deaths (1).

Magnetic resonance imagining (MRI) is a non-invasive imaging technique that provides information about the location and prevalence of malignancy as well as evaluates tissue characteristics, which can aid in monitoring and predicting treatment response and guide patient management. However, some authors went beyond diagnostic characteristics and investigated the efficacy of MRI in the response to chemotherapy. We further investigated this subject and showed the sensitivity of MRI by monitoring the chemotherapy response of molecular subtypes (2). MRI provides functional features not only with morphological parameters but also through kinetic curves

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related to tumor biology (3). Some publications have stated that dynamic contrast-enhanced breast MRI parameters are correlated with tumor vascularity and may display differences between histopathological types (4-9).

Invasive BC is often classified primarily by its histological appearance. Today, some subtypes have been defined, including their molecular properties. These subtypes were first classified in 2,000 on the basis of gene expression studies, which are still valid today (8). In this classification, invasive cancers are identified as luminal A, luminal B, human epidermal growth factor receptor-2 (HER2), and triple-negative (TN) BC according to their biological markers. These different molecular subtypes display differences in disease prognosis, treatment approach, and post-treatment follow-up according to estrogen receptor (ER), progesterone receptor (PR), HER-2 positivity, and nuclear Ki-67 expression. The luminal- A subtype (ER-positive, HER2 negative, or PR weak or strong positive) responds to hormone therapy and usually has an excellent prognosis. Luminal B (can be ER positive, HER2 negative or positive, PR positive or negative) exhibits a worse prognosis than Luminal A but tends to be better than the HER2 (+) subtype in general.

The HER2 (+) (HER2 positive, ER and PR negative) subtype, on the other hand, is more aggressive but can be treated with monoclonal antibodies targeting the erbB-2 membrane receptor. TN, BC (ER, PR, and HER2 negative) is the most aggressive subtype and usually responds to chemotherapy (2). Therefore, early detection of BC subtypes can help start treatment and determine prognosis without wasting time.

This study aimed to retrospectively show the correlation of dynamic contrast-enhanced MRI-derived parameters between BC molecular subtypes according to the Breast Imaging Reporting and Data System (BI-RADS).

METHODS

Data of 265 patients who underwent preoperative contrast-enhanced breast MRI between June 2015 and October 2020 and were diagnosed with invasive BC by biopsy and whose subtypes were determined were retrospectively screened from the hospital system. Ethics committee approval was obtained for this study from the Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital with decision number 2020/538 and dated 21.12.2020.

Patients were compared in terms of demographic characteristics and radiological and histological/histopathological findings. Immunohistochemical data in pathology reports obtained with the biopsy of BC molecular subtypes were classified into 4 subgroups according to ER and PR receptor status, HER2, and Ki-67 levels. Molecular subtypes of BC according to the latest St. Gallen Internotional Expert Consensus (2013) immunohistochemical findings were categorized into 4 subtypes: luminal A [ER (+) or PR (+) and Ki-67 ≤20%], luminal B [ER (+) or PR (+) and Ki-67 ≥20% and HER-2 (+) and ER (+) and Ki-67 insignificant], HER-2 rich (ER and PR positive\negative and HER-2 positive), and (TN) BC basal-like cases [ER (-), PR (-) HER-2 (-) (Table 1)].

Inclusion criteria were patients with preoperative contrast-enhanced breast MRI findings belonging to patients who were histopathologically (tru-cut, excisional, or incisional biopsy) diagnosed with invasive BC and whose molecular subtypes were determined were included in the study.

Exclusion criteria were as follows: patients with insufficient MRI results for diagnosis, receiving neoadjuvant chemotherapy prior to MRI, operated for BC and receiving chemotherapy treatment, recurrence of cancer, patients with breast implants, and patients with unknown tumor histology (Figure 1).

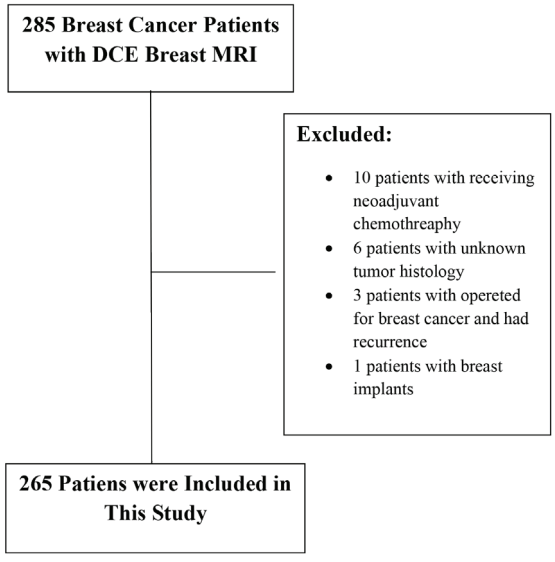

Figure 1. Flow chart of study population

Table 1. Biomarker profile of breast cancer molecular subtypes

Molecular subtype	Immunohistochemical biomarker profile
Luminal A	ER+ and/or PR+, HER2 (-) and low Ki67 (<20%)
Luminal B	ER+ and/or PR+, HER2 (+) (luminal HER2 group)- ER+ and/or PR+, HER2 (-) and high Ki67 (>20%)
HER2(+)	ER-, PR- and HER2 (+)
Triple negative (Basal-Like)	ER-, PR-, HER2-

Dynamic Contrast-Enhanced Magnetic Resonance Imaging

MRI examinations were performed in the prone position using a breast coil with the 3.0 Tesla MRI (Siemens, Verio Healthcare, Erlangen, Germany) device in our clinic. Fat-suppressed axial SE T2-weighted, pre-contrast axial T1-weighted, contrast-enhanced dynamic fat-pressed axial T1-weighted, and post-contrast fat-pressed axial and sagittal T1-weighted sequences were obtained for all patients. In dynamic examinations, following the acquisition of non-contrast-enhanced images, contrast-enhanced images were obtained with IV administration of 0.1-0.2 mmol/kg gadolinium-containing contrast agent at a rate of 2 mL/s based on the weight of the patient. Six phasic serial images were obtained for each section at 30-s intervals for dynamic contrast-enhanced T1-weighted sequences.

Pre-contrast images were extracted from the corresponding post-contrast images using a subtraction program through special software on the MR device console over the dynamic images obtained.

Lesions were grouped and examined using the latest BI-RADS according to dynamic contrast-enhanced MRI findings. Following this, they were morphologically categorized as focus, mass, non-mass enhancement, and mass/non-mass enhancement groups. Mass lesions were examined according to shape, margin, and internal enhancement patterns, whereas non-mass enhanced lesions were examined according to distribution and internal enhancement patterns.

The dynamic contrast enhancement curves of the cases were examined using the Syngo Via device. Dynamic curves were created according to the peak contrast enhancement values. Dynamic curves were classified as Types 1, 2, 3.

Statistical Analysis

Descriptive data were expressed as mean, standard deviation, median, highest and lowest values, frequency, and ratio. The distribution of variables was tested using the Kolmogorov-Smirnov test. Quantitative independent data were analysed using the Mann-Whitney U test. Dependent quantitative data were analyzed using the Wilcoxon test.

The chi-square test was used for the analysis of qualitative independent data, whereas Fisher's Exact test was used when the chi-square test requirements were not met. Intraclass correlation analysis was performed to analyse the correlations. Data analysis was performed using IBM SPSS Statistics for Windows (Version 27.0) program.

RESULTS

General Characteristics of the Patients

The study was conducted with 265 patients diagnosed with BC between June 2015 and October 2020. The mean age of the patients was 50.41±81.02 years (Tables 1 and 2).

According to the pathological biopsy results of 265 cases diagnosed with BC, 248 had IDC, 12 had ILC, and 5 had IDC and ILC combined (Table 3).

The most common molecular subtypes were luminal A (35%) and luminal B (29.8%), followed by TNBC (19.3%) and HER2+ (15.8%).

Radiological and Pathological Findings

Of the cases included in the study, 170 had ER, 137 had PR, and 71 had HER2 positives (+). Considering these findings, the classification of Ki-67 percentages and molecular subtypes revealed that 93 patients had luminal A, 79 patients had luminal B, 42 patients had HER2 (+), and 51 patients had TNBC subtypes (Table 4).

Axillary lymph node involvement did not differ between BC subtypes. Among the patients with lymph node involvement (+), luminal B was observed at a rate of 33.59%, luminal A at 28.24%, HER2 (+) tumors at 21.37%, and TNBC at 16.79% (Table 5).

According to the MRI findings, evaluation of mass presentation as mass, non-mass enhancement, and mass/non-mass enhancement revealed a statistically significant difference between the molecular subtypes ($p<0.0001$). The non-massive enhancement rate alone and the association of mass/non-mass enhancement in the HER2 (+) group were found to be higher than those in the other groups (Figures 2 and 3)

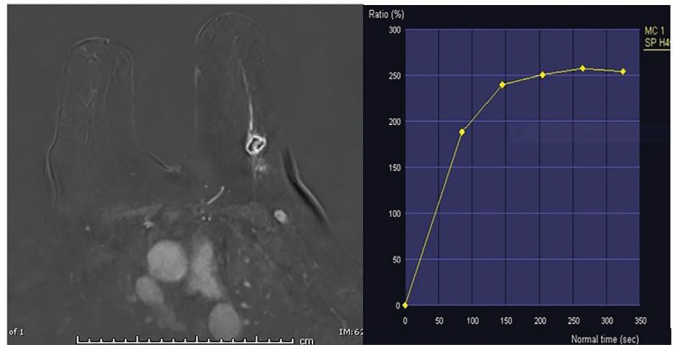

Figure 2. Triple negative breast cancer in 60- year-old women-Substracted T1-weighted contrast-enhanced image shows oval shape mass with circumscribed margins and rim enhancement. The lesion shows a Type 2 contrast enhancement pattern

Statistical analyses revealed a significant difference between molecular subtypes in terms of mass shape (p<0.001). TNBC, in particular, often displayed more regular shapes (oval, round). Luminal A lesions mostly displayed an irregular shape. A comparison of mass margins revealed a significant difference between the molecular subtypes (p<0.001). The luminal A and luminal B subtypes displayed irregular and spiculated margins, whereas the TNBC group displayed significantly sharper margins. There was no significant difference in contrast enhancement patterns between the subtypes (p=0.23). In addition, no significant difference was observed in enhancement kinetic

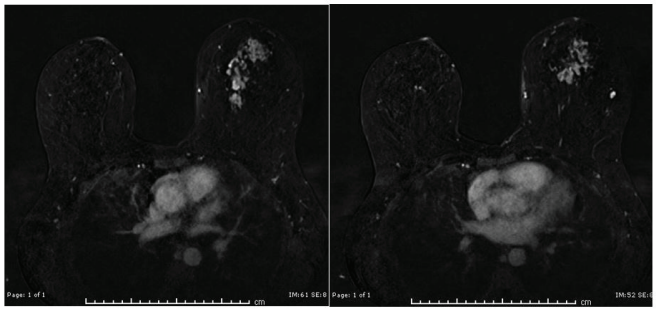

Figure 3. HER2 (+) breast cancer in 53 year-old women-substracted T1 weighted contrast enhanced image shows heterogenous non mass enhancement and regional distribution dynamic series

Table 2. Demographic and molecular findings of the patients

		Min-max	Median	Mean + SD/n-%	
Age		27-81	48.0	50.41±12.02	
Pathological size		3-80	25.0	25.02±11.60	
MRI mass size		6.0-113	30.0	31.75±16.56	
ER	(-)			95	35.8%
	(+)			170	64.2%
PR	(-)			128	48.3%
	(+)			137	51.7%
HER2	(-)			194	73.2%
	(+)			71	26.8%

Min: Minimum, Max: Maximum, SD: Standard deviation

Table 3. Distribution of histopathological findings of molecular subtypes

		Luminal A n=93		Luminal B n=79		HER2 pozitive n=42		Triple N. n=51	
		n	%	n	%	n	%	n	%
Histological type	IDC	79	84.9%	77	97.5%	41	97.6%	51	100%
	ILD	14	15.1%	2	2.5%	1	2.4%	0	0.0%
Histological grade	Low	17	18.3%	3	3.8%	0	0.0%	1	2.0%
	Intermediate	52	55.9%	51	64.6%	20	47.6%	17	33.3%
	High	12	12.9%	12	15.2%	8	19.0%	20	39.2%

Table 4. Distribution of pathological and MRI findings of molecular subtypes

	Luminal A n=93		Luminal B n=79		HER 2 pozitive n=42		Triple N. n=51	
	Mean ± SD/n-%		Mean ± SD /n-%		Mean ± SD /n-%		Mean ± SD /n-%	
Age	56.6±12.0		48.3±13.3		51.7±10.1		48.7±10.9	
Pathological size	22.8±10.5		26.7±11.0		31.4±18.0		25.3±10.8	
MRI mass size	25.6±13.9		35.1±17.4		37.6±17.7		33.0±15.6	
Kİ 67	8.6±5.9		39.1±21.9		36.0±21.9		47.5±27.8	
Premenopausal	48	51.6%	32	40.5%	23	54.8%	21	41.2%
Postmenapausal	45	48.4%	47	59.5%	19	45.2%	30	58.8%

SD: Standard deviation

Table 5. Comparison of axillary lymph node metastasis of molecular subtypes

		Luminal A n=93		Luminal B n=79		HER2 pozitif n=42		Triple N. n=51	
		n	%	n	%	n	%	n	%
Axillary lymph node metastasis	No	56	60.2%	35	44.3%	14	33.3%	29	56.9%
	Yes	37	39.8%	44	55.7%	28	66.7%	22	43.1%

curves between molecular subtypes, whereas plateau and wash out occurred at a higher rate in all subtypes.

Among the molecular subtypes of BC, the presence of accompanying foci also showed a minimally significant difference between the groups (p=0.008).

In cases with non-mass enhancement, no significant difference was noted between the subtypes in terms of distribution or enhancement pattern. However, the segmental and diffuse non-mass enhancement rate was significantly higher (p<0.05) in HER2 (+) cases than in HER2 (-) cases. The rates of focal, linear,

Table 6. Comparison of molecular subtypes according to BI-RADS features

		Group				
		Luminal A	Luminal B	HER2	Triple negative	P
		n (%)	n (%)	n (%)	n (%)	n (%)
Metastasis	Unifocal	67 (33.67)	58 (29.15)	28 (14.07)	46 (23.12)	0.202
	Multifocal	18 (39.13)	14 (30.43)	10 (21.74)	4 (8.7)	
	Multicentric	7 (36.84)	7 (36.84)	4 (21.05)	1 (5.26)	
Axillary lymph node involvement	No	56 (41.79)	35 (26.12)	14 (10.45)	29 (21.64)	0.015
	Yes	37 (28.24)	44 (33.59)	28 (21.37)	22 (16.79)	
Focal	No	81 (39.71)	55 (26.96)	27 (13.24)	41 (20.1)	**0.008**
	Yes	12 (19.67)	24 (39.34)	15 (24.59)	10 (16.39)	
Presentation	Focal	0 (0)	0 (0)	0 (0)	0 (0)	**0.0001**
	Mass	71 (37.97)	64 (34.22)	16 (8.56)	36 (19.25)	
	Non-mass contrast enhancement	0 (0)	2 (40)	3 (60)	0 (0)	
	Mass + non-mass enhancement	22 (30.14)	13 (17.81)	23 (31.51)	15 (20.55)	
Mass shape	Oval	3 (14.29)	5 (23.81)	0 (0)	13 (61.9)	**0.0001**
	Round	6 (17.14)	12 (34.29)	3 (8.57)	14 (40)	
	Irregular	84 (41.18)	60 (29.41)	36 (17.65)	24 (11.76)	
Mass margin	Sharp	4 (12.12)	4 (12.12)	2 (6.06)	23 (69.7)	**0.0001**
	Irregular	45 (30.82)	53 (36.3)	23(15.75)	25 (17.12)	
	Spiculated	44 (54.32)	20 (24.69)	14 (17.28)	3 (3.7)	
Enhancement pattern	Homogeneous	6 (66.67)	1 (11.11)	1 (11.11)	1 (11.11)	0.230*
	Heterogeneous	63 (36)	57 (32.57)	26 (14.86)	29 (16.57)	
	Circular enhancement	24 (31.58)	19 (25)	12 (15.79)	21 (27.63)	
	Contrast-enhanced/non-enhanced septations	0 (0)	0 (0)	0 (0)	0 (0)	
Non-mass contrast-enhancement distribution	Focal	1 (9.09)	5 (45.45)	4 (36.36)	1 (9.09)	0.333*
	Linear	4 (33.33)	2 (16.67)	3 (25)	3 (25)	
	Segmental	15 (34.09)	6 (13.64)	13 (29.55)	10 (22.73)	
	Regional	2 (40)	1 (20)	1 (20)	1 (20)	
	Multi-regional	0 (0)	0 (0)	1(50)	1(50)	
	Diffuse	0 (0)	2 (33.33)	4 (66.67)	0 (0)	
Non-mass contrast enhancement pattern	Homogeneous	0 (0)	0 (0)	1 (100)	0 (0)	0.8268*
	Heterogeneous	7 (21.88)	5 (15.63)	11 (34.38)	9 (28.13)	
	Cobblestone/cluster	12 (33.33)	8 (22.22)	11 (30.56)	5 (13.89)	
	Clustered rings	3 (27.27)	3 (27.27)	3 (27.27)	2 (18.18)	
Kinetic curve pattern	Type I	6 (50%)	0	0	6 (50%)	
	Type II	49 (34.5%)	48 (33.8%)	21 (14.8%)	24 (16.9%)	
	Type III	38 (34.3%)	31 (27.9%)	21 (18.9%)	21 (18.9%)	

*Fisher Freeman Halton test
Chi-square analysis

regional, and multiple regional non-mass enhancement did not differ significantly (p>0.05) between in the HER2 (-) and HER2 (+) groups (Table 6).

DISCUSSION

In this study, we aimed to investigate the relationship between different molecular subtypes of breast carcinoma and MRI findings according to the BI-RADS classification. In our study, a comparison of mass presentation patterns between molecular subtypes revealed that non-mass enhancement and coexistence of mass and non-mass enhancement had a significantly higher rate in the HER2 (+) subtype (p<0.0001). In addition, the comparison of HER2 (+) and HER2 (-) cases revealed that only mass and presentation were significantly lower (p<0.05). Similar to our study, Navarro Vilar et al. (10) found a significantly higher distribution of non-mass enhancement in the HER2 (+) subtype (p=0.003). In the study by Süha Öztürk et al. (12), no significant difference was found with respect to subtypes between mass and non-mass enhancement patterns and no significant difference between subtypes in the distribution and patterns of non-mass enhancement.

A significant difference was observed in the comparison of mass shapes by subtype among the cases presenting with mass and mass/non-mass enhancement (p<0.0001). In our study, although the oval shape was significantly higher in TNBC cases compared with other subtypes, the irregularly circumscribed mass was found to be significantly higher in the luminal A subtype. Again, significant differences were observed among the mass margins of the 4 subtypes (p<0.0001). While circumscribed margins were more common in TNBC cases (69.7%), spiculated margins were significantly more common in luminal cases (54.32%). The study by Navarro Vilar et al. (10) reported similar results to our study. In this study, TNBC cases were frequently in the form of a mass and presented with a round shape and circumscribed margins. Luminal A cases mostly exhibited mass enhancement with irregular shape and spiculated margins (10). In their review, Ab Mumin et al. (11) compared MRI findings of molecular subtypes and reported that oval/round shape (n=6) was more frequent in TNBC cases, whereas only one study reported lobule shape (n=1). Again, in the same review, mass margins were mostly circumscribed in TNBC cases.

In our study, HER2 (+) cases mostly presented with mass + non-mass enhancement; however, HER2 (+) cases with mass enhancement presented with highly irregular mass shapes and often irregular and spiculated mass margins. When compared with similar studies, our results show significant consistency in terms of mass margin but differ in terms of mass shape. For example, Youk et al. (13) and Navarro Vilar et al. (10) yielded similar results in their studies, reporting mostly round and oval shapes and spiculated margins in the HER 2 (+) subtype. In the review of Ab Mumin et al. (11), mass shape was evaluated in 6 of 19 HER2 (+) studies, in which 4 studies reported frequently irregular shapes and 2 studies reported round shapes. Additionally, there were 4 studies reporting spiculated/irregular margins and 2 studies reporting circumscribed margins in the same review, similar to our study.

In our study, most luminal B cases (64/79) presented with mass lesions often with irregular and irregular/spiculated contours. In another study, mass presentation was mostly observed in the luminal B subtype, similar to this study, often displaying round/irregular shapes and spiculated margins (10). Additionally, although the same study reported similar morphological characteristics between luminal B, luminal A, and HER2 (+) tumors, the number of luminal B and HER2 (+) tumors in the study was significantly lower compared with our study (10). Although 19 of our luminal B subtype cases were HER2 (+) and 60 were HER2 (-), no morphological comparison was performed between the cases in this study.

Although we found no significant difference in mass enhancement patterns among molecular subtypes (p=0.23), our results are consistent with the results of available studies. Heterogeneous enhancement was observed at a rate of 56.9% and rim enhancement at a rate of 41.2% among (TN) BC cases included in our study. Heterogeneous enhancement was more predominant in luminal A, luminal B, and HER2 (+) at 59.5%. In a similar study by Navarro Vilar et al. (10), mass enhancement patterns differed significantly between subtypes (p=0.045), with rim enhancement (68.7%) and heterogeneous enhancement patterns (31%) being significantly higher in (TN) BC cases. In addition, no homogeneous contrast enhancement was detected among (TN) BC cases in this study. In the same study, rim enhancement was observed in 33%, and septation enhancement was observed in 30% of luminal A cases. In a similar study by Algazzar et al. (14), a comparison of radiological findings according to molecular subtypes and HER2 receptor expression revealed significantly higher rim enhancement in (TN) BC cases 66.7%. In the same study, heterogeneous enhancement was observed at a rate of 70.6% in luminal A cases, 70% in luminal B cases, and 85% in HER2 (+) cases.

In the study by Uematsu et al. (15) comparing (TN) BC cases with ER (+)\PR (+)\HER2 (-) cases, ER (+)\PR (+)\HER2 (-) cases displayed irregular\oval shape, irregular margins, and heterogeneous

enhancement. Similar MRI findings were found in the study by Youk et al. (13).

Dynamic contrast-enhanced MRI provides information not only on mass morphology but also tissue perfusion and enhancement kinetics. It helps display strong and early enhancement and wash out in the late phases, especially in lesions with high vascularization, such as BC (16). In our study, no significant difference was observed in the kinetic contrast enhancement curves between the subtypes, whereas wash out and plateau curves were frequently observed in the late phases.

A meta-analysis by Kazama et al. (17) reported that the wash out curve was very common in BC cases but was insufficient to identify subtypes. Again, in the same meta-analysis, it was emphasized that the type 3 curve was observed at a higher rate in HER2 (+) cases than in HER2 ( ) cases, with no significant difference in ER (+) and ER ( ) cases. In a similar study, Navarro Vilar et al. (10) found no significant difference between dynamic contrast enhancement curves and subtypes, frequently observing plateau and wash out curves.

In our study, only non-mass enhancement was observed at a significantly higher rate in HER2 (+) cases. In addition, segmental distribution was prominent in all subtypes. Non-mass enhancement distribution and pattern were not found to differ significantly between subtypes, which is consistent with current publications. In similar studies, Navarro Vilar et al. (10) and Issar et al. (18) reported no significant difference in non-mass contrast enhancement distribution and patterns between molecular subtypes, as in our study.

We also investigated the accompanying focus in our study. None-of the molecular subtypes displayed focus presentation alone. However, the frequency of accompanying focus presentation was significantly higher in the luminal B subtype (p=0.008). Focus presentations are defined as morphological features that cannot be distinguished from ground contrast enhancement in terms of shape and margins because of insufficient contrast, often below 5 mm (19). However, the ACR BI-RADS Atlas provides limited data on focus presentation, and very few available studies have investigated the frequency of focus among molecular subtypes.

Our results also revealed significant differences between molecular subtypes in terms of axillary lymph node metastasis among BC cases (p=0.015). The most common subtype was luminal B in cases with positive axillary lymph nodes, which was attributed to the high number of luminal B cases. In fact, the highest prevalence belonged to HER2 (+) tumors at a rate of 66.7%, followed by luminal B at 55.7 (TN) BC at 43.1%, and luminal A at 39.8%. In addition, we observed axillary lymph node metastasis at a significantly higher rate in HER2 (+) tumors compared to HER2 (-) tumors ($p<0.05$). In their study, He et al. (20) reported axillary lymph node metastasis less frequently in (TN) BC cases than in other subtypes. In another study by Singh and Mukherjee (21), axillary lymph node metastasis was significantly higher in HR-\HER2+ cases, whereas HR +\HER2- cases exhibited significantly lower rates compared with other subtypes ($p<0.001$).

Study Limitations

Another study examining the difference between axillary lymph node metastasis and molecular subtypes yielded similar results to our study, reporting axillary lymph node metastasis at a significantly higher rate in triple-positive (HR+\HER2+) cases (22).

There are some limitations to our study. The single-center and retrospective design of our study was the main limitation. Unlike the BI-RADS atlas, the fact that the presentations were categorized as focus, mass alone, non-mass enhancement alone, and mass and non-mass enhancement alone groups may have caused the results to differ from the literature.

CONCLUSION

In conclusion, similar to our study, many available studies have reported morphological and physiological correlations between dynamic contrast-enhanced breast MRI findings and molecular subtypes (4-7). We believe that prospective studies with larger series should be conducted combining artificial intelligence with MRI so that MRI findings can better predict subtypes and prognostic factors.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for this study from the Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital with decision number 2020 /538 and dated 21.12.2020.

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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Women's Knowledge Levels in Protection from Gynecological Cancers and Affecting Factors

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Abstract

Objective: Gynecological cancers (GC) are among the most common cancers in women. In this study; it was aimed to examine the knowledge levels of women for protection from GC and the affecting factors.

Methods: This cross-sectional study was conducted with 611 women who applied to the Family Medicine Outpatient Clinic of a Tertiary Hospital between December 2021 and September 2022 and met the inclusion criteria. The patient information form and Gynecological Cancer Prevention Information Scale (GCPIS) were used to obtain data. A p-value of <0.05 was considered statistically significant.

Results: The mean age of the 611 women included in the study was 33.92±11.12 years [minimum (min): 18- maximum (max): 65], and the mean total score of GCPIS was 15.17±7.08 (min: 0-max: 35). The total GCPIS score of the participants in the 36-65 age group were significantly higher than those in the 18-35 age group (p=0.048). A statistically significant difference was found between education and income levels in terms of total scores of GCPIS (p=0.002; p=0.004; respectively). Those who did not menstruate, had a history of a gynecological disease, had regular gynecological examinations, had knowledge of GC and screening tests, and had Pap-smear tests had significantly higher GCPIS total scores. (p=0.033; p=0.026; p=0.031; p=0.001; p=0.018, respectively).

Conclusion: According to this study, women's knowledge of GC prevention was moderate. High education and income level, amenorrhea, gynecological disease history, obtaining information about GC and screening tests, and having regular gynecological examinations and Pap smear tests were the factors positively affecting the level of knowledge about the prevention of GC.

Keywords: Family medicine, knowledge level, gynecological cancers

INTRODUCTION

Gynecological cancers (GC) are among the most common cancers in women and may differ in terms of incidence, risk factors, symptoms, signs, treatment responses, and prognosis according to their region of origin (1,2). In addition to causing morbidity and mortality, GC significantly affects the quality of life by disrupting the function of the reproductive system of women. Therefore, preventing their development, diagnosing, and treating any precancerous lesion at an early stage is vital for prognosis (3).

Among GC, there are only screening tests for cervical cancer [human papillomavirus (HPV) test/Pap-smear test] (4). Since there is no simple and reliable way to screen for other GC, it is crucial for public health to increase people's awareness of GC and to avoid modifiable risk factors (5).

Many factors affect women's awareness of GC, especially age and educational status (6). Unfortunately, some studies conducted recently have shown that women's awareness of GC, the rate of regular gynecological examinations, and cervical cancer screening were low (5,7,8). However, there are also studies reporting that women's awareness and attitudes towards

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protection from GC are above the moderate level (6,9-13). This study examines the knowledge level of women between the ages of 18 and 65 for preventing GC and the factors affecting it.

METHODS

This study was planned as a single-center cross-sectional study. This study was conducted with 611 volunteers who met the inclusion criteria among the women who were admitted to the family medicine outpatient clinic of a tertiary hospital between 20.12.2021 and 09.09.2022. All participants included in the study were informed in detail, and their verbal and written consent were obtained. All procedures were performed according to the Declaration of Helsinki. The study was conducted with the approval of the local ethics committee (date: 08.12.2021, no: 390).

Inclusion Criteria of the Study

Women between the ages of 18 and 65 years, who could understand and answer the questions asked, who had no known GC history, who had no history of GC in their first-degree relatives, who were literate, and who agreed to participate in the study were included in the study.

Exclusion Criteria of the Study

Those who were under the age of 18 and over the age of 65, could not communicate (uncooperative, had hearing and speech disorders), had a previous history of GC or other active malignancies, had a first-degree relative with a history of GC, and were illiterate were excluded from the study.

Data Acquisition Tools

Patient Information Form

Sociodemographic characteristics (age, gender, marital status, educational status, income status, chronic disease history), obstetric characteristics (total pregnancy, live birth, age at first birth), and gynecological characteristics (presence of menstrual bleeding, gynecological disease history, sexual activity status, regular gynecological examinations, screening tests for GC) of the participants were questioned with the patient information form created by the authors using the literature.

Gynecologic Cancer Prevention Information Scale

The Gynecologic Cancer Prevention Information Scale (GCPIS), developed by Bekar et al. (14) in 2021, is a 35-item scale to measure the knowledge level of women about protection from GCs. Cronbach's alpha value was found to be 0.951. The 5 sub-dimensions of the scale and the items it contains are as follows; protection from female reproductive organ cancer (22, 24, 25, 26, 27, 28, 29, 30, 32, 33, 34, 35), FRO cancer symptoms (5, 6, 7, 8, 9, 13, 14, 19, 20, 23), observations regarding diagnosis (15, 16, 17, 18, 21, 31), early diagnosis and physiological factors (1, 2, 3, 4), and risks related to delivery (10,1,12). The "correct" answers given by the participants are scored with 1 (one) point, and the "wrong" or "don't know" answers are scored with 0 (zero). Items 10, 11, 12, 16, 17, 18, 21, 28, and 31 are reverse scored. In addition to the total overall score on the scale, the total score for each subdimension is calculated separately. A score between 0 and 35 can be obtained from the scale, and an increase in scores indicates that women's level of knowledge about protection from GC has increased (14).

Statistical Analysis

After collecting the data, IBM SPSS Statistics v22 program was used for statistical analysis. The suitability of the parameters to the normal distribution was evaluated with Kolmogorov-Smirnov and Shapiro-Wilks tests, and it was determined that the parameters did not show normal distribution. While evaluating the study data, the Kruskal-Wallis test was used for the comparison of the parameters between groups in the comparison of quantitative data as well as descriptive statistical methods [minimum (min), maximum (max), mean, standard deviation (SD), median, frequency]. The Mann-Whitney U test was used to compare parameters between the 2 groups. The chi-square test was used to compare qualitative data. Spearman's rho correlation analysis was used to examine the relationships between parameters that did not conform to the normal distribution. Significance was evaluated at the $p<0.05$ level.

RESULTS

This study was conducted with 611 women with a mean age of 33.92±11.12 years (min: 18-max: 65). The distribution of sociodemographic and medical characteristics of the women participating in the study is given in Table 1.

Examination of the participants' knowledge about GC and their characteristics regarding screening tests and HPV vaccines are given in Table 2.

The total mean score of the participants' GCPIS was 15.17±7.08 (min: 0-max: 35), and the distribution of the total and sub-dimension scores of the participants' GCPIS is given in Table 3.

The distribution of the GCPIS sub-dimension and total scores according to various variables is given in Table 4. The total scores of the participants in the 36-65 age group were significantly higher ($p=0.048$). Significant differences were found between education and income levels in terms of total scores of GCBPS

(p=0.002; p=0.004, respectively). Those who were in menopause, those with a history of a gynecological disease, and those who underwent regular gynecological examinations had statistically significantly higher total scores of GCPIS (p=0.043; p=0.026; p=0.031, respectively) (Table 4).

As shown in Table 5, the total scores of GCPIS were statistically significantly higher for those who had received information about GC and screening tests and had Pap-smear tests (p=0.001; p=0.018, respectively). There was also a statistically significant difference between HPV vaccination statuses in terms of total scores of GCBPS (p=0.001) (Table 5).

Table 1. Sociodemographic and medical characteristics of the study group

		Min-max	Mean ± SD (median)
Age (years)		18-65	33.92±11 (12)
Gravida (n=382)		0-10	2.52±1.5 (2)
Age of first intercourse (n=421)		13-55	22.49±4.27 (22)
		n	**%**
Age groups	18-35 years	372	60.9
	36-65 years	239	39.1
Education level	Literate	13	2.1
	Primary school	88	14.4
	Middle school	43	7.0
	High school	148	24.2
	University	319	52.2
Marital status	Single	222	36.3
	Married	389	63.7
Income level	Low	267	43.7
	Middle	283	46.3
	High	61	10.0
Presence of a chronic disease	No	392	64.2
	Yes	219	35.8
Presence of a gynecological disease	No	406	66.4
	Yes	205	33.6
Regular gynecological examination	Yes	185	30.3
	No	426	69.7
Menstruation status	Yes	76	12.4
	No	535	87.6
Sexual activity	Yes	376	61.5
	No	235	38.5

Data are presented as mean ± SD (median), min: Minimum, max: Maximum, n (%) of the participants

DISCUSSION

Main Findings

In this study, which aimed to examine the knowledge status of women between the ages of 18 and 65 about protection from GC and the factors affecting it, according to the score obtained from the scale, participants' knowledge about prevention from GC was at a moderate level. The level of knowledge about GC prevention was higher among those who were university graduates, had medium-high income, had no menstruation, had a history of gynecological disease, had regular gynecological examinations, had received information about GC and screening tests before, and had Pap smear test.

Table 2. Participants' knowledge about gynecological cancers and their characteristics regarding screening tests and HPV vaccinations

		Min-max	Mean ± SD (median)
Age of first Pap smear		17-51	32.64±7.32 (32)
Age at the first HPV-DNA test		18-56	33.76±10.57 (31)
		n	**%**
Obtaining information about gynecological cancers and screening	No	369	60.4
	Yes	242	39.6
Having had a Pap smear test	No	398	65.1
	Yes	213	34.9
Having had an HPV DNA test	No	567	92.8
	Yes	44	7.2
HPV vaccination status	Done	37	6.1
	Planned	142	23.2
	Rejected	432	70.7

Data are presented as mean ± SD (median), min: Minimum, max: Maximum, n (%) of the participants, HPV: Human papilloma virus

Table 3. Total and sub-dimension scores of the gynecological cancer prevention information scale

	Min-max	Mean ± SD	Median
GCPIS total score	0-35	15.17±7.08	15
PFFRC	0-12	6.52±3.21	7
FRCS	0-10	2.73±2.85	2
OFRSRD	0-6	2.27±1.78	2
EDFRSCPF	0-4	2.98±1.11	3
BRRFRS	0-3	0.66±0.84	0

Data presented as mean ± SD (median), min: Minimum, max: Maximum, BRRFRS: Birth-related risks of the female reproductive system; EDFRSCPF: Early diagnosis of female reproductive system cancers and physiological factors; FRCS: Female reproductive cancer symptoms; OFRSRD: Observations on female reproductive system-related diagnosis; PFFRC: Prevention of female reproductive cancers

Comparison with the Existing Literature

Some studies conducted recently have shown that women's level of knowledge about various GC and screening methods, regular gynecological examinations, and especially cervical cancer screening rates are low (5,7,8). Fonnes et al. (15) investigated how often people in the community knew about GC compared with other types of cancer and reported that only 41% of the participants had heard of one or more cancers in female genital organs. It was observed that women's awareness of GC is higher than that of men (15). In our country, there are various studies investigating the awareness of different types of GC. Evcili and Bekar (16) found that women aged 18 years

Table 4. Total and sub-dimension scores of the scale according to the socio-demographic and medical characteristics

		PFFRC	FRCS	OFRSRD	EDFRSCPF	BRRFRS	GCPIS total score
		Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)
Age groups	18-35	6.47±3.29 (7)	2.47±2.78 (1)	2.19±1.86 (2)	2.97±1.17 (3)	0.67±0.85 (0)	14.77±7.43 (14)
	36-65	6.59±3.1 (7)	3.14±2.91 (2)	2.4±1.67 (2)	3.02±1.02 (3)	0.64±0.83 (0)	15.79±6.48 (15)
	[1]p	0.771	**0.002***	0.077	0.915	0.686	**0.048***
Education level	Literate	6.85±3.69 (9)	4±2.86(4)	2.46±1.98 (3)	2.38±1.5 (2)	0.54±0.78 (0)	16.23±8.79 (18)
	Primary s.	5.97±3.25 (6)	3.31±3 (3)	1.93±1.68 (1)	2.95±1.04 (3)	0.58±0.78 (0)	14.74±6.94 (14)
	Middle s.	5.91±3.37 (6)	2.6±2.71 (2)	1.51±1.39 (1)	2.86±1.3 (3)	0.67±0.92 (0)	13.56±6.77 (13)
	High s.	5.77±3.22 (6)	2.31±2.41 (1)	1.86±1.55 (2)	2.84±1.13 (3)	0.66±0.78 (0)	13.43±6.21 (14)
	University	7.09±3.07 (8)	2.73±2.99 (2)	2.65±1.87 (3)	3.11±1.07 (4)	0.69±0.88 (0)	16.27±7.29 (16)
	[2]p	**0.000***	0.095	**0.000***	**0.044***	0.869	**0.002***
Marital status	Single	6.69±3.27 (7)	2.57±2.67 (2)	2.21±1.88 (2)	3.05±1.13 (4)	0.66±0.87 (0)	15.18±7.41 (15)
	Married	6.42±3.19 (7)	2.82±2.95 (2)	2.31±1.73 (2)	2.96±1.1 (3)	0.66±0.83 (0)	15.17±6.9 (15)
	[1]p	0.274	0.742	0.360	0.224	0.830	0.949
Income level	Low	6.15±3.22 (6)	2.4±2.63 (1)	1.99±1.69 (2)	2.88±1.17 (3)	0.54±0.77 (0)	13.96±6.76 (14)
	Middle	6.81±3.16 (7)	2.98±2.94 (2)	2.51±1.85 (2)	3.05±1.07 (3)	0.8±0.91 (1)	16.14±7.15 (15)
	High	6.80±3.33 (7)	3±3.24 (2)	2.39±1.74 (2)	3.2±1 (4)	0.57±0.76 (0)	15.97±7.46 (16)
	[2]p	0.054	0.075	**0.004***	0.105	**0.002***	**0.004***
Chronic disease	No	6.68±3.15 (7)	2.7±2.89 (2)	2.23±1.78 (2)	2.96±1.14 (3)	0.62±0.82 (0)	15.19±6.94 (15)
	Yes	6.22±3.31 (7)	2.79±2.79 (2)	2.34±1.8 (2)	3.05±1.05 (3)	0.74±0.88 (0)	15.14±7.35 (15)
	[1]p	0.104	0.489	0.502	0.502	0.134	0.952
Gynecological disease	No	6.38±3.32 (7)	2.5±2.67 (2)	2.17±1.82 (2)	2.98±1.13 (3)	0.65±0.82 (0)	14.68±7.03 (14)
	Yes	6.79±2.99 (7)	3.19±3.13 (2)	2.47±1.71 (2)	3.01±1.07 (3)	0.69±0.89 (0)	16.15±7.11 (15)
	[1]p	0.216	**0.021***	**0.028***	0.835	0.816	**0.026***
Regular gynecological examination	Yes	6.75±3.06 (7)	3.09±2.89 (2)	2.56±1.67 (2)	3.03±1.14 (3)	0.68±0.84 (0)	16.1±6.76 (16)
	No	6.42±3.28 (7)	2.58±2.82 (2)	2.15±1.83 (2)	2.97±1.1 (3)	0.66±0.85 (0)	14.77±7.19 (14)
	[1]p	0.318	**0.014***	**0.004***	0.376	0.681	**0.031***
Menstruation status	Yes	7.76±3.38 (7.5)	3.91±3.17 (3)	2.42±1.80 (2)	3.01±1.04 (3)	0.56±0.77 (0)	16.67±7.41 (17)
	No	6.48±3.19 (7)	2.56±2.76 (1)	2.25±1.78 (2)	2.98±1.12 (3)	0.67±0.85 (0)	14.96±7.02 (14)
	[1]p	0.363	**0.001***	0.448	0.979	0.340	**0.043***
Sexual activity	Yes	6.43±3.08 (7)	2.74±2.84 (2)	2.32±1.7 (2)	2.97±1.1 (3)	0.67±0.84 (0)	15.13±6.64 (15)
	No	6.67±3.42 (7)	2.72±2.87 (2)	2.2±1.93 (2)	3.01±1.13 (3)	0.65±0.86 (0)	15.25±7.75 (15)
	[1]p	0.235	0.971	0.212	0.525	0.670	0.917

Data presented as mean ± SD (median), min: Minimum, max: Maximum, [1]Mann-Whitney U test, [2]Kruskal-Wallis test, *p<0.05 BRRFRS: Birth-related risks of the female reproductive system, EDFRSCPF: Early diagnosis of female reproductive system cancers and physiological factors, FRCS: Female reproductive cancers symptoms, OFRSRD: Observations on female reproductive system related diagnosis, PFFRC: Prevention from female reproductive cancers

and older had moderate knowledge of GC prevention. Erenoğlu (17) also reported that adult women's awareness of GC is at a sufficient level. However, there are also studies reporting that women's awareness of protection from GC is above the moderate level (6,9,10,12). However, even if women's awareness of GC is high, there may be a lack of correct information and preventive measures (18). awareness of GC increases as health literacy increases (13). In our study, participants' knowledge of GC prevention was found to be moderate. Necessary interventions should be made to increase women's knowledge of GC prevention, and an effective cancer screening program should be conducted.

Various factors such as age, socioeconomic level, and health status can affect women's level of knowledge and awareness about GC (6). In a study conducted by Teskereci et al. (5) in 2021, it was reported that as women's age increased, their awareness of GC increased. In the study of Evcili and Bekar (16), the knowledge of women aged 35-49 on protection from GC was found to be significantly higher than women aged 18-34 years. There are also studies showing that women's awareness of GC decreases as their age increases (10,12). In our study, similar to the literature, the knowledge of the participants in the 36-65 age group to prevent GC was higher than that in the 18-35 age group. In addition to women whose risk for GC increases with age, it is necessary to increase the level of knowledge in all age groups.

There is a relationship between education level and cancer awareness (19). Özcan and Demir Doğan (10) reported that women with higher education and income levels found higher awareness of GC. Evcili and Bekar (16) found that those with high school or higher education had a higher level of knowledge about GC protection. However, it was found that those with "good" economic status had a higher level of knowledge about protection from GC than those who defined it as "bad" and "moderate" (16). In the study conducted by Atlas and Er Güneri (12), it was found that as the level of education increased, the awareness about GC also increased, but there was no difference in terms of income levels. On the other hand, in the study of Teskereci et al. (5) and Kaya Şenol et al. (9), no significant difference was found in terms of awareness about GC according to the education and income level of the participants. In our study, the knowledge level of university graduates on GC prevention was significantly higher than that of secondary and high school graduates. The level of knowledge about protection from GC was found to be higher for those with a middle income level than for those with a low income level. It should be taken into account that people with low socioeconomic status may have a low level of knowledge about cancers due to the inadequacy of access to health services and low health literacy.

Atlas and Er Güneri (12) found that those who had 2 or fewer pregnancies had higher awareness of GC than those who had 3 or more pregnancies, but they did not find a significant correlation

Table 5. Total and sub-dimension scores of the scale according to participants' knowledge about gynecological cancers and characteristics of screening tests and HPV vaccination

		PFFRC	FRCS	OFRSRD	EDFRSCPF	BRRFRS	GCPIS total score
		Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)
Obtaining information about gynecological cancers and screening	No	6.08±3.21 (6)	2.36±2.59 (1)	1.85±1.69 (2)	2.86±1.16 (3)	0.59±0.8 (0)	13.74±6.74 (14)
	Yes	7.19±3.11 (8)	3.3±3.12 (2)	2.91±1.74 (3)	3.18±1.01 (4)	0.78±0.9 (1)	17.36±7.05 (17)
	[1]p	**0.001***	**0.001***	**0.001***	**0.001***	**0.010***	**0.001***
Having had a Pap smear test	No	6.47±3.36 (7)	2.53±2.75 (1)	2.07±1.85 (2)	2.98±1.13 (3)	0.68±0.86 (0)	14.73±7.44 (14)
	Yes	6.61±2.94 (7)	3.11±3 (2)	2.65±1.6 (2)	3±1.08 (3)	0.64±0.82 (0)	16±6.3 (15)
	[1]p	0.873	**0.015***	**0.001***	0.957	0.728	**0.018***
Having had an HPV DNA test	No	6.52±3.24 (7)	2.67±2.84 (2)	2.22±1.8 (2)	2.97±1.12 (3)	0.67±0.84 (0)	15.05±7.16 (15)
	Yes	6.5±2.85 (6.5)	3.45±2.86 (3)	2.95±1.49 (3)	3.23±0.99 (4)	0.55±0.85 (0)	16.68±5.89 (15.5)
	[1]p	0.681	**0.043***	**0.004***	0.156	0.249	0.093
HPV vaccination status	Yes	5.51±2.78 (5)	1.49±1.91 (1)	1.54±1.24 (1)	2.76±1.14 (3)	0.62±0.86 (0)	11.92±5.01 (12)
	Planning	7.47±3.23 (8)	3.26±3.13 (2)	3.04±1.8 (3)	3.18±0.99 (4)	0.89±0.93 (1)	17.84±7.81 (17)
	Rejected	6.29±3.18 (7)	2.66±2.78 (2)	2.08±1.75 (2)	2.94±1.14 (3)	0.59±0.8 (0)	14.57±6.74 (14)
	[2]p	**0.001***	**0.003***	**0.001***	**0.047***	**0.002***	**0.001***

Data presented as mean ± SD (median), minimum: Min, maximum: Max, [1]Mann-Whitney U test, [2]Kruskal-Wallis test, *p<0.05, HPV: Human papilloma virüs

with the number of births. In another study, it was reported that as women's gravida and parity increased, their awareness of GC decreased (10). Teskereci et al. (5), on the other hand, did not find a significant relationship between gravida, parity, and knowledge levels of prevention from GC. In our study, there was no statistically significant relationship between the number of pregnancies and the knowledge level on GC prevention.

There are studies in the literature showing that women of reproductive age have a higher awareness of GC (9,12,20). In one study, no statistically significant difference was found in terms of participants' awareness of GC according to their menopausal status (20). In our study, the knowledge level of women who went through menopause to prevent GC was found to be higher than that of people who did not go through menopause.

Women who have regular gynecological examinations and self-external genital organ follow-ups have a higher level of knowledge about the prevention of GC (16,21). However, awareness of GC among those who admit to a physician when they have a gynecological complaint may be higher than among those who admit for routine control (12). In our study, similar to the literature, those who went to regular gynecological examinations and those with a history of gynecological disease had a high level of knowledge about prevention from GC. It was thought that women who went to gynecological examination due to any gynecological complaint/disease might be informed by health professionals.

In addition to routine gynecological examination, the Pap smear test and HPV test can detect GC and precancerous lesions early. HPV vaccination also reduces the risk of cancer (22). The way to increase the number of attempts to prevent GC is to provide a sufficient level of knowledge (10,17). However, the rate of awareness of cervical cancer screening, Pap smear test, and HPV vaccine among women in our country is quite low (23). Awareness of GC was found to be higher in those who participated in the screenings, as in regular examinations (5,16,24). On the other hand, Tiiti et al. (25) did not find a statistically significant relationship between the previous Pap smear status and the level of knowledge about cervical cancer risk factors. Atlas and Er Güneri (12) did not find a statistically significant difference in the awareness of GC according to HPV vaccination status. Among the women who participated in our study, those who had knowledge about GC and screening tests had a higher level of knowledge about GC prevention. It was observed that those who had Pap smear test before and those who were planning to have an HPV vaccine had a higher level of knowledge about GC prevention. The data we have obtained emphasize once again that informative materials for society should be delivered to all women who need to be screened as much as possible. Awareness of all health professionals who can come into contact with women who need GC screening should also be increased through in-service training.

Study Limitations

The main limitation of our study is that it is single-centered and cannot be generalized to the population.

CONCLUSION

According to this study, women's knowledge of prevention from GC is at a moderate level, and those who have a university degree, with a medium and high-income level, who are in the postmenopausal period, with gynecological diseases, who go to regular gynecological examinations, who have information about GC and screening tests before, and who have had Pap-smear test had a higher level of knowledge about prevention from GC. Along with regular gynecological examinations, women should be made aware and encouraged about screening programs and vaccination.

Ethics

Ethics Committee Approval: The study was conducted with the approval of the local ethics committee (date: 08.12.2021, no:390).

Informed Consent: The participants were informed verbally, and in writing, and written consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

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The Relationship Between Diabetes Mellitus and Fournier's Gangrene

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Abstract

Objective: Fournier's gangrene is necrotizing fasciitis with polymicrobial infection involving the scrotum, perineum and perianal region, sometimes spreading to the abdomen and chest with a high mortality. The purpose of the present study was to examine whether diabetes mellitus (DM) has an effect on Fournier's gangrene mortality, length of hospital stay and laboratory values.

Methods: The patient files with a history of hospitalization in University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital were used in the study. The epicrisis of 250 patients who were diagnosed with necrotizing fasciitis and gangrene between January 2014 and July 2021 were read and 50 patients who had Fournier's gangrene were identified from epicrisis. Demographic analyzes, physical examination and laboratory findings of the identified patients, and the drugs they used were reviewed retrospectively.

Results: DM was detected in 28 (56%) of 50 patients hospitalized with the diagnosis of Fournier's gangrene in the study. The patients were divided into 2 groups as those with and without diabetes mellitus. No statistically significant differences were detected between the discharge and death distributions of the diabetic and non-diabetic groups (p=0.371). The length of hospital stay was statistically significantly higher in the diabetic group than in the non-diabetic group (p=0.017).

Conclusion: Diabates mellitus has an important place among the risk factors for Fournier's gangrene disease and it was detected in more than half of the patients in the present study. It was found that diabetes prolonged the hospitalization period of patients who had Fournier's gangrene, but had no effect on mortality.

Keywords: Diabetes mellitus, Fournier's gangrene, SGLT-2 inhibitors, necrotizing fasciitis

INTRODUCTION

Fournier's gangrene (FG) is a necrotizing fasciitis that develops because of the synergistic polymicrobial infection of the perineal, genital, or perianal regions (1). Despite all treatments, it has a high mortality rate (20-40%) (2). The most common causes are gastrointestinal system with 30-50%, genitourinary system with 20-40%, and cutaneous causes with 20% (3). There are many risk factors that prepare the ground for the formation of the disease and facilitate its spread. Diabetes mellitus (DM) is one of these risk factors and is found in 32-66% of all FG patients (4). FG was also reported in patients using Sodium Glucose Co-Transporter 2 (SGLT-2) inhibitors, which are among the oral antidiabetic drugs used in the treatment of DM (5). In the present study, the purpose was to investigate the relationship between FG and DM.

METHODS

The study was planned retrospectively. Patients with FG were determined by reading the epicrisis of patients diagnosed with A48.0 gas gangrene, R02 gangrene, and M72.5 fasciitis among the patients who were hospitalized in the University of Health Sciences Turkey Prof. Dr. Cemil Taşcıoğlu City Hospital between January 2014 and July 2021. The patients' history, additional diseases, demographic characteristics, hospitalization physical examination findings, standard biochemistry analyses, treatments

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(oral antidiabetic drugs, insulin), mortality, and hospitalization times of patients diagnosed with FG were evaluated. Patients who were diagnosed with FG were divided into 2 groups as those with and without DM. The clinical, laboratory, and endpoints were also compared. Study University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital It was examined in the meeting of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee dated 07/06/2021 and was found to be ethically appropriate according to the decision numbered 225. Ethics committee approval decision/protocol number: E-48670771-514.10. Our study is retrospective; therefore, there is no need for a patient consent form. In the power analysis of our study performed with the G*power 3.1 program, the effect size for the presence of DM in the study group was found to be 0.40 (FG: Review of 120 patients and predictors of mortality) (alpha error probability =0.05); In the sample size analysis performed by taking the power value of 0.80, the total number of samples required to be taken in total was found to be 50.

Statistical Analysis

In this study, statistical analyses were performed with Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) package program. In the evaluation of the data, in addition to descriptive statistical methods (mean, standard deviation, median, interquartil range), the distribution of the variables was examined with the Shapiro-Wilk normality test, the independent t-test for the comparison of the paired groups of the variables with normal distribution, and the Mann-Whitney U test for the comparison of the pairwise groups of the non-normally distributed variables. The chi-square test was used to compare the qualitative data. The results were evaluated at the significance level of $p<0.05$.

RESULTS

A total of 50 patients who had FG diagnosed because of retrospective screening were included in the study. All 50patients were receiving antibiotic therapy and had a post-surgical intensive care history. DM was diagnosed in 28 of the 50 patients (56%), and hypertension was accompanied by 48%, cardiovascular disease in 28%, chronic kidney failure in 10%, and malignancy in 8% after diabetes. Among the 50 patients, 27 (54%) were male and 23 (46%) were female. The patients were divided into 2 groups: those with and without diabetes mellitus. No statistically significant differences were detected between the gender distributions of the diabetic and non-diabetic groups (p=0.226). In the diabetic group, 11 (39.2%) patients were using only oral antidiabetic, 9 (32.1%) patients were using only insulin therapy, 6 (21.4%) were using both oral antidiabetic and insulin therapy. One patient was using an SGLT-2 inhibitor (empagliflozin) and 2 patients (7.1%) were not using medication, although they had diabetes. The mean age of the diabetic group was 56.39 found to be 56.39±13.44 years, and the mean age of the non-diabetic group was 59.36±13.82 years. No statistically significant differences were detected between the mean age of the diabetic and non-diabetic groups (p=0.447) (Table 1).

When the clinical characteristics of the groups with and without FG diabetes during hospitalization were examined, no significant differences were detected in terms of fever (p=0.156) and pulse (p=0.063) values (Table 2).

When the laboratory values were evaluated, no significant differences were detected in leukocytes (p=0.557), hemoglobin (p=0.367), creatinine (p=0.277), potassium [p=0.247, alanin aminotransferaz (ALT) (p=0.710), C-reaktive protein (CRP) (p=0.257), and bicarbonate (HCO_3) levels (p=0.364)]. The mean sodium levels of the group with diabetes were found to be lower than those of the non-diabetic group at a statistically significant level (p=0.001). The mean fasting glucose value of the diabetic group was found to be 201 mg/dL, and the mean glucose level of the non-diabetic group was 93 mg/dL (Table 2).

Discharge and mortality were excluded from the statistics because 1 out of 50 patients who had FG left the hospital by

Table 1. Demographic and clinical characteristics of the patient group

	DM (-) (n=22)		DM (+) (n=28)		p
Age mean ± SD	59.36±13.82		56.39±13.44		0.447
Male	14	63.64%	13	46.43%	0.226
Female	8	36.36%	15	53.57%	0.226
HT	5	22.73%	19	67.86%	**0.002**
CVD	4	18.18%	10	35.71%	0.171
CRF	3	13.64%	2	7.14%	0.447
Malignancy	2	9.09%	2	7.14%	0.801

HT: Hypertension, CVD: Cardiovascular disease, CRF: Chronic kidney failure, DM: Diabetes mellitus, SD: Standard deviation, Statistically significant p values are indicated in bold

signing a treatment refusal, and 1 patient was transferred to the intensive care unit. In the remaining 48 patients, the mortality rate was 31.25%. No statistically significant differences were detected between the distribution of discharge and death rates between the groups with and without diabetes (p=0.371) (Table 3).

The mean hospital stay was 52 days in the group with diabetes and 29 days in the non-diabetic group. The length of stay in the group with diabetes was found to be higher than that in the non-diabetic group at a statistically significant level (p=0.017) (Table 3).

No statistically significant differences were detected between the mean Fournier gangrene severity index (FGSI) of the diabetic and non-diabetic groups (p=0.480).

DISCUSSION

DM was detected in 56% of the 50 patients who had FG. When divided into diabetic and non-diabetic groups, the hospitalization time of the diabetic group was found to be higher than -the non-diabetic group at a statistically significant level. No statistically significant differences were detected when the mortality of the diabetic and non-diabetic groups was compared.

FG is a necrotizing fasciitis that develops because of a polymicrobial infection that affects the scrotum, perineum, and perianal regions and sometimes spreads to the abdomen and chest (1).

There are many risk factors that prepare the ground for the formation of the disease and facilitate its spread. DM is among these risk factors (4).

The common characteristic of all risk factors in FG is that they reduce cellular immunity and impairs immune resistance (3). Diabetics have many bacteria on their skin, making the risk of skin infection easier. Immune functions, such as chemotaxis and phagocytosis, are impaired in diabetes. As a result of this, the spread of the bacteria increases. Diabetic angiopathy impairs blood circulation in the disease area, facilitating anaerobic infection (6). Impaired blood flow causes tissue ischemia in small vessels. Diabetic neuropathy increases the risk of urinary infection in patients with urethral obstruction and prepared the ground for FG (7). Diabetic neuropathy also delays the clinical course of FG (8).

Table 2. The comparison of the clinical and laboratory characteristics of the patient groups

		DM (-) (n=22)	DM(+) (n=28)	p
Pulse	**Mean ± SD**	86.32±8.94	93.36±15.44	0.063
Temperature	**Mean ± SD**	36.5±0.47	36.73±0.62	0.156
WBC	**Mean ± SD**	18758.64±8299.26	20313.21±9894.96	0.557
Hemoglobin	**Mean ± SD**	11.15±2.44	11.85±2.27	0.367
Creatinine	**Mean ± SD**	1.87±2.07	1.12±0.7	0.277
	Median (IQR)	1.05 (0.78-2.05)	0.85 (0.63-1.38)	
Na	**Mean ± SD**	136.91±4.26	132.14±4.96	**0.001**
K	**Mean ± SD**	4.06±0.71	4.30±0.69	0.247
ALT	**Mean ± SD**	29.73±37.67	22.75±15.37	0.710
	Median (IQR	16 (8.75-36)	17 (11.25-33.75)	
CRP	**Mean ± SD**	212.5±111.13	260.86±144.65	0.257
	Median (IQR)	185 138.75-263.5)	222.5 (158.5-374.5)	
HCO_3	**Mean ± SD**	19.38±5.01	21.5±7.07	0.364
Glucose	**Mean ± SD**	93.64±20.91	201±106.67	**0.0001**

WBC: White blood cell, Na: Sodium, K: Potassium, ALT: Alanine aminotransaminase, CRP: C-reactive protein, HCO_3: Bicarbonate, DM: Diabetes mellitus, SD: Standard deviation, Statistically significant p values are indicated in bold

Table 3. The comparison of the types of discharge (death and discharge with recovery) and length of stay of the patient groups

	DM (-) (n=22)	DM (+) (n=28)	p
Discharge-death	15-5	18-10	0.371
Hospitalization period	29.05±21.89	52.57±51.07	**0.017**

DM: Diabetes mellitus

It was reported that 32-66% of patients with FG also have DM (4). In a previous study that examined 1,726 patients who had FG, 20% of patients who had diabetes were identified (3). In another study that was conducted with 41 patients who had FG in our country, 41.4% of diabetic patients were detected (9). Also, in a study conducted with 120 patients who had FG in our country, the rate of patients who had diabetes was found to be 57.5% (10). In this study, DM was detected in 56% of 50 patients who had FG, similar to the literature data. As reported in many studies, DM was found to be an important risk factor for patients with FG in our study.

Despite all treatments, it has a high mortality rate (20-40%) (2). In a study that was conducted with 1,641 patients who had FG, its mortality was found to be 16% (3). In another study conducted in our country, mortality was found to be 20.8% (10). Mortality was found to be 31.25% in our study.

In some previous studies, it was reported that DM has no effect on mortality in patients with FG (4,11-13). However, DM was found to have a higher mortality rate in a 17-year systematic review and meta-analysis (14). In our study, although mortality was higher in the group with DM, no statistically significant difference was detected compared to those without DM (p=0.371).

Also, there are different results in studies conducted on length of hospital stay. In a study, DM did not affect the length of hospital stay (4). In another study that was conducted in our country, it was found that the length of hospital stay was longer in patients who had DM FG (15). In our study, the average length of hospital stay in the diabetic group was 52 days, and it was 29 days less in the non-diabetic group. The length of hospital stay was statistically and significantly higher in the diabetic group than in the non-diabetic group (p=0.017). There are multiple levels of dysfunction in the immune system in diabetes. Cytokine signals are affected in innate and adaptive immunity. Diabetes suppresses many cytokines. Neuropathy increases susceptibility to lesion in the skin barrier, which is the first defense system. Diabetes does not develop an appropriate immune response because of poor vascular flow at sites of infection and predisposes to secondary infections, making recovery more difficult. It was considered that making efforts to regulate blood sugar in patients with DM may affect the length of hospital stay.

Leukocytes (p=0.557), hemoglobin (p=0.367), creatinine (p=0.277), potassium (p=0.247), ALT (p=0.710), CRP (p=0.257) and HCO_3 (p=0.364) values were not significantly different in the diabetic group compared to the non-diabetic group. Sodium was significantly lower in the diabetic group. The reason for this is that glucose is high in the diabetic group (mean fasting glucose is 93 mg/dL in the non-diabetic group, 201 mg/dL in the diabetic group).

FGSI, which is a scoring system, was developed by Laor et al. (16) by using vital signs and some laboratory data to determine the severity of infection and prognosis in cases of FG. Temperature, pulse, respiratory rate, hematocrit, leukocytes, creatinine, serum sodium and potassium, and HCO_3 are used in this scoring system. In their study, Laor et al. (16) found the mortality risk to be 75% if the FGSI was >9 and the survival rate to be 78% if it was ≤9%. No statistically significant differences were found in our study between the FGSI of the groups with and without diabetes (p=0.480).

Cases of FG were reported in the treatment of SGLT-2 inhibitors. The FDA defined 55 cases of FG in patients who were receiving SGLT2 inhibitors between March 1, 2013 and January 31,2019 (5). In the present study, one of 28 diabetic patients was using an SGLT-2 inhibitor.

The study was conducted in a single center and had a retrospective design limited to a relatively low number of patients.

CONCLUSION

DM has an important place among the risk factors for FG disease. It prolonged the hospital stay but had no effect on mortality. In addition, no effects were detected on the laboratory values and the FGSI, which is considered to show the severity of the disease, in patients who had diabetes FG. It is considered that SGLT-2 inhibitors that are used in the treatment of DM are not related to FG.

Ethics

Ethics Committee Approval: Study University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital. It was examined in the meeting of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee dated 07/06/2021 and was found to be ethically appropriate according to the decision numbered 225. Ethics committee approval decision/protocol number: E-48670771-514.10.

Informed Consent: Our study is retrospective; therefore, there is no need for a patient consent form.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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

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Effect of COVID-19 Pandemic on Diagnosis and Treatment Delays in Primary Bladder Cancer in Turkey: Single-Institution Experience, 36 Month Screening

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Abstract

Objective: The pandemic caused delays in the diagnosis and treatment of many diseases, and bladder cancer is one of them. The aim of this study is to investigate the effect of the pandemic on primary bladder cancer by comparing the pre- and post-coronavirus disease 2019 pandemic within an 18-month spectrum, based on March 2020 in patients with primary bladder cancer who applied to our clinic.

Methods: Only patients operated for primary bladder tumors were included in the study, they were divided into two groups as those who underwent surgery before and after the 18-month period. Those operated before March 2020 were classified as group A, those operated after March 2020 were classified as group B. The characteristics of the two groups, such as age, gender, smoking status, tumor size, tumor multiplicity, and pathological stage, were compared.

Results: The existing bladder tumor was examined according to its size, tumor multiplicity and pathological stage, and it was observed that there were significant differences between the groups ($p<0.05$).

Conclusion: Delays in the diagnosis of diseases such as bladder cancer may cause to progression of the disease.

Keywords: COVID-19, bladder cancer, bladder cancer follow-up

INTRODUCTION

Bladder cancer is a significant cause of morbidity and mortality. The tumor-node-metastasis staging system combined with tumor grade guides us in terms of treatment management. Without a doubt, stage is one of the most important prognostic factor in bladder cancer (1). The tumor stage has a one-to-one relationship with the depth of the tumor in the muscle. The time the patient will receive treatment is very important in increasing the muscle depth and in the progression of the stage. Delays in bladder cancer treatment are likely to worsen the prognosis of patients (2).

In the period since the beginning of 2020, the coronavirus disease of 2019 (COVID-19) continues to spread all over the world and still has not been brought under control. The disease has progressed very rapidly and continues to spread on a global scale despite all the precautions taken. After the World Health Organization declared a pandemic on March 11, 2021, radical changes occurred in the provision of healthcare. Many healthcare professionals had to focus on their COVID-19 patients (3-5). As the pandemic flared up, non-COVID-19 patients in hospitals began to be unable to receive adequate and fast health care. Lockdowns, restrictions, and stay-at-home calls have reduced the number of hospital admissions of non-COVID-19

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patients. The focus of almost all healthcare institutions and healthcare professionals on the struggle against COVID-19 has led to a prolongation of the diagnosis and treatment times of some diseases such as cancer (6). As a result of this situation, it can be thought that the diagnosis of many patients with bladder cancer is delayed, and thus the pandemic contributes poorly to the prognosis of bladder cancer.

The aim of this study is to investigate the effect of the pandemic on primary bladder cancer by comparing the pre- and post-COVID-19 pandemic within an 18-month spectrum, based on March 2020, in patients with primary bladder cancer who visited our clinic. In healthcare institutions and healthcare professionals, an increase in bladder cancer stage should be expected compared to the pre-COVID-19 period, due to the decrease in the hospital admissions due to the increased workload and the recommendations of the goverments to stay at home.

METHODS

Study Design

This study was conducted at Sakarya Training and Research Hospital. The data of all patients who were registered in the urology department of our institution and operated due to a bladder tumor between September 2018 and September 2021 were collected from their medical documents. The files of 1,075 patients who underwent surgery for bladder tumor were reviewed. These patients were included in the study according to certain criteria. Only patients operated for primary bladder tumors were included in the study. If the operated individuals required ReTUR after the first operation, the pathology report with advanced stage was taken into consideration, and if the pathological stage was reported the same, it was counted. The patient needed ReTUR but decided not to have the operation voluntarily or if the patient wanted to continue his treatment in another center was excluded from the study. Regardless of the pathological diagnosis of the patient, if there was metastasis on imaging, the patient was grouped assuming a minimum T2 bladder tumor. If the patient underwent radical cystectomy without a pathological diagnosis of T2, the pathology report of the radical cystectomy material was considered.

The above-mentioned criteria were considered and 218 primary bladder tumor patients were included in the study. Based on the date of March 2020, when the first COVID-19 case was seen in Turkey, the patients were divided into 2 groups: as those who underwent surgery before and after the 18-month period. Those operated before March 2020 were classified as group A, and those operated after March 2020 were classified as group B (Figure 1). The characteristics of the 2 groups, such as age, gender, smoking status, tumor size, tumor multiplicity, and pathological stage, were compared. The size written in the operation note by the surgeon performing the operation was accepted as the tumor size. Information about tumor multiplicity was also obtained from the operation note. Smoking status was analyzed as 3 different conditions: as never smoker, ex-smoker, and active smoker. The pathological stage was divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) and then analyzed.

Statistical Analysis

Data were analyzed using SPSS 20.0 software (SPSS, Version 20.0; International Business Machines Corp, Armonk, NY). Chi-square and t-tests were used for statistical analysis. Distribution was analyzed using the Shapiro-Wilk test. Variables with normal distribution were analyzed using a Student's t-test. Chi-square test was used for the analysis of qualitative data. $P<0.05$ value was defined as statistically significant.

RESULTS

There were 124 and 94 patients in groups A and B, respectively. Characteristics of all patient, before and after the outbreak of COVID-19 are shown in (Table 1). The mean age in group A and B were 64.6 64.6±7.6 and 63.4±9.4, respectively. There was no statistically significant difference between the 2 groups (p=0.327). When groups A and B were compared based on gender, it was seen that there was no statistical difference between the groups (p=0.209). When the patients were examined according to their

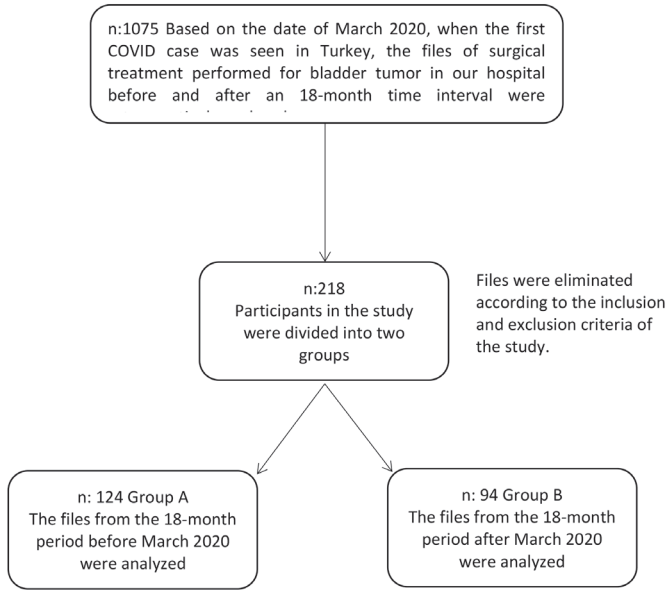

Figure 1. Study algorithm

Table 1. Characteristics of all patients before and after the outbreak of COVID-19

Parameters	Grup A (n=124)	Grup B (n=94)	p value
Age	64.6±7.6	63.4±9.4	0.327[a]
Gender			
Male	106	86	0.209[b]
Female	18	8	
Smoking status			
None	11	5	0.122[b]
Past smoker	44	24	
Active smoker	69	65	
Tumor size (centimeters)	3.5±2.5	4.49±2.5	**0.04[a]**
Multiplicity			
Single	84	38	**<0.01[b]**
Multipl	40	56	
Pathologic stage			
PLUMP[c],Ta,T1 (NMIBC[d])	99	64	**0.048[b]**
T2 (MIBC[e])	25	30	

[a]Variables with normal distribution were analyzed using Student's t-test
[b]Chi-square test was used for the analysis of qualitative data.
[c]Papillary urothelial neoplasm with low malignant potential
[d]Non-muscle invasive bladder cancer
[e]Muscle-invasive bladder cancer

smoking use, no significant difference was observed between never-smokers, past smokers, and active smokers (p=0.122).

The existing bladder tumor was examined according to its size, tumor multiplicity, and pathological stage, and significant differences were observed between the groups. The tumor diameter was recorded in centimetres, with the size noted by the surgeon who performed the operation. The mean tumor diameter was calculated as 3.5±2.5 cm for group A and 4.49±2.5 cm for group B. It was found that tumors in group B were statistically significantly larger in tumor diameters (p=0.04). The groups were compared according to whether the tumor in the bladder was multiple or single. For group A, the number of patients with a single tumor was 84, and the number of patients with multiple tumors was 38. For group B, the number of patients with a single tumor was 40, and the number of patients with multiple tumors was 56. Multiple tumors were more common in group B, and there was a statistically significant difference between the two groups (p<0.01). The pathological stages of the patients were examined as NMIBC and MIBC. It was seen that the number of NMIBCs for group A was 99 and the number of MIBC was 25. For group B, the number of NMIBC was 64 and the number of MIBC was 30. A statistically significant difference was observed in the comparison between the groups. It was observed that tumoral stages were more advanced in group B (p=0.048).

DISCUSSION

After the outbreak of the COVID-19 pandemic in 2020, there have been major changes in the management of world health systems (7). Many healthcare organizations have been taking care of COVID-19 patients, and accordingly, dramatic decreases have been observed in the number of healthcare professionals dealing with non-COVID-19 diseases. Some health institutions shutted down their operating theaters or reduced their capacity. Some operating rooms were converted into intensive care units. As the COVID-19 pandemic progressed, the number of non-COVID-19 patients examined by physicians decreased, so the diagnoses of diseases decreased, and the necessary treatments were interrupted (8). The duration of use and reporting of some tests, such as computed tomography and ultrasonography, which are required to diagnose non-COVID-19 patients, have been prolonged because of the excess of patients. In addition, patients' admissions to the hospital decreased. With some restrictions and closures imposed by the governments, individuals without an emergency disease had problems in applying to health institutions (7). In some diseases, delay in applying to health institutions can be tolerated, but in diseases such as cancer, which may progress rapidly, delay in seeing a doctor may cause serious damage to the progression of the disease and accordingly to human health.

In our study, based on March 2020, the date of the first COVID-19 case in Turkey, we scanned the period 18 months before and 18 months after this date. In these periods, we evaluated the factors that may affect the course of the disease, such as the stage, tumor size, and multiplicity of primary bladder cancer cases. The reason why we included primary bladder cancer in our study because the patients with a diagnosis are already in a follow-up protocol and that they will not have any problems in applying to the health institution, even if there is a pandemic. However, it can be assumed that even if primary bladder cancer has symptoms such as hematuria, it is possible to delay applications to health institutions because of the pandemic and stay-at-home suggestions. Therefore, it is not wrong to conclude that primary bladder tumors may progress more aggressively during the pandemic period.

Delays in cancer diagnosis due to thedisruptions in the health system during the pandemic were shared with some publications in the literature. As an example, in a study conducted in the United Kingdom published by Maganty et al. (9), it has been revealed

that the death rate from breast, colorectal, lung, and esophageal cancers increases as a result of decreased screening during the closure times of the pandemic period. Li et al. (7) examined the diagnosis and treatment delays of urological diseases of the COVID-19 pandemic in their single-center but large patient population publication in China where they examined urological diseases. In the post-COVID-19 outbreak period, the rate of use of beds in the hospital due to urological disease decreased by 44.8%. Despite this, the rate of hospitalization due to urological malignancies was found to be statistically significantly increased ($p<0.01$) (7). In a newly published multicenter study in Turkey, the effects of delaying cystoscopic surveillance on recurrence and progression in NMIBC patients during the COVID-19 pandemic were investigated. This multicenter study showed significant increases in recurrence and progression after delay in follow-up cystoscopies in the patients with NMIBC (3). In the study published by Wallace et al. (2) on delay in diagnosis of bladder cancer, it was shown that a shorter delay resulted in a lower tumor stage and a 5% better 5-year survival.

In addition to the effects of the COVID-19 pandemic itself on people, changes in the functioning of the health system and on human behavior indirectly have negative effects on human health due to delays in the diagnosis and treatment of non-COVID-19 diseases. Additionally, as a result of studies conducted in China, it has been shown that patients with cancer are more negatively affected by COVID-19, and this may lead to worse outcomes in these patients compared with the normal population (10). However, delaying an established treatment for cancer may also have negative consequences for the chance of a cure. May have a significant impact on the prognosis of the disease. Due to the general morbidity and life-threatening aggressive nature of bladder cancer, it is necessary to adapt to the COVID-19 period in order to evaluate patients who may have bladder cancer and to make a diagnosis without delay.

Study Limitations

Our findings must be considered in the context of several limitations. First of all, this is a single-center retrospective study with a small sample size. The local based intensity of the pandemic was not considered. Different results may be found in different regions. Secondly, carcinoma in situ was not considered because of lack of data. Third, we do not know whether the patients included in the study did not go to the doctor for examination because of the pandemic. If they have not seen a doctor for any reason other than the pandemic, statistical differences may occur. Fourth, as the distance of the patients from the health centers where they live increases, it can be expected that their access to health services will be more delayed than the patients who live in city centers during the pandemic. In the study, the distance of the residential areas of the patients and the health center was not questioned. Fifth, although T1 and Ta have different progression risks, they were not compared by making two separate groupings.

CONCLUSION

In conclusion, it is inevitable that the pandemic, which causes radical changes in health systems globally and increases the workload in health facilities, will prevent non-COVID-19 patients from receiving quality and uninterrupted health services. Delays in the diagnosis of diseases such as bladder cancer, which can be quickly diagnosed and controlled with the right treatment, may cause many bladder cancer cases to be undetected, and consequently the progression of the disease. Continuing screening and using cancer diagnostic tests in health systems will enable us to prevent patients from being harmed by cancer during the pandemic.

Ethics

Ethics Committee Approval: This study was conducted at Sakarya Training and Research Hospital. The data of all patients who were registered in the urology department of our institution and operated due to a bladder tumor between September 2018 and September 2021 were collected from their medical documents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: R.B.D., Design: Y.M.A., Data Collection or Processing: F.H., Analysis or Interpretation: A.G., Literature Search: R.B.D., H.S.K., K.D., F.H., Writing: Y.M.A.

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

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ORIGINAL ARTICLE

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Humerus Fractures Resulting from Wrist Wrestling: An Observational Diagnostic Study

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Abstract

Objective: Wrist wrestling is a sport in which two individuals position themselves on a table or a bar facing each other, with their elbows resting on the table, aiming to touch their opponent's hand to the table surface. Among adults participating in this sport, humerus shaft fractures are the most commonly observed injuries. In this study, our goal was to perform a systemic video analysis of humerus fractures occurring during wrist wrestling and to examine the mechanisms of these injuries. We assumed that identifying the positions commonly associated with injuries could be useful for injury prevention.

Methods: On May 1, 2023, a search was conducted on YouTube using the terms "arm wrestling fracture," "arm wrestling humerus," and "arm wrestling humerus fracture." Inclusion criteria were videos clearly showing humerus fractures and allowing clear evaluation of athletes. Videos suspected of having humerus fractures, repeated videos, videos with unclear athlete evaluation, and videos not related to wrist wrestling were excluded. Authors examined body tilt nad rotation, coronal shoulder position, sagittal shoulder position, shoulder rotation, sagittal elbow position, coronal elbow position, forearm rotation and sagittal wrist position.

Results: All 31 athletes included in the study were male. When examined for intra- and inter-observer agreement, it was observed to be nearly excellent ($k=0.959$, $p<0.001$; $k=0.946$, $p<0.001$). Out of the wrist wrestling matches, 19 (61.3%) were conducted with the athletes standing, while 12 (38.7%) were performed with them in a seated position.

Conclusion: Humerus fractures occurring during wrist wrestling do not appear to be significantly influenced by the athlete's shoulder, elbow, and wrist positions or whether the athlete is standing or sitting. Body position and changes in the center of mass during the competition might be contributing factors to humerus fractures.

Keywords: Humerus fracture, video analysis, wrist wrestling

INTRODUCTION

Wrist wrestling is a sport in which 2 individuals position themselves on a table or a bar facing each other, with their elbows resting on the table, aiming to touch their opponent's hand to the table surface (1). Among adults participating in this sport, humerus shaft fractures are the most commonly observed injuries (2).

Fractures of the humerus during wrist wrestling can be influenced by the morphological characteristics of the bone, muscle contractions, and body positions during wrist wrestling (3-7). Forearm length discrepancy between wrist wrestlers, control of the center of mass, and stabilization of the arm at the shoulder (glenohumeral) joint are crucial for preventing injuries (5). Additionally, wrist wrestling rules define a dangerous scenario as follows: "A straightened arm in a critical position or beyond the restraining line of the attacker's shoulder in the attacking direction of the humerus can be classified as dangerous" (7). When a wrestler straightens the arm of the competing side and lowers their shoulder below the plane of the table, a risky

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position emerges. This position seems to protect the wrestler from defeat. Furthermore, this position places significant stress on the elbow and shoulder joints, potentially leading to severe injuries (7).

Understanding the injuries and mechanisms involved in wrist wrestling is crucial for implementing safe practices in this sport (8). Video analysis is a method used to thoroughly determine the injury mechanisms (9). In this way, the body and extremity positions of the athletes at the time of injury and the maneuvers associated with the injury can be revealed. As far as we know, a systematic video analysis of wrist wrestling injuries is not currently available in the literature. In this study, we aimed to perform a systemic video analysis of humerus fractures occurring during wrist wrestling and to examine the mechanisms of these injuries. We assumed that identifying the positions commonly associated with injuries would be useful for injury prevention.

METHODS

On May 1, 2023, a search was conducted on YouTube using the terms "arm wrestling fracture," "arm wrestling humerus," and "arm wrestling humerus fracture." Videos were watched by an author to identify those featuring humerus fractures. No Ethical Committee approval or informed consent was required for this study, as the athletes' information is in the public domain and freely available on the web without any restriction. However, the privacy of the athletes was maintained as no direct reference to their identity was made in the text. The inclusion criteria were videos clearly showing humerus fractures and allowing clear evaluation of athletes. Videos suspected of having humerus fractures, repeated videos, videos with unclear athlete evaluation, and videos not related to wrist wrestling were excluded. Four videos with unclear images, ten repeated videos, eight videos showing non-humerus fracture injuries, and 19 videos removed by YouTube during evaluation by observers were excluded. The remaining 31 injury videos were included in this study.

The included videos were watched at 0.25x speed. The authors examined body tilt (ipsilateral, contralateral), body rotation (ipsilateral, contralateral), coronal shoulder position (neutral, abduction, adduction), sagittal shoulder position (neutral, flexion, extension), shoulder rotation (neutral, internal, external), sagittal elbow position (flexion, extension), coronal elbow position (neutral, varus, valgus), elbow rotation (supination, pronation), and sagittal wrist position (neutral, extension, flexion). The authors determined the moment of injury by watching the video together. Taking into account the timing of the injury, the exact moment of humerus fracture during the injury event, the athlete's facial expression, the time when deformity began in the arm, and the initial reaction to the injury, the authors identified the time of injury (10). Subsequently, body positions at the moment of injury were blindly evaluated by 2 observers. These data were statistically analyzed, and inter-observer and intra-observer agreement were assessed.

Whether the athlete was sitting or standing at the time of injury, the level of the shoulder relative to the table, the positions of the shoulder, body, elbow, and wrist, and whether the athlete was professional or amateur were evaluated. The obtained data were analyzed statistically.

Statistical Analysis

Intra- and inter-observer agreement was investigated using the Fleiss kappa (k) statistics for categorical data. The inter-observer agreement percentages were calculated by dividing the number of occasions of the complete agreement by the total number of occasions. It was interpreted as follows: <0.00= poor agreement; 0.00-0.20= slight agreement; 0.21-0.40= fair agreement; 0.41-0.60= moderate agreement; 0.61-0.80= substantial agreement; and 0.81-1.00= almost perfect agreement. Statistical significance was set at $p<0.05$. SPSS® version 25.0 was used forin the statistical analyses.

RESULTS

All 31 athletes included in the study were male. Of these, 18 (58.1%) were amateurs, while 13 (41.9%) were professionals. When examined for intra-and inter-observer agreement, it was observed to be nearly excellent (k=0.959, $p<0.001$; k=0.946, $p<0.001$) (Table 1). At the moment of injury, in 10 individuals (32.3%), the opposing player brought their shoulder below the table level, whereas in 2 individuals (6.5%), the injured athlete managed to bring their shoulder below the table level. Out of the wrist wrestling matches, 19 (61.3%) were conducted with the athletes standing, while 12 (38.7%) were performed with them in a seated position. The body, shoulder, elbow, and wrist positions of the injured athlete at the moment of injury are summarized in Table 2.

DISCUSSION

The most important finding of this study was that humerus fractures in arm wrestling frequently occurred when the body was leaning forward, with the shoulder in flexion and external rotation, the elbow in flexion and in a valgus position, and the wrist in flexion with the forearm in supination (Figure 1). However, even though the most common positions were as

described, it is noteworthy to mention that no dominant position was identified in this research.

The seemingly harmless competition of wrist wrestling can result in humerus fractures as a consequence of high rotational force applied to the upper extremity (1). While some studies during wrist wrestling argue that the players' position (seated or standing) could increase the risk of fractures, the literature suggests that players' position, stage of the match, side, and dominant extremity do not make a difference (1,5,11-13). The results of this study also supported this notion. There was no significant positional dominance observed during fractures in the shoulder, elbow, and wrist positions. As previously mentioned in other studies, sudden muscle contractions during wrist wrestling could be a key factor in humerus fractures (5,14). On the other hand, the proportion of athletes standing was high in this study. However, due to the nature of injury videos included in the study being collected through a video platform, it is not possible to claim that standing injuries were more frequent.

Differences in forearm length among wrist wrestlers, control of the center of mass, and stabilization of the arm at the

Table 1. Fleiss-kappa values and percentages of intraobserver and interobserver agreement

	k	%
Intraobserver agreement	0.959	91.6
Interobserver agreement	0.946	86.5

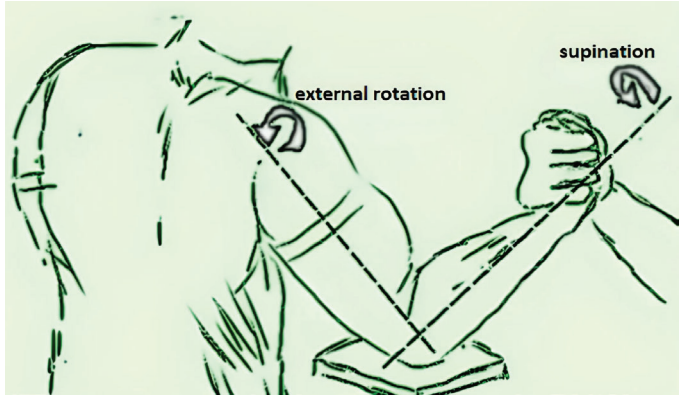

Figure 1. Humerus fractures in arm wrestling frequently occurred when the body was flexion, with the shoulder in flexion and external rotation, the elbow in flexion and in a valgus position, and the wrist in flexion with the forearm in supination position

Table 2. Distribution of body, shoulder, elbow and wrist positions of athletes at the time of injury

Anatomical part	Position	Position of movement relative to planes	Number of cases (n)	Distribution of cases (%)
Trunk	**Trunk position**	***Flexion***	31	100
	Trunk tilt	***Neutral***	1	3.2
		Ipsilateral	15	48.2
		Contralateral	15	48.2
Shoulder	**Shoulder position (sagittal)**	***Flexion***	31	100
	Shoulder position (coronal)	***Neutral***	14	45.2
		Abduction	10	32.3
		Adduction	7	22.6
	Shoulder rotation	***Neutral***	9	29
		Internal	2	6.5
		External	20	64.5
Elbow	**Elbow position (sagittal)**	***Flexion***	31	100
	Elbow position (coronal)	***Neutral***	11	35.5
		Valgus	20	64.5
Wrist	**Wrist position (sagittal)**	***Neutral***	11	34.5
		Flexion	17	54.8
		Extension	3	9.7
	Wrist position (coronal)	***Ulnar deviation***	10	32.3
		Neutral	21	67.7
Forearm	**Rotation**	***Supination***	16	9.7
		Pronation	3	51.6
		Neutral	12	38.7

shoulder are important factors for injuries (2,5,15,16). Marks et al. (5) emphasized the importance of maintaining participants' balance (center of mass) for preventing humerus fractures during wrist wrestling. In this study, athletes frequently altered their body positions to either defeat their opponents or resist them during the competition. As previously suggested by Marks et al. (5), control of the center of mass by referees throughout the match could be effective in preventing humerus injuries.

Winning in wrist wrestling involves flexing the elbow while anchoring the body to the table during the first half of the match. This position could be explained by the importance of elbow flexion and proximity between the elbow and the body in gaining an advantage in wrist wrestling (17). When the wrestler straightens the arm of the competing side and lowers their shoulder below the plane of the table, a risky position emerges. This position seems to protect the wrestler from defeat. Furthermore, this position places significant stress on the elbow and shoulder joints, potentially leading to severe injuries (7). In this study, approximately % of cases used the strategy of lowering their body below the table level to gain an advantage and win the match. This maneuver could potentially apply extra stress to the opponent's humerus, leading to fracture.

Study Limitations

This study has some limitations. First, the study is retrospective and relies on video footage from social media platforms. This can introduce bias, as the videos are likely to be shared for entertainment or to gain followers. Additionally, the videos evaluated often come from a single camera angle chosen by the sharer, making it impossible to accurately measure joint angles. Another limitation is the lack of access to X-rays of the injuries. Evaluating the relationship between the position of the athlete during the match and the type and location of the fracture is not possible. However, some authors believe that the position of the arm during the competition can determine the location and type of fracture (18). Despite these limitations, this study is the first to provide a systematic video analysis of humerus fractures in wrist wrestling. We believe that this study provides valuable insights into this subject.

CONCLUSION

Humerus fractures occurring during wrist wrestling do not appear to be significantly influenced by the athlete's shoulder, elbow, and wrist positions or whether the athlete is standing or sitting. The impact of confounding factors such as body position and centering mass should be further investigated in future studies.

Ethics

Ethics Committee Approval: No Ethical Committee approval or informed consent was required for this study, as the athletes' information is in the public domain and freely available on the web without any restriction.

Informed Consent: No Ethical Committee approval or informed consent was required for this study, as the athletes' information is in the public domain and freely available on the web without any restriction.

Peer-review: Internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., M.Y., N.E., A.F.U., H.G., Concept: A.Y., M.Y., N.E., A.F.U., H.G., Design: A.Y., M.Y., N.E., A.F.U., H.G., Data Collection or Processing: A.Y., M.Y., N.E., A.F.U., Analysis or Interpretation: A.Y., M.Y., N.E., A.F.U., Literature Search: A.Y., M.Y., N.E., A.F.U., H.G., Writing: A.Y., M.Y., N.E., A.F.U., H.G.

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

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Effect of Immune Plasma Therapy on Prognosis and Mortality in COVID-19 Patients

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Abstract

Objective: Since the exact treatment was not known in the coronavirus disease 2019 (COVID-19) pandemic, one of the traditional methods, immune plasma therapy, was also widely used. Our aim with this study is to examine the effect on prognosis and mortality of the patients hospitalized in the intensive are unit with the diagnosis of COVID-19 and receiving immune plasma therapy.

Methods: We retrospectively analyzed the files and electronic media records of 209 patients over the age of 60 or between the ages of 18-60, with comorbid diseases and who received immune plasma therapy in the intensive care units of our hospital's anesthesiology and reanimation clinic, whose diagnosis of COVID-19 was confirmed by polymerase chain reaction test. As a control group, we analyzed the files of 50 patients with similar demographic data who were not given immune plasma therapy. We recorded demographic data of the patients, the day of admission to the intensive care unit, the number of days of hospitalization, comorbid diseases, duration of symptoms and lab parameters of leukocyte count, lymphocyte count, neutrophil count, C-reactive protein, procalcitonin, creatine, D-dimer, fibrinogen, ferritin, interleukin-6; also PaO_2/FiO_2 ratio, oxygen requirement and ventilation status before and after immune plasma treatment. We statistically analyzed these data in terms of mortality and prognosis prediction in patients diagnosed with COVID-19 who received immune plasma therapy.

Results: Despite significant improvement in laboratory findings, 62.2% (n=132) of the 209 patients in our study group and 62% (n=31) of the control group died.

Conclusion: Immune plasma therapy does not provide benefit as a rescue treatment and does not reduce mortality in patients with severe COVID-19.

Keywords: COVID-19, immune (convalescent) plasma therapy, mortality

INTRODUCTION

Immune plasma convelesan plasma (CP) therapy, which is a passive vaccination strategy used in the treatment of infectious diseases, is also used in coronavirus disease 2019 (COVID-19) patients. We examined the effect of CP treatment on prognosis and mortality in the intensive care unit patients of our hospital.

At the beginning of the COVID-19 epidemic, the pathogenesis of the agent was not fully known, and there were no effective and safe drugs for the treatment of the agent. Conventional interventions previously applied for various infections have been experimented. One of these interventions is immune plasma therapy CP, a passive vaccination strategy used in the treatment of infectious diseases. CP is obtained by taking apheresis from live individuals who developed antibodies against the pathogenic agent after they have been exposed to the disease. In the COVID-19 Situation Report published by the World Health Organization on January 28, 2020, it was stated that immune plasma can also be used for severe acute respiratory syndrome coronavirus 2 virus (1,2). Immune plasma therapy is routinely

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given to the patients admitted to the intensive care unit due to COVID-19 as an emergency passive vaccination strategy in the case of indication (3).

METHODS

This study was carried out by evaluating the files and electronic media records of 221 intensive care inpatients who were diagnosed with COVID-19 following the diagnosis guideline of the COVID-19 science board (3) and were given immune plasma therapy in the intensive care units affiliated to the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Anesthesiology and Reanimation Clinic in between 20.04.2020 and 30.12.2020, with the approval of the ethics committee of our hospital, dated 19/04/2021 and decision number 167. We conducted our study retrospectively and observationally. According to the immune (convalescent) plasma guideline of the Ministry of Health, adults over the age of 60 years, patients between the ages of 18 and 60 years with severe comorbidity, and patients without immunglobulin A deficiency who were diagnosed with COVID-19 and given immune plasma therapy, were examined. Informed consent was obtained from the patients who could cooperate and from the first degree relatives of the patients who could not cooperate. Patients who did not consent to the study, patients under the age of 18, pregnant women, patients whose treatment was interrupted due to the patient's death, patients who were transferred to the service while their treatment was ongoing, and patients whose adequate clinical data could not be reached were excluded from the study. Demographic data, co-morbidities, number of hospitalization days, duration of symptoms, and number of mortality of the patients included in the study were recorded. In addition, white blood cell count, lymphocyte count, neutrophil count, C-reactive protein (CRP), procalcitonin, creatine, D-dimer, fibrinogen, ferritin, IL-6, PaO_2/FiO_2 ratio, oxygen requirement, and ventilation status were evaluated before and after immune plasma treatment.

The recorded data were statistically analyzed in terms of mortality and prognosis prediction in patients diagnosed with COVID-19 who received immune plasma therapy using either alone or more than 1 parameter together.

In order to be a control group in terms of mortality, a total of 50 patients with a diagnosis of COVID-19 who were admitted to our intensive care unit in the same period of time and did not receive immune plasma therapy were evaluated. The mortality rate of the patients was recorded.

Statistical Analysis

The Windows version of SPSS 15.0 was used for the statistical analysis. Descriptive statistics include numerical variables such as mean, standard deviation, minimum, maximum, or median, interquartile range, and numbers and percentages for categorical variables. The chi-square test was used to compare rates between independent groups. Student's t-test was used to compare 2 independent groups when the numerical variable satisfied the normal distribution condition, and the Mann-Whitney U test was used when it did not. The Friedman test was used to perform dependent group analyses since the differences in the numerical variables did not meet the requirements for a normal distribution. Wilcoxon analysis and Bonferroni correction were used to interpret the subgroup analyses. The accepted statistical alpha threshold for significance is $p=0.05$.

RESULTS

Two hundred twenty one patients were evaluated for the study. Seven patients were excluded due to lack of data, 2 patients died on the first day of transfusion, and 2 patients were excluded due to transfer to another center, and the total of 209 patients were included in the analysis. Of the patients, 139 (66.5%) were male and 70 (33.5%) were female, with a mean age of 66.2±12.5 (22-95%). 83 (39.7%) of the patients had diabetes mellitus, 111 (53.1%) hypertension, 55 (26.3%) coronary artery disease, 18 (8.6%) left ventricular hypertrophy, 21 (10%, 0 had malignancy, 30 (14.4%) chronic obstructive pulmonary disease, 20 (9.6%) CRF, 3 (1.4%) liver-C. The symptom duration of the patients before the immune plasma treatment was 8.6±5.3 (1-31%) days. The number of patients who received 1 dose of immune plasma treatment was 69 (33.0%), the number of those who received 2 doses of immune plasma treatment was 48 (23.0%), and the number of those who received 3 doses of immune plasma treatment was 92 (44.0%). Of the patients who received CP treatment, 79 (37.8%) survived and 130 (62.2%) died (Table 1).

The mean age and CRF rate of the deceased patients were found to be statistically significantly higher than those of the surviving patients.

Thirty-one (62%) of 50 patients who did not receive immune plasma therapy and were evaluated in the control group resulted in death. There was no statistical difference in mortality in patients who received CP treatment compared with the control group (Figure 1).

There was a significant increase in leukocyte count in the patients who died. The lymphocyte level of the patients was lower than before the treatment, and the neutrophil level was

higher. These significant differences were observed more clearly in the patients who died.

Procalcitonin, CRP, and creatinine were significantly higher in deceased patients compared to surviving patients. D-dimer, fibrinogen, and ferritin levels decreased in all of the patients we examined. Since IL-6 was not routinely evaluated in every patient, sufficient data could not be obtained. Therefore, we could not take IL-6 levels into consideration.

An increase in the PaO_2/FiO_2 ratio was observed in all patients during the treatment process, but there was no increase in those who passed away; however it was observed that there was an increase in those who survived.

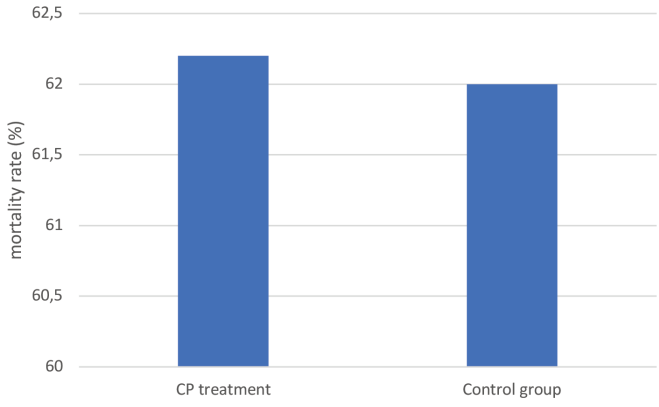

Figure 1. Mortality rates between groups

Although minor and major complications can be seen in immune plasma therapy, no complications were observed in our patients.

DISCUSSION

In our study, we obtained results that CP treatment had no effect on mortality. Although there are articles with different opinions on the treatment of CP in the literature, it is seen that in those studies, CP treatment was applied to patients at different stages of the disease. Only severe cases receiving non-invasive or invasive mechanical support in the intensive care unit were the focus of our study, and we found that CP treatment had no effect on mortality in these cases. There are studies in the literature indicating that it may not be effective as a rescue agent and may not reduce mortality in critically end-stage patients (4,5). This result supports the conclusion that plasma therapy was not beneficial in the patients in our study.

In the literature, Leukocyte elevation, lymphopenia, and neutrophilia are observed in COVID-19 patients. In our patients with severe COVID-19, no improvement was observed in leukocyte, neutrophil, and lymphocyte levels with CP treatment.

Table 1. Comparison of the patients in the study group by demographic data, duration of symptom and number of CP doses

		Alive		Mortality		
		n	%	n	%	p#
Sex	Male	51	64.6	88	67.7	0.641
	Female	28	35.4	42	32.3	
Age (mean ± SD)		61.8±12.8		68.9±11.6		**<0.001***
Comorbidity	Diabetes mellitus	25	31.6	58	44.6	0.063
	Hypertension	43	54.4	68	52.3	0.766
	Coronary artery disease	16	20.3	39	30.0	0.121
	Cerebrovascular disease	7	8.9	11	8.5	0.921
	Malignancy	6	7.6	15	11.5	0.358
	Chronic obstructive pulmonary disease	7	8.9	23	17.7	0.077
	Chronic kidney disease	1	1.3	19	14.6	**0.001**
	Lung disease	1	1.3	2	1.5	1.000
Symptom duration	Median (IQR)	7 (4-11)		8 (5-12)		0.089**
Number of CP	1	25	31.6	44	33.8	0.933
	2	19	24.1	29	22.3	
	3	35	44.3	57	43.8	

#chi-square test, *Student t-test, **Mann-Whitney U test, CP: Convelesan plasma, SD: Standard deviation

Procalcitonin, CRP, ferritin, D-dimer, and fibrinogen levels increase, resulting in thromboembolic events in COVID-19. As the severity of the disease increases, the PaO_2/FiO_2 ratio decreases. In our study, we have observed all these situations that are in parallel with the literature. We obtained significant findings regarding the improvement in these values with CP treatment.

Since IL-6 is not a routine parameter in our hospital's protocol, we could not reach sufficient data. In the light of these circumstances, we observed that we do not have enough data to examine the effect of immune plasma therapy on IL-6 levels.

In the literature, it is stated that CP treatment should be given within 14 days from the onset of symptoms (6-8). In our patients, we found that the mean time to start treatment was 8.6 days from symptom onset. Although we started the treatment at the right time, we attribute no change in mortality to the fact that the patient population consists of severe cases. This situation does not contradict with the literature.

Complete data on neutralizing antibody titers in immune plasma units were not available in our study, limiting its power to assess the correlation between donor plasma quality and efficacy. Although we applied immune plasma therapy ranging from 200 mL to 600 mL in our patients, the neutralizing antibody titer in the existing plasma is not known. *In vivo* studies have shown that the effects of neutralizing antibodies in immune plasma are not only limited to viral clearance but also include acceleration of infected cell clearance and are considered important in protection against viral diseases. Treatment efficacy was correlated with the titer of neutralizing antibodies in immune plasma (8). For this reason, we think that it would not be accurate to evaluate the treatment efficacy and mortality according to the number of immune plasma doses received by our patients.

In terms of being a guide in a possible COVID-19 pandemic in the future, we can state the following: CP treatment is not beneficial when applied with traditional methods. However, further studies are required for determining its effectiveness at high titers by measuring antibody titers.

Study Limitations

There are several limiting factors in our study. First, patients are not given immune plasma therapy alone. In addition, the standard treatment protocol recommended by the Ministry of Health for patients diagnosed with COVID-19 was applied. We consider that concomitant treatments will affect the correct assessment of CP effectiveness, another factor is that the neutralizing antibody titer level in the immune plasma is not routinely measured. This situation prevents us from evaluating the effectiveness and quality of the treatment. The fact that our patients did not know the duration of symptoms before the time of admission to the hospital and that our patients could not give reliable information about this period is another important limiting factor in this study. The effects that occur due to the fact that the patient group we included in the study consists of intensive care treatment, mostly intubated patients, the presence of concomitant diseases, the antibiotics applied due to superimposed infections or prophylaxis, and the complicated mixed treatments used for the COVID-19 virus, when the treatment is not known exactly, are multifactorial. Although efforts are made for standardization, many factors cannot be ruled out. These are inevitable limiting factors in these type of studies.

CONCLUSION

Immune plasma therapy has no effect on mortality in severe COVID-19 cases. CP treatment does not benefit patients under non-invasive/invasive mechanical support and does not affect mortality outcomes in patients with severe COVID-19 diagnosis according to symptom duration and immune plasma dose level.

CP therapy may be helpful in the beginning. However, for patients with severe COVID-19, this study found no benefits to immune plasma therapy.

Ethics

Ethics Committee Approval: This study was carried out by evaluating the files and electronic media records of 221 intensive care inpatients who were diagnosed with COVID-19 following the diagnosis guideline of the COVID-19 science board (3) and were given immune plasma therapy in the intensive care units affiliated to the Ministry of Health Prof. Dr. Cemil Taşcıoğlu City Hospital Anesthesiology and Reanimation Clinic in between 20.04.2020 and 30.12.2020, with the approval of the ethics committee of our hospital, dated 19/04/2021 and decision number 167.

Informed Consent: Informed consent was obtained from the patients who could cooperate and from the first degree relatives of the patients who could not cooperate.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.D., F.G., N.T., T.Y., Concept: E.D., F.G., N.T., Design: E.D., F.G., N.T., Data Collection or Processing: F.G., N.T., T.Y., Analysis or Interpretation: E.D., F.G., Literature Search: E.D., F.G., N.T., T.Y., Writing: E.D., F.G., N.T.

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