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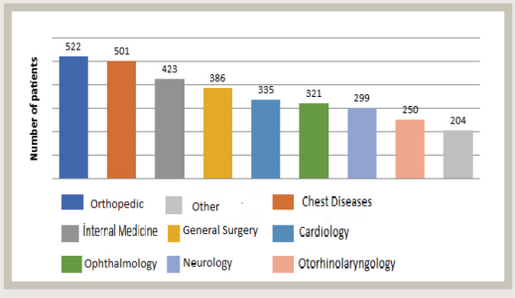

Figure 3. Number of consultations by the departments

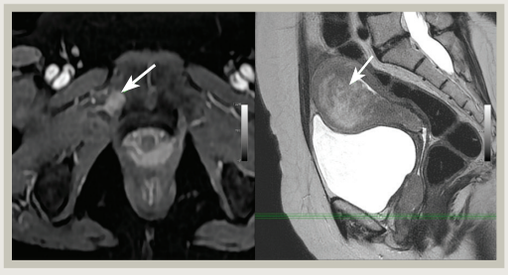

Figure 3. The left side of the picture shows bone metastasis in the right pubic bone. The right side of the picture shows endometrioid carcinoma in the uterus

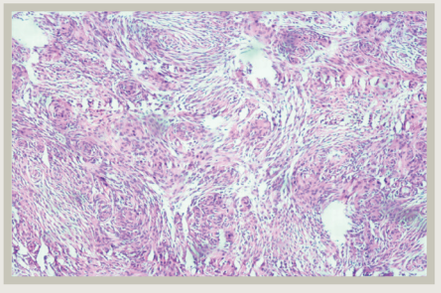

Figure 1A. Grade 1 meningothelial meningioma consisting of atypical meningothelial cells forming whorl structures (HEX100)

CAM & SAKURA MEDICAL JOURNAL

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About Us

Journal History

Cam ve Sakura Medical Journal (CSMJ) is an international, scientific, open access periodical published journal. It has independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Basaksehir Cam & Sakura City Hospital. It is published three times per year (April, August, December). A special supplement including interesting, novel and attractive theme has also been published every year. The publication language of the journal is English.

Title: Cam ve Sakura Medical Journal

Official abbreviation: CSMJ, Csmedj

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Aims and Scope

Cam ve Sakura Medical Journal (CSMJ) is an international, scientific, open access periodical published journal. It has independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Basaksehir Cam & Sakura City Hospital. It is published three times per year (April, August, December). A special supplement including interesting, novel and attractive theme has also been published every year. The publication language of the journal is English.

Cam & Sakura Medical Journal publishes original experimental or clinical research, review articles, case reports, technical reports, diagnostic puzzle, clinical images, video article, novel insight, and letters to the editor in the field of general medicine. Review articles will be only prepared by expert academicians upon invitation. The journal's target audience includes academics and expert physicians working in all fields of general medicine.

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The editorial and publication process of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

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Peer Review, Publication Ethics and Malpractice Statement

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Our publication team works devotedly to ensuring that the evaluation process is conducted impartially, considering all these situations.

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The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

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

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

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

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

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

Manuscripts are accepted only online and can be submitted electronically through web site (http://csmedj.org) after creating an account. This system allows online submission and review. The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be done at http://orcid.org. The manuscripts gathered with this system are archived according to ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index Rules. Rejected manuscripts, except artworks, are not returned.

All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide a better understanding. The rules for the title page, references, figures and tables are valid for all types of articles published in this journal. Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

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prevention of pain and suffering should be declared in the manuscript. For manuscripts concerning experimental research on humans, a statement should be included that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. The authors have the responsibility to protect the patients' anonymity carefully. For photographs that may reveal the identity of the patients, signed releases of the patient or their legal representative should be obtained, and publication approval must be provided in the manuscript. Authors must provide disclosure/acknowledgement of financial or material support, if any was received, for the submitted study. If the article includes any direct or indirect commercial links or if any institution provided material support to the study, authors must state in the cover letter that they have no relationship with the commercial product, drug, a pharmaceutical company. Concerned; or specify the type of relationship. Authors must provide a conflict of interest statement and an authorship contribution form.

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All manuscripts selected for full peer review will be assessed by a statistical editor, and their comments must be addressed in full.

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The title page should include the full title of the manuscript; information about the author(s) including names, affiliations, highest academic degree and ORCID numbers; contact information (address, phone, mail) of the corresponding author. If the content of the paper has been presented before, and if the summary has been published, the time and place of the conference should be denoted on this page. If any grants or other financial support has been given by any institutions or firms for the study, information must be provided by the authors.

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Instructions to Authors

c. Keywords

A list of minimum 4, but no more than 6 keywords must follow the abstract. Keywords in English should be consistent with "Medical Subject Headings (MESH)".

d. Original Article

The instructions in general guidelines should be followed. The main headings of the text should include "Introduction, Material and Methods, Results, Discussion, Study Limitations and Conclusion". The introduction should include the rationale and the background of the study. The results of the study should not be discussed in this part. "Materials and methods" section should be presented in sufficient details to permit the repetition of the work. The statistical methods used should be clearly indicated. Results should also be given in detail to allow the reproduction of the study. The Discussion section should provide a correct and thorough interpretation of the results with the relevant literature. The results should not be repeated in the Discussion Part. The references should be directly related to the findings of the authors. Study Limitation should be detailed in the section. The conclusion section should be highlighted and interpreted with the study's new and important findings.

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

Original Articles should be no longer than 3500 words and include no more than 6 tables and 7 or a total of 15 figures and 40 references. The abstract word limit must be 250.

Introduction

The article should begin with a brief introduction stating why the study was undertaken within the context of previous reports.

Materials and Methods

These should be described and referenced in sufficient detail for other investigators to repeat the work. Ethical consent should be included, as stated above.
The name of the ethical committee, approval number should be stated. At the same time, the Ethics Committee Approval Form should be uploaded with the article.

Results

The Results section should briefly present the experimental data in text, tables, and/or figures. Do not compare your observations with that of others in the results section.

Discussion

The Discussion should focus on the interpretation and significance of the findings with concise and objective comments that describe their relation to other work in that area and contain study limitations.

Study Limitations

Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion

The conclusion of the study should be highlighted.

e. References

The reference list should be typed on a separate page at the end of the manuscript. Both in-text citations and references must be prepared according to the Vancouver style. Accuracy of reference data is the author's responsibility. While citing publications, preference should be given to the latest, most up-to-date references. The DOI number should be provided for citation of ahead-of-print publication, Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. All authors should be listed in the presence of six or fewer authors. If there are seven or more authors, the first three authors should be listed, followed by "et al." References should be cited in text, tables, and figures should be cited as open source (1,2,3,4) in parenthesis numbers in parentheses. References should be numbered consecutively according to the order in which they first appear in the text. The reference styles for different types of publications are presented as follows:

i) Standard Journal Article

Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. JAMA 2015;313:2340-2348.8.

ii) Book

Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

iii) Chapter of a Book

Volpe JJ: Intracranial hemorrhage; in Volpe JJ (ed): Neurology of the Newborn, ed 5. Philadelphia, Saunders, 2008, pp 481-588.

Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-380.

If more than one editor: editors.

iv) Conference Papers: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10;Geneva, Switzerland: North-Holland; 1992. p. 1561-1565.

v) Journal on the Internet: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

vi) Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

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f. Tables, Graphics, Figures, Pictures, Video:

All tables, graphics or figures should be numbered consecutively according to their place in the text and a brief descriptive caption should be given. Abbreviations used should be explained further in the figure's legend. The text of tables especially should be easily understandable and should not repeat the data of the main text. Illustrations already published are acceptable if supplied by permission of the authors for publication. Figures should be done professionally, and no grey colors should be used. Authors are responsible for obtaining permission to publish any figures or illustrations that are protected by copyright, including figures published elsewhere and pictures taken by professional photographers. The journal cannot publish images downloaded from the Internet without appropriate permission.
Figures or illustrations should be uploaded separately.

Special Sections

Reviews

Reviews will be 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 and subjects will be invited by the journal. All reviews within the scope of the journal will be taken into consideration by the editors; also, the editors may solicit a review related to the scope of the journal from any specialist and experienced authority in the field.

The entire text should not exceed 25 pages (A4, formatted as specified above).

Reviews should be no longer than 5000 words and include no more than 6 tables and 10 or a total of 20 figures and 80 references. The abstract word limit must be 250.

Case Reports

Case reports should present important and rare clinical experiences. It must provide novel and/or rare clinical data or new insights to the literature. Case reports should consist of an unstructured abstract (maximum 150 words) that summarizes the case. They should consist of the following parts: introduction, case report, discussion. Informed consent or signed releases from the patient or legal representative should be obtained and stated in the manuscript.
Reviews should be no longer than 1000 words and include no more than 200 tables and 10 or a total of 20 figures and 15 references. The abstract word limit must be 150.

Clinical Images

The journal publishes original, interesting, and high quality clinical images having a brief explanation (maximum 500 words excluding references but including figure legends) and of educational significance. It can be signed by no more than 5 authors and can have no more than 5 references and 1 figure or table. Any information that might identify the patient or hospital, including the date, should be removed from the image. An abstract is not required with this type of manuscripts. The main text of clinical images should be structured with the following subheadings: Case, and References.

Video Article

Video articles should include a brief introduction on case, surgery technique or a content of the video material. The main text should not exceed 500 words. References are welcomed and should not be more than 5. Along with the main document, video material and 3 images should be uploaded during submission. Video format must be mp4 and its size should not exceed 100 MB and be up to 10 minutes. Author should select 3 images, as highlights of the video, and provide them with appropriate explanations. Video and images must be cited within main text.

Technical reports

Technical reports are formal reports designed to convey technical information in a clear and easily accessible format. A technical report should describe the process, progress, or results of technical or scientific research or the state of a technical or scientific research problem. It might also include recommendations and conclusions of the research. Technical reports must include the following sections: abstract, introduction, technical report, discussion, conclusions, references. Technical reports should contain less than 20 references.

Diagnostic puzzle

Diagnostic puzzles report unusual cases that make an educational point. Since the aim of these articles is to stimulate the reader to think about the case, the title should be ambiguous and not give away the final diagnosis immediately. Diagnostic puzzles should include an introduction and answer part. The introduction part should include a brief clinical introduction to a case (maximum 250 words) followed by an image and a question designed to stimulate the reader to think about what the image shows. The legend should not indicate the diagnosis but should simply describe the nature of the image. Then, the answer part should appear later (maximum 250 words) outlines a brief description of the key diagnostic features of the image, the outcome, and a teaching point.
Diagnostic puzzles will not include more than 5 references. The quality of the image must be at least 300dpi and in TIFF, JPEG, GIF or EPS format. Videos are also welcome and should be in .mov, .avi, or .mpeg format.

Novel insight

This section will offer an opportunity for articles instead of the traditional category of Case Reports. Submissions to this section should contribute significant new insights into syndromological problems, molecular approach and real novelties on recognized or entirely new genetic syndromes or a new technique. The novel aspect(s) can be in the phenotype and/or genotype, the presentation, and the investigation. Submissions can be based around a single case or serial cases. Manuscripts for this section will go through the usual peer reviewing process. The manuscripts should contain abstract (maximum 150 words), a brief introduction, case report(s) and discussion.

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Instructions to Authors

Letters to the Editor

This section welcomes manuscripts that discuss important parts, overlooked aspects, or lacking parts of a previously published article in this journal. In addition, articles on subjects within the scope of the journal that might have an attraction including educative cases, may also be submitted in the form of a "Letter to the Editor." The manuscripts for this section should be written in an unstructured text including references. The editor may request responses to the letters. There are no separate sections in the text.

Letter to the editors should be no longer than 500 words.

Revision Process

During the submission of the revised version of a manuscript, the authors should submit a detailed "Response to the reviewers and editors" that states point by point how each issue raised by the reviewers and/or editors has been replied to 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 should 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 cancelled.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue.

LIMITATION TABLE

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	5000	250	60	6	10 or total of 20 images
Case Report	1000	150	20	200	10 or total of 20 images
Letter to the Editor	500	No Abstract		No tables	No media
Video Article	500		5		
Diagnostic Puzzle	250 (as a brief clinical introduction		5		
Clinical Images	500 (as a brief explanation)		5	1	1
Technical Reports			20		

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Letter From The Chief Physcian

Dear Colleagues,

It is my great pleasure to be with you as the coordinator Chief Physcian of Basaksehir Cam & Sakura City Hospital. Our hospital serves as a tertiary referral center in Istanbul with several clinical, educational and scientific activities. Cam and Sakura Medical Journal (CSMJ), the official journal of our hospital, serves as a scientific contributor for all fields of general medicine.

The third issue of this year has just been published. We believe that CSMJ will be indexed in several important databases in the following years with your scientific support. Therefore, we welcome all types of manuscripts to be submitted for publication in our journal. I also thank to all editors, editorial board, reviewers and authors for their help in the publication process of three issues.

I wish happy and healthy new year. Hoping to meet you in the following issues of CSMJ in 2022.

Nurettin Yiyit
Chief Coordinator Physcian
Cam & Sakura City Hospital

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Editorial

Dear Colleagues,

We are really happy to be with you in the third issue of Cam and Sakura Medical Journal (CSMJ). We are moving forward step by step to our aims and as a result of these efforts, CSMJ has been indexed in J-Gate. We hope to be included more indexes in 2022. Therefore, I would like to thank to all Editorial Board and also to the authors of the articles published in this issue.

In the last issue of 2021, you can read the review about COVID-19 vaccines in children and adolescents, one of the most popular subject during the delta and omicron peaks of the pandemics. I believe that review will gain attention of all readers and will be cited in future studies and reviews. The consultations requested from emergency service is one of the articles in this issue. Another important article is about the evaluation of a new scoring scale for prediction of mortality in intensive care unit. You can also read the article which investigated the possible relationship between the histopathological grade and levels of immune checkpoint molecules in meningiomas. Another article aimed to establish the demographic data of patients admitted to emergency service. A case report series about the bone metastases of endometrial carcinoma has also been published in this issue. We think that all these articles from different fields of general medicine will take your attention.

I want to state that our primary objective is to include CSMJ in well establihed indexes in near future. your contributions including reviews, articles and case reports are very important for this purpose.

We wish all of you a very happy, healthy and Covid-free new year.

Hoping to meet you on the first issue of 2022.

On behalf of Deputy Editors, Associate Editors and Editorial Secretary

Merih Cetinkaya

Editor in Chief

Cam & Sakura Medical Journal

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COVID-19 Vaccines in Children and Adolescents

Ener Çağrı Dinleyici

Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Eskişehir, Turkey

ABSTRACT

The coronavirus disease-2019 (COVID-19) pandemic has an effect on children, either directly or indirectly. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) immunization in children and adolescents plays a role in containing the COVID-19 pandemic. As of December 2021, a limited number of COVID-19 vaccines have been approved for use in children and/or adolescents. Both mRNA vaccines (BNT162b2 and mRNA 1273) were found to be well tolerated and effective in large phase 2 and phase 3 clinical trials. BNT162b2 vaccine was approved for children and adolescents aged 5 to 18, and mRNA-1273 vaccine for children aged 12 to 17. CoronaVac, an inactivated SARS-CoV-2 vaccine, was also found to be safe and immunogenic in a phase 1/2 clinical trial in China, and is presently used for pediatric immunization in some countries as a routine. As COVID-19 is less severe in children than it is in adults, the benefit of its vaccination in children is less than that of adults. Immunization with an effective and safe vaccine in children and adolescents is likely to provide protection against severe COVID-19 infection. Pediatric COVID-19 vaccines may also protect against the long-term effects of COVID-19 (MIS-C and long COVID) and community transmission, as well as mitigate the indirect effects of the pandemic on them. Vaccination should be prioritized for children and adolescents who have an increased risk of severe COVID-19 infection. If vaccines were evenly distributed worldwide, they would be the safest way to return normal life. Otherwise, low- and middle-income countries will crash, resulting in mortality, undermining global recovery, and allowing more virulent variants (such as Omicron) to emerge. If health officials incorporate the COVID-19 vaccine into routine immunization, they should also regularly evaluate their benefits and potential risks.

Keywords: COVID-19, SARS-CoV-2, pandemic, children, vaccine, mRNA vaccine

CAM & SAKURA MEDICAL JOURNAL

Introduction

The coronavirus disease-2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus is still ongoing, with recent estimates of more than 270 million cases diagnosed worldwide and more than 5.3 million deaths by the end of 2021 (1). The pandemic primarily affects adults. Adults and the elderly have mortality rates related to COVID 19, and the presence of underlying condition such as cardiovascular disease, diabetes, cancer, chronic lung disease, and immunocompromised condition were linked to these rates (2). While adult patients account for the vast majority of cases and deaths, the pandemic significantly affects children worldwide directly or indirectly (3,4,5).

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Regarding previous pandemic experiences, a pandemic could only be controlled with widespread use of safe and effective vaccines. Several COVID-19 vaccines have been under study since the first definition of the virus. The first COVID-19 vaccine was created and tested on humans within two months of the publication of the SARS-CoV-2 genomic sequence. There are 168 types of vaccines still being tested in 536 clinical trials in 62 countries worldwide. These vaccines include whole-cell inactivated virus vaccines, mRNA vaccines, DNA vaccines, adenoviral-vectored vaccines, protein-subunit vaccines, and virus-like particle vaccines (6). By December 2021, at least 1 of the 28 COVID-19 vaccines has been approved for emergency use in 194 countries (7). Vaccines are currently available through their full approval, conditional marketing approval, and emergency use authorization (EUA). A majority of these approved vaccines are shown to be effective and safe in adults and were authorized for adult immunization, including increased risk groups such as the elderly, and health-care workers. However, the use of vaccines is limited in children and adolescents. There are currently more than 20 ongoing clinical trials on vaccines in children, including infants of at least 6 months, as well as adolescents (4,8).

COVID-19 in Children and Adolescents

Children and adolescents are underrepresented in terms of frequency (a small percentage of the total number of COVID-19 cases) and severity when compared to adults since the beginning of the pandemic (4). From December 2019 and October 2021; children under the age of 5 accounted for 2% of reported global cases and 0.1% of reported global deaths. Children aged between 5 to 14 years accounted for 7% of reported global cases and 0.1% of reported deaths, and adolescents and young adults (15 to 24 years) accounted for 15% of reported cases and 0.4% of deaths (9). Despite these results, there were differences in test capacity and other infection control strategies among countries.

The acute infection with SARS-CoV-2 is generally asymptomatic or mild in children and adolescents (3,4,5). It should be noted that children and adolescents are tested less frequently, and cases may go unnoticed (9). Children with mild infection (mainly admitted with fever and/or cough) can be managed safely without hospitalization and they represent the vast majority of pediatric cases (3,4,5,10). A small percentage of children develop severe disease and require hospitalization (only 1.5% of all COVID-19 hospitalizations) (4). During the recent Delta wave, children had the highest rate of confirmed SARS-CoV-2 infection though hospitalization rates remained low (11,12). Risk factors for severe disease and mortality in children include newborn and young age, obesity, and the presence of underlying conditions such as asthma, congenital cardiac disease, neurological disease, Down syndrome, diabetes mellitus, and cancer (5,13).

The rate admission in the intensive care unit (ICU) ranged from 2% to 13%; the risk of death from SARS-CoV-2 infection was 0.005% in children and adolescents, and 0-0.7% in those hospitalized with COVID-19 (10). In the United States, from March 2020 to June 2021; 26.5% of hospitalized children and adolescents with COVID-19 were admitted to an ICU, while 6.1% required invasive mechanical ventilation (14). The involvement of the respiratory system is the leading cause of hospitalization and the need for intensive care. Extrapulmonary system involvement (cardiac and neurological findings) are relatively uncommon and frequently coexist with pulmonary disease (5). Mortality from COVID-19 is extremely low in children, accounting for only 0.08% of all COVID-19 deaths (4). The majority of evidence on the risk of severe COVID-19 and death in children and adolescents comes from studies in high-resource settings. Mortality rates vary greatly between countries due to factors such as malnutrition, health-care access, and delayed diagnosis. A recent systematic review demonstrated that the impact of pediatric COVID-19-related fatalities could be greater in low- to middle-income countries than in high-income countries (3,9).

The age distribution of SARS-CoV-2 infection varies according to circulating variants, mitigation strategies and vaccine coverage in the community. During the most recent Delta variant dominant period, 38% of all cases reported in the United States were children aged 5-11 years (15). More than 8,300 hospitalizations for severe COVID-19 infection in children aged 5 to 11 years were reported and approximately one-third of them required ICU admission (15). As with other respiratory viruses, the primary management priorities in children with COVID-19 are adequate hydration and supportive care. Recommendations for COVID-19 therapy in children (remdesivir, dexamethasone, and tocilizumab) are primarily extrapolated from adult regimens (2).

Children of all ages can become infected and spread the virus to others. The majority of children become infected through contact with an adult. Infection rates in children and adults were comparable whether schools were open or closed. According to secondary attack rates, children were less affected than adolescents and adults (9,16). However, there is little or no information available on the effects of the recent Omicron (B.1.1.529) variant on children and adolescents (17).

In addition to complicated and uncomplicated acute COVID-19 infection, long-term consequences of SARS-CoV-2 infection could be more of a concern in the pediatric age group (10). Multi-system inflammatory syndrome in children (MIS-C) is characterized by fever, rash, conjunctival injection, gastrointestinal symptoms, and shock due to myocardial dysfunction (3). Children with MIS-C have a history of COVID-19 or an exposure about 4-6 weeks prior to the onset of symptoms. MIS-C cases were typically observed 3-6 weeks after the peak incidence of COVID-19 in the general population (4). The peak age for MIS-C was 9-10 years (3). MIS-C affects 0.5-3.1% of all diagnosed and 0.9-7.6% of all hospitalized pediatric COVID-19 patients according to a large international cohort study (18). Coronary artery dilatation or aneurysms occurred in 15-25% of cases (3). Patients frequently presented with shock or hemodynamic instability: 60-80% required hospitalization in an ICU, and 50% required inotropes and/or fluid resuscitation (4). In addition to supportive care, intravenous immunoglobulin (IVIG) and corticosteroids -either alone or in combination- were effective for children with MIS-C (3). In the short to medium-term, the prognoses were promising, with low rates of coronary artery aneurysms and even lower mortality (4). COVID-19 vaccines should be delayed for children with a previous history of MIS-C until clinical recovery has been achieved or 90 days after diagnosis (19). Children who received a 1-2 g/kg dose of IVIG for the treatment of MIS-C could receive their live vaccines (MMR, varicella) at least 11 months after their treatment. Another significant post-infectious manifestation associated with SARS-CoV-2 is “long COVID” in children. Long COVID, defined by the persistence of symptoms for more than 3 months, is more common in people aged 12 and older. This condition causes a wide range of symptoms such as fatigue, shortness of breath, and impairs the daily life activities of the patients (3). The risk of long COVID is lower in children compared to other age groups (20). Existing evidence is highly heterogeneous, resulting in a wide range of prevalence estimates as 0% to 27% (3).

In addition to the direct effects of SARS-CoV-2 on children, children have suffered some of the most severe indirect effects of the pandemic. These include the impact on mental health and wellbeing, school closures, with large disruptions to in-person school, limited peer interactions, increased body mass index, delayed routine well-care visits and routine immunizations, delayed health-seeking behaviors, more prone to child abuse and neglect, and increased cyberbullying (5,9,10,21). Some children have lost their parents, relatives, or caregivers.

COVID-19 Vaccines in Children and Adolescents

Severe illness from acute COVID-19 is uncommon in healthy children; however, it can occur, especially in those with pre-existing conditions. Children and adolescents play an important role in SARS-CoV-2 transmission (3,4,5,10,13,16). With widespread adult immunization, younger people account for a greater proportion of COVID-19 infections. The pandemic has disrupted the education of students due to long period of school closures. As a result, the direct benefits of vaccination to the individual is lower compared to that in other age groups: However, immunization of children and adolescents with an effective and safe vaccine is likely to promote disease prevention directly and stop the spread of the infection, thereby reducing the disease burden. Vaccinating children and adolescents will facilitate their reintegration into schools and the society (4,5,8,10,16,22).

As of December 2021, a limited number of COVID-19 vaccines had been approved for children and adolescents. There is limited evidence on the efficacy and safety of COVID-19 vaccines in children and adolescents. This article does not contain arguments for or against vaccinating children. COVID-19 vaccines have been approved for use in children and/or adolescents in a number of countries, including CoronaVac (Sinovac), BNT162b2 (Comirnaty; Pfizer-BioNTech) and mRNA1273 (Spikevax; Moderna). In most countries, primary vaccination would be recommended and started in children and adolescents regardless of underlying medical conditions. Those with a known current SARS-CoV-2 infection should postpone vaccination at least until their recovery. Serologic testing for previous infection is not recommended (4).

mRNA-based Vaccine Developed by Pfizer and Biontech (BNT162B2; Comirnaty)

The Pfizer-BioNTech vaccine, BNT162b2, is made up of a nucleoside-modified mRNA molecule encoding the SARS-CoV-2 spike glycoprotein in a prefusion state, enveloped within a lipoprotein nanoparticle (5). Two doses of BNT162b2 elicited high neutralizing titers and robust T-cell responses against SARS-CoV-2 in healthy adults. A double-blind randomized controlled phase III trial of over 43,000 people aged 16 and above who received either a 2-dose BNT162b2 vaccine (30 g doses) or a placebo showed a 95% [95% confidence interval (CI) 90.3-97.6; 8 cases in BNT162b2 group versus 162 cases in placebo] prevention rate of symptomatic COVID-19 from seven days after dose 2 (23). BNT162b2 had a favorably safe profile in phase 2 trials involving 16-18-year-old adolescents (22,23). The side effects are mild to moderate pain at the injection site, fever, fatigue, and headache. In a six-month

follow-up report, the vaccine efficacy against symptomatic disease remained high, but slightly decreased from 96% to 84% between four and six months after administration (24). According to studies, plasma from individuals vaccinated with BNT162b2 retain the neutralizing activity of the vaccine against concerned variants, though the levels of neutralizing antibodies generated are lower against Beta (B.1.351), Delta (B.1.617.2) and Omicron (B.1.1.529) (25,26). The vaccine is also effective against Delta variants especially in severe patients requiring hospitalization (27).

On December 2020, BNT162b2 vaccine was authorized by the Food and Drug Administration (FDA) for emergency use in the prevention of disease in people aged 16 and older (28). BNT162b2 is approved for use in 118 countries (7). The vaccine was expanded to 12-to-15-year-old individuals in May 2021, and to 5-to-11-year-old individuals on October 29, 2021 (28). The primary series of Pfizer-BioNTech COVID-19 vaccine is two intramuscular doses given three weeks (21 days) apart to all age groups. Individuals with certain immunocompromizing conditions are given a 3rd dose at least 28 days after the second dose. A booster dose, defined as one dose given at least six months after the last dose in the primary series, is recommended for all people aged 16 and older. The only contraindications to vaccination are allergic reactions to the vaccines or their components (29).

Children aged between 12-15 years old: The immunogenicity, safety, and efficacy of the BNT162b2 vaccine were assessed in a phase 3 trial involving 2,260 adolescents aged 12 to 15 years (22). Its immunogenicity in 12-15-year-old adolescents was not inferior to that in 16-25-year-old young adults. Vaccine efficacy against symptomatic infection was 100% seven days after the second dose (95% CI; 78.1-100). After two doses, the vaccine efficacy was also higher among 1,983 adolescents aged 12 to 15 years without evidence of previous SARS-CoV-2 infection; vaccine efficacy was 100%; seven or more days after dose 2 (95% CI 75.3-100; no cases in BNT162b2 recipients against 16 cases among placebo group). In this age group, there were no cases of severe COVID-19 infection (22). The EUA of BNT162b2 vaccine was expanded to include 12 to 16-year-old individuals by May 2021. In a study of 464 people aged 12 to 18 who were hospitalized in the United States during the summer of 2021, the vaccine effectiveness against COVID-19-related hospitalization was estimated to be 93% (14).

Children aged between 5-11 years old: The Pfizer-BioNTech BNT162b2 vaccine is being tested in a randomized, placebo-controlled phase trials in healthy children (28). A dose of ten mcg was chosen for the phase 2 and 3 trials in 5-11 year-old children, based on the reactogenicity observed in the initial cohort of the phase 1 trial. Thus, 4,647 children (48.6% female, 20% had an underlying comorbidity) aged 5 to 11 were given either two doses of the vaccine or a placebo 21 days apart in the United States, Finland, Poland, and Spain. Approximately 10% of participants were seropositive SARS-CoV-2, at baseline infection. BNT162b2 vaccine was safe, well tolerated, and induced robust neutralizing antibodies. Compared with neutralizing antibody titers induced in recipients aged 16 to 25 years, those induced in recipients aged 5 to 11 years with a lower dose of the vaccine were similar. The efficacy of a lower vaccine dose (given in a two-dose series) was 90.7% among 2,186 children aged 5 to 11 years with no evidence of prior infection (95% CI; 68-98; three cases among 1,305 vaccine recipients versus 16 cases among 663 placebo recipients) (28). The preliminary data did not include vaccine efficacy against hospitalization, MIS-C, or death. In the United States, COVID vaccination among 5-11 year-old individuals is expected to accelerate the decline in numbers (expected 8%; 600,000 cases) from November 2021 to March 2022 (15).

The primary series for children aged 5 to 11 years constitutes of two intramuscular doses of 0.1 mL (10 mcg) given three weeks apart. In Canada, BNT162b2 vaccine (10 mcg) could be given to children aged 5 to 11 years with an interval of at least 8 weeks. Those who turn 12 after the first dose of the series should finish it with the dose recommended for adolescents of 12 years of age; however, if they received the lower dose after turning 12, no need for it to be repeated. BNT162b2 vaccine for children aged 5 to 11 years should not be given concurrently with other live or inactivated vaccines. It is best to wait at least 14 days before or after administering other vaccines (11).

There are some differences between the adult/adolescent (12 years and older) and pediatric (5-11 years) formulations of the Pfizer-BioNTech COVID-19 vaccine. The adult and adolescent formulations have purple vial caps, while pediatric formulations have orange vial caps. The diluent volume is 1.8 mL for adult/adolescent formulation, the dose is 0.3 mL (30 mcg), and there are six doses per vial. However, the diluent volume is 1.3 mL for pediatric formulation, the dose is 0.2 mL (10 mcg), and there are ten doses per vial. The post-dilution time is 6 hours at room temperature for the adult/adolescent formulation and 12 hours for the pediatric formulation (30).

The Safety of BNT162b2 Vaccine in Children and Adolescents

Children and adolescents receiving BNT162b2 vaccine reported more local and systemic events (generally mild to moderate severity) in both cohorts (5-11 and 12-15 years

old). These local and systemic events typically resolved within one or two days. Injection site pain, fatigue, headache, and fever were common in 12-15 year-old, as they were in young adults and adults. Fever occurred after second dose in 20% of 12-to-15-year-old individuals and in 17% of 16-to-25 year-old individuals. Severe adverse events were reported in 0.6% in children aged 12 to 15 years and 1.7% of those aged 16 to 25 years. During these trials, there were no serious adverse events related to the vaccine (cases of myo/pericarditis, MIS-C, or deaths). After routine use of vaccine, myocarditis/pericarditis have been rarely reported (detailed discussed in later part) (11,22,28).

Moderna mRNA-based Vaccine (mRNA1273; Spikevax)

Moderna mRNA-based vaccine (mRNA-1273), is made up of a nucleoside-modified mRNA molecule encapsulated within a lipoprotein nanoparticle (4). This double-blind placebo-controlled study with over 30,000 adults (two doses given 28 days apart) demonstrated a 94.1% efficacy in preventing COVID-19 infection, including severe COVID-19 disease (31). After an average of 5.2 months, the vaccine efficacy was still at 93.2% for symptomatic infection and 98.2% for severe disease (32). During the clinical trials, no safety concerns were identified. On December 18, 2020, the FDA granted the vaccine EUA for people aged 18 and older. A recent phase 3 clinical trial (with 3,700 participants) with mRNA1273 vaccine found that it could be well tolerated and effective in children and adolescents aged 12 to 17 years old (not published, 33). Immunogenicity in adolescents aged 12 to 17 years is comparable to or greater than that seen in young adults. European Medicines Agency's (EMA) human medicines committee has recommended granting an extension of indication for the mRNA1273 to be used equally in children aged 12 to 17 years in Europe (33). Vaccination with the mRNA1273 vaccine for children as young as 12 years old is now recommended in some countries. These vaccines are linked to a rare risk of myocarditis (which occurs more frequently in adolescents and young adults) (34).

Inactivated SARS-COV-2 Vaccine (CoronaVac, Sinovac)

CoronaVac, is an inactivated SARS-CoV-2 vaccine and clinical trials revealed that this vaccine was safe, immunogenic and effective in adults aged 18 and older (35,36). According to a phase III trial with 10,000 participants in Turkey, the vaccine efficacy at 14 days after full vaccination was 83.5% (95% CI 65.4-92.1) (37). In a Chilean observational study involving over 10 million people, the vaccine effectiveness was estimated at 70% in preventing COVID-19 and 86-88% in preventing hospitalization or deaths (38). A subsequent study in Brazil demonstrated lower vaccine effectiveness among adults over the age of 70 in the context of the prevalent Gamma variant (47%, 56%, and 61% against COVID-19, hospitalizations, and deaths, respectively) (39). Since the end of 2020, CoronaVac has been one of the most widely used vaccines among adults worldwide. This vaccine is available in China and a few other countries, including Brazil, Chile, Indonesia, Mexico, and Turkey (7).

In a double-blind, randomized, controlled, phase 1/2 clinical trial in China, Han et al. (40) assessed the safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents aged 3 to 17 years. Between October and December 2020, 72 participants were enrolled in the phase 1 study, while 480 participants were enrolled in phase 2. This vaccine was safe and well tolerated, and it elicited humoral responses. After two doses of vaccination, the seroconversion rates of neutralizing antibodies were greater than 96%, and the neutralizing antibody titers induced by the 3.0 μg dose were higher than those induced by the 1.5 μg dose. The most common reactions were injection site pain (13%), followed by fever (5%). The limitations of this study include the lack of assessment of T-cell responses and the fact that all participants were recruited from a single country, China (40). Furthermore, this is a phase 1-2 study, and there is no prior evidence on the vaccine efficacy/effectiveness. China, Chile, and Turkey have been using this vaccine with an emergency authorization in children and adolescents; the effectiveness of the vaccines from these countries will highlight their effect on COVID-19 epidemiology in these age groups. This vaccine has not yet received authorization for emergency use in children form the World Health Organization (WHO) (9).

Other Pediatric COVID-19 Vaccines

Another inactivated vaccine, BBIBP-CorV (Sinopharm), was approved for children and adolescents aged between 3 to 17 years in China. Covaxin is another adjuvant inactivated vaccine developed by Bharat in India, and was approved in India for 12-17-year-old individuals. ZycovD, a novel DNA vaccine, has been approved by the Indian regulatory authorities for the same age group. These three vaccines not yet received authorization from the WHO emergency use listing procedure (9).

Routine use of COVID-19 Vaccines Among Children/ Adolescents and Real-world Effectiveness Data

Pfizer-BioNTech BNT162b vaccine is one of the most commonly used vaccine among children and adolescents. There is only one study about the real-world effectiveness of pediatric COVID-19 vaccines. Following the introduction of the BNT162b vaccine in United States, among 68 hospitalized adolescents; four were fully and five were partially vaccinated while 59 were unvaccinated. The hospitalization rate among unvaccinated adolescents was ten times higher than that of fully vaccinated adolescents, indicating that vaccines were highly effective at preventing serious COVID-19 illness during a period when the Delta variant predominated (14).

The EMA approved the Pfizer-BioNTech BNT162b vaccine for children aged 12-15 in May 2021 and for children aged 5-11 in November 2021, making it the first COVID-19 vaccine to receive such approval in the European Union (41). The EMA also approved the Moderna mRNA1273 vaccine for use in children aged 12 to 17 in July 2021 (33). A majority of European countries initiated the routine use of these vaccines in children and adolescents. In England, all adolescents aged 16 and 17 years started receiving vaccines on August 23, 2021, followed by 12-15 year-old individuals in September. By the December 2021, approximately 1.3 million children aged 12 to 15 had received at least one dose. Initially, this age group was only given one dose, but due to concerns about the Omicron variant, a second dose has been recently introduced (only 29,000 children are fully vaccinated) (42). In Scotland, 59% of children have received at least one dose of the mRNA vaccine, as well as 54% in Wales and >60% in Ireland (43). In Italy, 75.5% of 12-19 year-old individuals had received at least one dose as of December 17, 2021, with 71.4% fully vaccinated. Italy recently approved the Pfizer-BioNTech BNT162b vaccine for children aged 5 to 11 years, and 28,000 children received their first dose already (44). In Germany, on August 16, 2021, STIKO decided to vaccinate all children over the age of 12. As of December 2021, 50% of children aged 12-17 years old had received both doses (45). In France, 70% of children aged 12 to 17 years old have received at least one dose of mRNA vaccine, and 77% are fully vaccinated (46). In Spain, as of December 17, 2021, 88.8% of children and adolescents aged 12 to 19 years old had received their first dose of mRNA vaccine, and 85.5% were fully vaccinated. The health authorities of Spain will initiate the vaccination of children aged 5 to 11 in December 2021 (47). In Turkey, both the Pfizer-BioNTech mRNA vaccine and the inactivated vaccine (CoronaVac) are approved for use in children over the age of 12. CoronaVac vaccine is routinely used in Chile in children over the age of six.

The Benefits and Risks of Pediatric COVID-19 Immunization Strategies

The WHO published a statement on COVID-19 vaccination for children and adolescents at the end of November 2021. When developing COVID-19 immunization policies and programs, vaccinating children and adolescents has advantages that go beyond direct and indirect health benefits (9).

When comparing adults and the elderly population, the rates of hospitalization, ICU admissions, and mortality are quite low (3,4,5); therefore, routine pediatric COVID-19 immunization is not as compelling as it is for adults. However, children are at risk for severe COVID-19, MIS-C, and long COVID (10). A SARS-CoV-2 vaccine for children and adolescents will be critical in containing the COVID-19 pandemic. Children and adolescents also play an important role in the spread of SARS-CoV-2 in communities (10). High vaccination rates in adults in the community must be encouraged to provide indirect protection to children. However, adult vaccination coverage fell short of the herd immunity threshold in most parts of the world. There are safe and effective vaccines that have been approved for pediatric use by health-care authorities. As a result, parents willing to immunize their children must have access to these vaccines. In addition, children at high risk of severe COVID-19 or those with specific conditions such as those with neurological cardiac, respiratory, and renal diseases, Down syndrome, immunodeficiencies, malignancies, obesity, and diabetes (13), should be prioritized for vaccination. Routine immunization would be beneficial in low/middle-income countries due to an increase in the number of cases with co-morbidities. In high-income countries, routine immunization for deprived and ethnic minority groups could equally be beneficial, because of severe disease and MIS-C are common in these groups (10).

In the pediatric age group, the risk-benefit balance of vaccination is more complicated (10). Zimmermann et al. (10) summarized the pros and cons of pediatric COVID-19 immunization. Considerations for vaccination in children include potential vaccine protection against COVID-19, severe COVID-19 infection, MIS-C, and long COVID; potential contribution to reducing community transmission, and potential impact against the spread of new variants. Widespread pediatric immunization is associated with avoiding isolation, quarantine, lockdown, and school closure, resulting in a faster return to pre-pandemic activity and economic stability. However, for the evidence backing up these potential benefits is very limited. Potential reasons for non-routine vaccination of children include a generally mild

course of disease during childhood, adverse events associated with vaccines, unknown efficacy against MIS-C or long COVID, and an unknown efficacy against SARS-CoV-2 transmission. Concerns about routine COVID-19 immunizations include vaccine cost, supply issues, and co-administration with other childhood vaccines (10). If health authorities decide to include the vaccine in routine immunization, the risks and benefits must be reevaluated on a regular basis as new variants could emerge, as well as new findings on its efficacy and adverse effects (9,10).

MIS-C and Long COVID

Multisystemic inflammatory syndrome in children is an important end-point for potential pediatric/adolescent immunization. The risk of MIS-C and overall mortality from MIS-C are low, but the majority of patients required ICU admission (4,7,10). The long-term consequences of MIS-C are unknown. Owing to its serious signs and complications requiring ICU, the cost of hospital stay, the requirement for IVIG-steroid and other biological treatment, and the fear and anxiety of MIS-C results in an important end-point for COVID-19 vaccine real-world effectiveness. To date, no evidence on vaccine efficacy/effectiveness against MIS-C is available. Since the pathogenesis of MIS-C is unknown, there is a theoretical risk that COVID-19 vaccination will cause MIS-C. By the end of October 2021, according to the EMA report, no substantial evidence on a possible link between mRNA COVID-19 vaccines and MIS-C have been demonstrated (48). Long COVID is another potential important end-point for COVID-19 vaccines in children and adolescents. There is little or no evidence on vaccine efficacy or real-world effectiveness against Long COVID.

The Safety of Pediatric/Adolescent COVID-19 Immunization

The main question for implementing any vaccine is "do the benefits of the vaccine in preventing disease outweigh any known or potential risks associated with vaccination?" (10). Many countries have authorized the use of previously discussed COVID-19 vaccines for EUA in children and adolescents, and millions of children and adolescents have been vaccinated worldwide. Vaccines are well tolerated for children and adolescents except for effects like pain at the injection site, fever, and fatigue. Following the routine use of mRNA vaccines, there have been some cases of myocarditis/pericarditis among adolescents and young adults, particularly among males (8). Following the second dose, Schauer et al. (49) estimated a 0.008% incidence of myopericarditis in adolescents aged 16-17 years and a 0.01% incidence in those aged 12 to 15 years. The majority of cases with myocarditis and pericarditis were mild and self-limiting, and recovered without complications (8). After receiving an mRNA vaccine, adolescents, and young adults who experienced new chest pain, palpitation, shortness of breath were reevaluated for myocarditis. Other causes of myocarditis should also be considered (50). Moreover, the risk of myocarditis associated with COVID-19 infection is higher in this age group, and there is limited information about the risk and long-term outcome of myocarditis/pericarditis due to acute COVID-19 infection in children and adolescents. As of December 12, 2021, the Pfizer-BioNTech vaccine had been administered to 7.1 million children in in the United States. The majority of reactions reported were injection site-related, mild to moderate in severity, most frequently reported the day after vaccination, and slightly more frequently reported after the second dose. Missing school was rarely reported, and only 1% sought medical attention. According to VAERS reports, eight cases with myocarditis (four girls and four boys, two after first dose and six after second dose) have been detected among children aged 5 to 11 years (51). As a precaution, the second dose of the mRNA COVID-19 vaccination series should be postponed in children who experience myocarditis or pericarditis following the first dose (11). As a result, it was determined that the benefit of COVID-19 vaccination for adolescents, outweighed the risk of peri/myocarditis associated with mRNA vaccination. In October 2021, the WHO Global Advisory Committee on Vaccine Safety also concluded that the benefits of mRNA COVID-19 vaccines outweighed the risks in all age groups (9). The definition, reporting, and long-term follow-up of myocarditis/pericarditis cases are critical.

Transmission and New Variants

Another potential benefit of immunizing children is that it helps to reduce transmission, thereby reducing severe cases in adults and the risk of emergence of new variants. For the Delta variant, it has been suggested that infected fully vaccinated adults are just as likely to transmit SARS-CoV-2 as infected unvaccinated individuals, within a shorter period of time. While transmission from children is quite low in educational settings, infants, and children may be the index case for household transmission. There are conflicting findings regarding the effectiveness in preventing virus transmission, particularly during the Delta variant's predominance season (10).

Several SARS-CoV-2 variants have been identified because of their potential for immune escape. Based on data from efficacy trials and immunogenicity studies, COVID-19 vaccines likely remain effective against the variants, but efficacy

may attenuate against Delta (B.1.617.2) and Beta (B.1.351) (27). Omicron (B.1.1.529) is a newly defined variant and preliminary reports suggest that neutralizing activity of sera from vaccinated individuals is lower against the Omicron variant compared to the wild-type virus (17). However, previously infected individuals who are vaccinated and individuals who receive booster vaccination retain adequate neutralizing titers against Omicron. In a population with a low number of vaccinated adults, infected children spread the variant of concern. Therefore, this is also stronger argument for vaccinating children who live with high risk household members.

Booster Dose

Booster dose has been recommended for adolescents over the age of 12, and there is no information on booster dose requirements/schemes for children under the age of 12.

Vaccine Supply, Vaccine Inequity, and Vaccine Hesitancy

Another important factor to consider is the limited global supply of COVID-19 vaccine. Vaccines are now best way to return to a normal life scenario, if equally distributed worldwide. To date, many low/middle-income countries have only been able to vaccinate less than 5% of their population. Available vaccines may be better prioritized for vaccinating adults with a higher risk of severe COVID-19, such as health-care workers. However, some countries start to immunize their population with 3rd or 4th booster dose or expanded their age coverage with children; many lower-middle-income countries still lack sufficient vaccine supply to offer a primary vaccination series to their highest priority-use groups. If this vaccine inequity does not end soon, it is likely that poorer countries will be left behind once again losing thousands of vaccine-preventable lives and leading to more virulent virus variants like Omicron to appear (10,52).

Vaccine hesitancy was an emerging concern for routine immunization prior to the pandemic, and it unfortunately increased during the pandemic period (21). Mandatory COVID-19 vaccination of children has been proposed in order to achieve population-level vaccination coverage and herd immunity. There is insufficient data to make a definitive decision on whether the COVID-19 vaccine should be made mandatory for children. Children, adolescents, and their parents should be supported and respected in their decisions regarding vaccinations for their children, regardless of the decisions they make (4).

Global health authorities, including WHO, EMEA, CDC, and other national health authorities have already authorized the emergency use of COVID-19 vaccines in children and adolescents. The WHO global vaccination strategy targets are 40% of each country's population by the end of 2021, and 70% for 2022 and to date, these targets have not yet been achieved (9). Increasing vaccine coverage among adults and the elderly is still beneficial for controlling pediatric disease burden, but the herd immunity threshold is still lower than expected. Although benefit-risk assessments clearly support the benefit of vaccinating all age groups, the direct health benefit of vaccinating children and adolescents is lower. Clinical trials of inactivated vaccines and mRNA vaccines in children and adolescents have revealed a favorable safety profile as well as immunogenicity. There are also promising results of mRNA vaccine's efficacy and real-world effectiveness. Vaccinating children is likely to provide a direct benefit of disease prevention as well as indirect benefits such as community protection. This benefit would be enhanced for vulnerable children who are at high risk of severe COVID-19. Short and long-term complications related with COVID-19 infection could benefit from pediatric vaccination. Vaccination may also help to reduce school closures and quarantine requirements (5,8,9,10). Global and national health authorities should also closely monitor and constantly assess the benefits and potential risks of vaccination in children and adolescents.

Ethics

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Analysis of Consultations that are Requested from the Emergency Department

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What is known on this subject?

In various studies conducted in different countries, the rate of requesting consultation in emergency services was reported to be between 20 and 56.4%. It was determined that the departments where the patients were hospitalized the most were general surgery (13.8%), neurology (13.4%), orthopedics and traumatology (12.0%), anesthesia (intensive care unit) (11.8%) and pediatric surgery (7.8%).

What this study adds?

It is reported that approximately 19.2% of the cases were consulted in our emergency department and this rate was similar to the literature. The departments with the highest number of hospitalizations in the hospital are respectively; general surgery, internal medicine, neurology, orthopedics. It was determined that the rate of hospitalization in the emergency department was 6.2% and was lower than the rates reported in the literature.

ABSTRACT

Objective: Emergency departments (EDs) are medical units that provide healthcare to patients with diseases that have sudden onset symptoms, patients with disorders, or patients with injuries that need immediate care on a 24/7 basis. In addition to emergency patients mentioned above, EDs provide healthcare services to patients who might have an emergency medical situation later, even if their situation is not emergent initially. Emergency medicine physicians perform all resuscitative interventions to stabilize patients, identify patients who need intensive care in an undifferentiated patient pool, and provide the most appropriate treatment to make them suitable for general ward care.

Material and Methods: The current study is a retrospective and descriptive study that was conducted by analyzing the computer-based patient records of all patients who were admitted to University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital's Emergency Service between 09.01.2020 and 10.01.2020. All 22,459 patients who were admitted to the ED within one month were included in the study. Age and gender characteristics of the patients who received consultation, departments that made the consultation, and hospitalization rates were determined.

Results: The total number of patients who were admitted to the ED between 09.01.2020 and 10.01.2020 was 22,459, the number of consultations was 4,290, and the number of hospitalizations was 1,405. Of the patients for whom consultations were requested, 2,577 were male and 1,713 were female. The mean age was 45.8 years. Of the 22,459 patients who were admitted, 1,786 (7.9%) were triaged with red tags, 9,994 (44.2%) were triaged with yellow tags, and 10,729 (47.9%) were triaged with green tags. The consultations were requested most frequently for orthopedics (522), pulmonology (501), and internal medicine (423). Furthermore, the list continues with general

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ABSTRACT

surgery (386); cardiology (335); ophthalmology (321); neurology (299); otorhinolaryngology (250); neurosurgery (204); obstetrics (138); infectious diseases (122); psychiatry (112); thoracic surgery (108); pediatric surgery (79); cardiovascular surgery (73); plastic surgery (71); anesthesiology and reanimation (140); and urology (55) departments. Of the patients for whom consultations were requested, 35.9% were hospitalized in general wards or intensive care units, whereas 64.1% were discharged.

Conclusion: This study shows that the number of daily admissions to the emergency room is very high, and it is increasing every day. In order to not disrupt the workflow in the ED, the consultations should be responded quickly. Moreover, if possible, consultants from the high demanding departments, such as orthopedics, pulmonologist, internal diseases, general surgery, cardiology, and ophthalmology should ensure that separate doctors (doctors whose only duty would be to attend patients in their respective departments) are on call for the ED.

Keywords: Consultation, emergency service, hospitalization, internal medicine

Introduction

The emergency department (ED) is a medical unit that provides healthcare on a 24/7 basis for patients with diseases that have sudden onset symptoms, patients with disorders, or patients with injuries that need immediate care. In addition to the abovementioned emergency patients, it provides healthcare to patients who might have an emergency medical situation later, even if their situation is not emergent initially. Emergency medicine physicians perform all resuscitative interventions to stabilize patients, identify patients who need intensive care in an undifferentiated patient pool, and provide the most appropriate treatment to make them suitable for general ward care (1,2).

With the increase in medical specialization and the number of specialists, there have been advances in patient management in many specialties. In cases requiring a multidisciplinary approach, physicians from various branches come together, exchange ideas, share their experiences, and collaborate to benefit patients. Therefore, consultation is an indispensable part of patient management in the ED.

The main reasons for requesting a consultation from EDs are as follows (3):

- To ensure that patients with valid indications for hospitalization are admitted to relevant clinics.

- To ask for help or advice in the diagnosis and treatment of patients.

- To organize a specific treatment or procedure for patients who require special care.

- To get approval in the discharge decision of patients with chronic diseases (such as oncology and hematology) from the ED (sharing the discharge responsibility).

- To arrange a detailed discharge planning and outpatient follow-up process for patients who will be discharged from the ED.

Material and Methods

This study is a retrospective and descriptive study that was conducted by analyzing the computer-based patient records of all patients who were admitted to University of Health Sciences Turkey, Başaksehir Çam and Sakura City Hospital's ED between 09.01.2020 and 10.01.2020. Approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (protocol number: 2021-183).

In this study, the following data were obtained by retrospectively analyzing the medical forms of patients that were recorded on the Turkcell Hospital Information Management System, which is the computer-based health record system of the hospital:

- The number of patients who were admitted to the emergency room with yellow, green, and red triage tags.

- The number of patients with yellow, green, and red triage tags that were consulted.

- Department-based analysis of requested consultations.

- The number of patients that were hospitalized after consultation.

- The average age and gender distribution of the consulted patients.

All 22,459 patients who were admitted to the ED within one month were included in the study. Moreover, the age and gender characteristics of the patients who received consultation, the departments that carried out the consultation, and the rate of hospitalization were investigated.

Statistical Analysis

Statistical Package for Social Sciences (Windows 20.0) software was used for the statistical analysis of all the data obtained. All the data were summarized in the tables during

the evaluation. Frequency tests for frequency, mean, and standard deviation values of the obtained data; Mann-Whitney U test to compare the mean values of the obtained data, Pearson chi-square (and Fisher Exact test when necessary) to compare the non-parametric data were used. Only results with confidence intervals above 95% and $p<0.05$ were considered significant.

Results

The total number of patients who were admitted to the ED during the study period was 22,459. The total number of consultations requested was 4,290, and the number of hospitalizations was 1,405. Of the patients who were consulted in any department, 2,577 were male and 1,713 were female. The mean age was recorded as 45.8 years (Figure 1).

Of the 22,459 patients who were admitted to the ED, 1,786 (7.9%) were triaged with red tags, 9,994 (44.2%) with yellow tags, and 10,729 (47.9%) with green tags (Figure 2).

Most of the patients that were admitted to the ED were seen in the green area. However, the highest numbers of consultations were requested in the yellow area. The comparison of the number of consultations with patient admissions revealed that the red area had the highest consultation rate.

The total number of consultations that were requested in this 1-month study period was 4,290. Orthopedics (522) was the most demanding medical department in terms of consultation requests, followed by pulmonology (501), and internal medicine (423). Furthermore, the list goes on with general surgery (386); cardiology (335); ophthalmology (321); neurology (299); ear, nose, and throat (250); neurosurgery (204); obstetrics (138); infectious diseases (122); psychiatry (112); thoracic surgery (108); pediatric surgery (79); cardiovascular surgery (73); plastic surgery (71); anesthesiology and reanimation (140); and urology (55) (Figure 3). Of the patients who were consulted in any medical department, 35.9% were hospitalized to either a hospital ward or an intensive care unit, whereas 64.1% were discharged.

When hospitalizations were assessed on a departmental basis, it was revealed that 137 patients were admitted to the general surgery department, 124 patients were admitted to the internal medicine department, 74 patients were admitted to the neurology department, and 74 patients were admitted to the orthopedics and traumatology department.

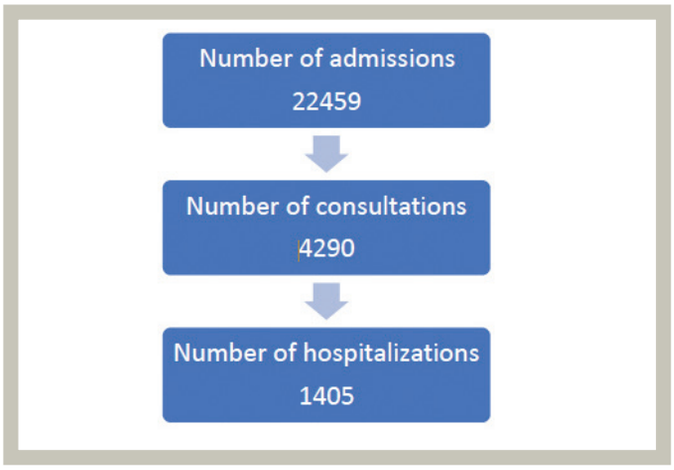

Figure 1. Flowchart

Discussion

Consultation can be vital in the management of patients in the EDs. In various studies conducted in different countries, the rate of consultation requests for emergency patients was reported to be between 20% and 56.4% (4,5,6,7). Lee et al. (8) analyzed 12 studies and discovered that the consultation rate in the EDs was between 20 and 40%. Similarly, in this study, the consultation rate was found to be 19.2%.

According to the study involving 32,800 patients, Köse et al. (9) stated that consultation was requested in 4.5% of all emergency clinic admissions. The consultation rates based on

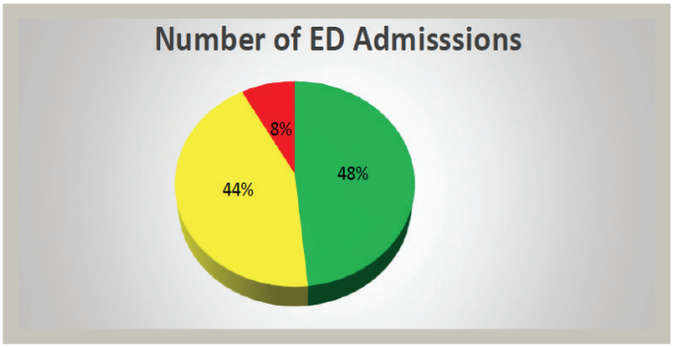

Figure 2. Number of ED admissions

ED: Emergency department

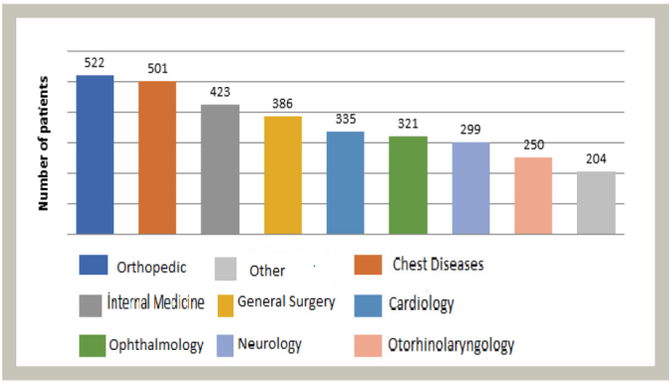

Figure 3. Number of consultations by the departments

requested departments were reported as follows: Orthopedics (16.1%), general surgery (15.5%), neurology (12.5%), internal medicine (12.2%), and pediatric surgery (8.4%). Similarly, in our study, orthopedic consultation was requested the most, and pulmonology consultation took the second position due to the current coronavirus disease-2019 pandemic. The reason orthopedic consultations were mostly requested could be traced to pediatric trauma patients who were also assessed in the adult emergency area.

According to the 33 studies carried out by Kılıçaslan et al. (10) in a large urban university hospital, the rate of hospitalizations from the ED was found to be approximately 12.5%. In the study by Aydın et al. (11), 12.2% of the patients admitted to the ED were hospitalized and 4.5% of them were referred to another hospital. In our study, the hospitalization rate was found to be 6.2%. The low hospitalization rate can be attributed to the high number of patients with green area admissions.

In the study conducted by Köse et al. (9), the rate of hospitalization was 1.4%. The departments that patients were hospitalized in the most were reported as follows: General surgery (13.8%), neurology (13.4%), orthopedics and traumatology (12.0%), intensive care (11.8%), and pediatric surgery (7.8%). Similarly, in our study, hospitalizations from the ED were mostly in the general surgery department, followed by internal medicine, neurology, orthopedics and traumatology, intensive care, and neurosurgery departments.

When the results of our study were compared with the literature, we could conclude that our consultation rates, hospitalization rates, and the departments that emergency patients consulted with are well-matched with the current medical literature.

Conclusion

In EDs, the number of daily admissions has been increasing rapidly in the last couple of years. Therefore, overcrowding has become a serious problem causing workflow issues. In this challenging environment, the response time to consultations and the functionality of consultant physicians have become extremely important.

According to the results of this study:

1. Approximately 19.2% of the patients were consulted in our ED and this rate was well-matched with the current medical literature.

2. The patients were mostly consulted with orthopedics, pulmonology, internal medicine, and general surgery units.

3. The rate of hospitalization from the ED is 6.2%. Even though it seems that our hospitalization rates are lesser than the rates given in the literature, the detailed analysis of patients on triage levels revealed that patients with green triage tags, which have the lowest hospitalization rates, dominated the ED admissions.

4. The departments with the highest number of hospitalizations in the hospital are; general surgery, internal medicine, neurology, and orthopedics respectively.

According to the data that were analyzed in this study, the number of emergency room admissions is very high, and this number is increasing every day. To not disrupt the workflow in the EDs, consultations should be responded to swiftly. If possible, the high demanding medical departments, such as orthopedics, pulmonologist, internal diseases, general surgery, cardiology, and ophthalmology should ensure separate doctors (doctors whose only duty would be to attend patients in their respective departments) are on call for the ED.

Ethics

Ethics Committee Approval: Approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (protocol number: 2021-183).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

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A New Scoring: Can Brescia-COVID Respiratory Severity Scale Predict Mortality in Intensive Care?

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What is known on this subject?

Intensive care mortality rates are estimating with acute physiology and chronic health evaluation II for many times. In coronavirus disease-2019 (COVID-19) pandemics, some new scales, algorithms and mortality scores were added to our practice.

What this study adds?

In this study, we aimed to use Brescia-COVID respiratory severity scale as a mortality predictor for COVID-19 related severe acute respiratory distress syndrome patients.

ABSTRACT

Objective: This study aims to compare the Brescia-coronavirus disease (COVID) severity scale (BCRSS) with acute physiology and chronic health evaluation II (APACHE-II) and sequential organ failure assessment (SOFA) scores in terms of predicting mortality in patients with severe coronavirus disease-2019 (COVID-19).

Material and Methods: BCRSS, SOFA, and APACHE-II scores of patients with severe COVID-19 were calculated when they were first admitted to the intensive care unit. BCRSS score calculation was repeated at the 48th hour. Further treatment, intubation rates, and the result of the intensive care process were recorded and compared.

Results and Conclusion: When the three scoring systems are evaluated as the mortality indicators, SOFA score did not provide a statistically significant difference ($p>0.05$), whereas the APACHE-II score was found to be significantly higher in the fatal cases ($p<0.01$). Furthermore, BCRSS scores at the time of intensive care unit admission and at 48 h were significantly higher in the fatal cases ($p<0.01$). As much as our experience with the disease has been increasing since the beginning of the pandemic, scoring systems are still used for patient triage area, intubation decisions, and directing the medical treatment. Although BCRSS, one of the COVID-19-specific scales, is yet to be validated, our results indicate its potential benefit for predicting IC mortality.

Keywords: Severe COVID-19, BCRSS, APACHE-II, SOFA, mortality, ICU

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Introduction

The initial period of the coronavirus disease-2019 (COVID-19) pandemic caused significant anxiety in health workers not only due to a rapid increase in the number of patients, but also in terms of questions regarding in which units' patients will be treated, which treatments will be used, who will be intubated, and the right time for intubation. Unfortunately, as the large-scale pandemic continues with variant viruses throughout the world, rational and fair use of patient beds and airway equipment remains an important issue.

Italy being among the first countries to face the rapid increase in caseload, a fast and solid scaling/algorithm to be used for patient triage area and making invasive and non-invasive support decisions was needed in the Lombardy region. This need led to the Brescia-COVID severity scale (BCRSS) score (1). Although, BCRSS was first used to determine respiratory heaviness of the patients, and was utilized as a guide for patient management, it was also observed to be beneficial for decisions regarding the use of dexamethasone and tocilizumab. Despite the potential it exhibits, this scale still has a limited use since it is yet to be validated.

In this study, we aim to compare BCRSS score with acute physiology and chronic health evaluation II (APACHE-II), which we use for predicting the patient mortality, and with sequential organ failure assessment (SOFA) score, which we use as an illness severity indicator.

Material and Methods

We retrospectively scanned the Hospital Information Management System for the demographic variables, comorbid diseases, and laboratory and clinical data of 144 patients, who were admitted to our third level pandemic intensive care units (ICU) between January 01, 2021, and March 31, 2021. APACHE-II and SOFA score calculated within the first 24 h of ICU admission were recorded. BCRSS score was calculated based on the patient files and the data provided on ICU admissions, using BCRSS-calculator of the MD-Calc application. Intubation status (yes/no), laboratory results, medical treatments provided, and the result of ICU-care were also noted. This retrospective study was conducted with permission from the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Ethical Committee (2021.10.231).

Statistical Analysis

Statistical analyses were conducted with Number Cruncher Statistical System Statistical Software (Utah, USA). In addition to the descriptive statistics (mean, standard deviation, median, frequency, ratio, interquartile range), Shapiro-Wilk test and box plot graphics were used to assess if variables were normally distributed. Non-normally distributed variables were analyzed by Mann-Whitney U test, and in-group follow-ups were compared with Wilcoxon signed-rank test. The relationship between the scores and mortality was evaluated with receiver operating characteristic (ROC) curve analysis, and values below the curve were compared using Binominal Exact test. Kaplan-Meier survival analysis and Log rank test was preferred for a survival analysis. Significance level was predetermined as $p<0.05$.

Results

The study was conducted with retrospective data of 144 patients, 38.9% female (n=56) and 61.1% male (n=88), who were hospitalized in a city hospital between January 1, 2021, and March 31, 2021. Age range of patients included in the study was between 26 and 91, with a mean of 64.63±11.76.

Among the 144 patients, 118 died and 26 were discharged. A total of 128 patients were intubated, and 16 patients were observed in the ICU without intubation. Descriptive data, additional diseases, APACHE-II, SOFA, intubation status, result of the IC, and duration of IC stay are presented in Table 1.

For the 144 cases, mean APACHE-II score was 21.68±9.12, mean SOFA score at ICU admission was 9.51±4.15, BCRSS score at ICU admission was 4.72±1.76, and BCRSS score in the 48th hour was 6.53±1.88.

Difference between the BCRSS scores was measured both at the admission and at the 48th hour, and the significance levels are presented in Table 2.

The two-unit-difference between the BCRSS score on ICU admission (hour 0) and the 48th hour was found to be statistically significant ($p<0.01$).

When the BCRSS scores are evaluated on the basis of the treatment received specifically for severe COVID-19 symptoms, the change in the 48th hour BCRSS score of the patients who did not receive pulse steroid treatment was statistically significant at the $p<0.05$ level, whereas it was at the $p<0.01$ level for patients who did receive the pulse treatment. BCRSS score between the two Anakinra subgroups was found to be significantly different in the 48th hour, in comparison to the score on ICU admission ($p<0.01$).

The change in the BCRSS score in the 48th hour was found to be significantly different for the two Anakira subgroups ($p<0.01$). BCRSS score was found to change significantly in the 48th hour in patients who did not receive tocilizumab treatment ($p<0.01$). This change was also significant for the

Table 1. Distribution of descriptive variables

Age	Min-max (median)	26-92 (65)
	Mean ± SD	64.63±11.76
Gender	**Female**	56 (38.9)
	Male	88 (61.1)
Comorbidities	**No**	34 (23.6)
	Yes	110 (76.4)
Diseases (n=110)	**Diabetes mellitus**	55 (50.0)
	Hypertension	70 (63.6)
	Hyperlipidemia	2 (1.8)
	COPD	17 (15.5)
	Malignancy	15 (13.6)
	CHF/ACS	25 (22.7)
	Rheumatic disease	1 (0.9)
	CVD	6 (5.5)
	Dementia/Alzheimer's	4 (3.6)
	Other	35 (31.8)
APACHE-II	Min-max (median)	7-48 (19.5)
	Mean ± SD	21.68±9.17
SOFA score	Min-max (median)	3-20 (9)
	Mean ± SD	9.51±4.15
Intubation	**Yes**	128 (88.9)
	No	16 (11.1)
Result	**Discharge**	26 (18.1)
	Death	118 (81.9)
Monitoring duration (days)	Min-max (median)	1-71 (11)
	M ± SD	13.63±11.38

Min: Minimum, Max: Maximum, SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, ACS: Acute coronary syndrome

Table 2. Comparison of Brescia-COVID severity scale scores at the time of admission and the 48th hour

	ICU admission Median (IQR)	48th hour Median (IQR)	Difference Median (IQR)	p
BCRSS score	4 (3-6)	7 (6-8)	2 (0-4)	[a]**0.001****

*[a]Wilcoxon signed ranks test, **p<0.01, IQR: 25-75% percentile, BCRSS: Brescia-COVID severity scale, IQR: Interquartile range*

patients who did receive tocilizumab treatment, but the significance level was p<0.05. As for the Plasmapheresis groups, the change in the 48th hour BCRSS score was found to be significantly different between the patients who received and did not receive the treatment (p<0.01). Similarly, when compared to the score on ICU admission, the change in the BCRSS scores in the 48th hour was statistically different between the two intravenous immunoglobulin subgroups (p<0.01). Evaluation of BCRSS scores based on the treatment subgroups is presented in detail in Table 3.

When the three scoring systems were evaluated as mortality indicators, SOFA score did not provide statistically significant results based on the mortality (p>0.05) whereas APACHE-II score was significantly higher in patients who were deceased (p<0.01). BCRSS scores on ICU admission and 48th hour were significantly higher in the deceased cases (p<0.01) (Table 4, 5, 6).

ROC Curve analyses of the scores are presented in Figure 1.

Table 3. Evaluation of Brescia-COVID severity scale scores based on different treatment subgroups

ICU admission Median (IQR)		BCRSS score 48th hour Median (IQR)	Difference (Δ) Median (IQR)		[a]p
Pulse steroid	No (n=12)	4 (4-6)	6 (4.5-8)	2 (0-2)	**0.028***
	Yes (n=132)	4 (3-6)	7 (6-8)	2 (0-4)	**0.001****
	p	[b]**0.887**	[b]**0.173**	[b]**0.552**	-
Anakinra	No (n=104)	4 (3-6)	7 (6-8)	2 (0-4)	**0.001****
	Yes (n=40)	4 (3-6)	7 (6.5-8)	2.5 (0-4)	**0.001****
	p	[b]**0.472**	[b]**0.450**	[b]**0.064**	-
Tocilizumab	No (n=130)	4 (3-6)	7 (6-8)	2 (0-4)	**0.001****
	Yes (n=14)	4.5 (4-7)	8 (6-8)	0.5 (0-2)	**0.048***
	p	[b]**0.182**	[b]**0.816**	[b]**0.238**	-
Plasmapheresis	No (n=124)	4 (3-6)	7 (5.5-8)	2 (0-4)	**0.001****
	Yes (n=20)	4.5 (4-6)	8 (7-8)	2 (0-4)	**0.001****
	p	[b]**0.256**	[b]**0.178**	[b]**0.384**	-
IVIG	No (n=118)	4 (3-6)	7 (6-8)	2 (0-4)	**0.001****
	Yes (n=26)	4 (4-6)	8 (6-8)	2.5 (0-4)	**0.001****
	p	[b]**0.735**	[b]**0.075**	[b]**0.076**	-

*[a]Wilcoxon signed ranks test, [b]Mann-Whitney U test, IQR: 25-75% percentile, *p<0.05, **p<0.01, BCRSS: Brescia-COVID severity scale, IQR: Interquartile range, ICU: Intensive care units, IVIG: Intravenous immunoglobulin*

Table 4. Evaluations based on mortality

		Survive	Exitus	p
SOFA	Mean ± SD	8.12±2.52	9.82±4.38	**0.116**
	Median (min-max)	8 (3-12)	9 (3-20)	
APACHE-II	Mean ± SD	14.81±5.37	23.19±9.15	**0.001****
	Median (min-max)	14 (8-30)	22 (7-48)	
BCRSS on ICU admission	Mean ± SD	3.65±1.16	4.96±1.78	**0.001****
	Median (min-max)	3 (2-7)	4 (2-8)	
BCRSS in 48th hour	Mean ± SD	3.88±1.99	7.11±1.27	**0.001****
	Median (min-max)	3 (0-8)	8 (3-8)	

*[b]Mann-Whitney U test, **p<0.01, Min: Minimum, Max: Maximum, SD: Standard deviation, SOFA: Sequential organ failure assessment, APACHE-II: Acute physiology and chronic health evaluation II, BCRSS: Brescia-COVID severity scale, ICU: Intensive care units*

Table 5. Receiver operating characteristic curve results based on mortality

Area under the curve Test result variable(s)	Area	Standard error[a]	Asymptotic p[b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
SOFA score	0.598	0.052	**0.117**	0.496	0.700
APACHE-II	0.792	0.046	**0.000****	0.701	0.882
BCRSS on ICU admission	0.723	0.051	**0.000****	0.623	0.824
BCRSS in 48th hour	0.891	0.042	**0.000****	0.809	0.973

***p<0.01, [a]Wilcoxon signed ranks test, [b]Mann-Whitney U test, SOFA: Sequential organ failure assessment, APACHE-II: Acute physiology and chronic health evaluation II, BCRSS: Brescia-COVID severity scale, ICU: Intensive care units*

Table 6. Evaluation of areas

Dual comparison of areas	p
SOFA-APACHE-II	0.005**
SOFA-BCRSS on ICU admission	0.102
SOFA-BCRSS 48th hour	<0.001**
APACHE-II- BCRSS on ICU admission	0.206
APACHE-II- BCRSS in 48th hour	0.021*
BCRSS on ICU admission - BCRSS in 48th hour	0.002**

*Binomial Exact test, **p<0.01, SOFA: Sequential organ failure assessment, APACHE-II: Acute physiology and chronic health evaluation II, BCRSS: Brescia-COVID severity scale, ICU: Intensive care units*

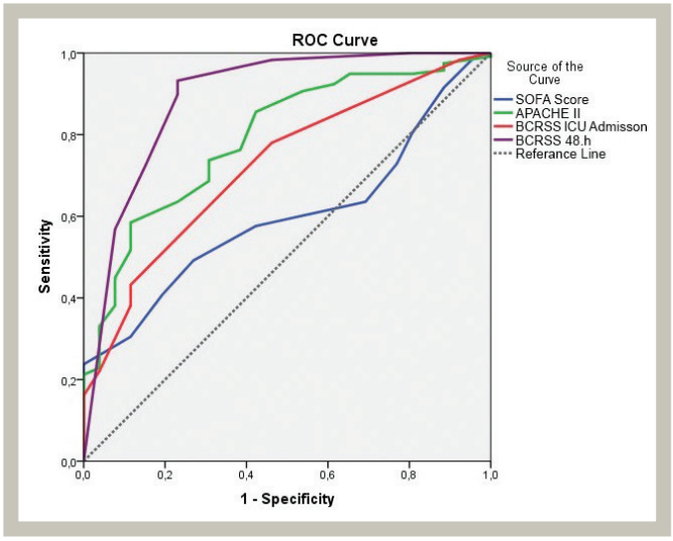

Figure 1. Receiver operating characteristic curves of SOFA, APACHE-II, and BCRSS

ROC: Receiver operating characteristic curves, SOFA: Sequential organ failure assessment, APACHE-II: Acute physiology and chronic health evaluation II, BCRSS: Brescia-COVID severity scale

Discussion

Rational management of ICUs has gained significant importance, beginning with the COVID-19 pandemic. As a result, new additions are being made to our scoring systems, which we use for ICU admissions, treatment management, and illness severity prediction. Scoring systems extensively used in ICUs are "prognostic scoring systems," which predict mortality, and "organ failure scoring systems," which evaluate morbidity. The most frequently used prognostic scoring systems are APACHE, simplified acute physiology score (SAPS), therapeutic intervention scoring system, and mortality prediction/probability models. Furthermore, SOFA, multiple organ dysfunction score, and logistic organ dysfunction score are some of the widely accepted organ failure scoring systems (2,3,4). APACHE-II, SAPS-II, SOFA scores could be calculated electronically in our hospital's information system.

At the beginning of the pandemic, BCRSS scoring system and quick COVID-19 severity index (qCSI) were developed for managing triage in the Lombardia region, where some of the first cases were observed. In our hospital, we still prioritize APACHE-II as an objective indicator for evaluating the possibility of mortality and illness severity during ICU admissions. Siddiqi and Mehra (5) define three stages in the diagnosis and treatment of COVID-19-related illnesses: Mild, moderate, and severe. According to this classification, patients included in our study were all in stage 3 (severe) since po2/fio2 was <300 for each one of them. In 144 patients, 128 were intubated and monitored during invasive mechanical ventilation.

Due to its significance in the diagnosis of sepsis and septic shock, SOFA is a scoring system that we use daily or, based on the clinician's preference, even more frequently could be used. The literature on SOFA scores of patients with COVID-19 indicate its potential use for predicting mortality. Rod and colleagues list 60 independent predictors for predicting the severity of COVID-19, and report that SOFA, age, D-dimer, high-sensitive C-reactive protein, body temperature, albumin level, and presence of comorbidity (e.g., diabetes mellitus) are highly related to illness severity (6). In the same study, authors suggest that SOFA score could be used as a parameter for hospital mortality prediction. Kodik et al. (7) investigated SOFA and some other mortality evaluation criteria, including subgroups of SOFA parameters, and reported that SOFA score could be used for mortality prediction. On the other hand, Raschke et al. (8) have conducted another study, which indicates low discriminative performance of SOFA score in mortality prediction, which was lower than the age factor alone. SOFA score uses six parameters to evaluate the six systems. However, for COVID-19, mostly three organ systems (respiratory, hepatobiliary, and renal) were found to be mortality-related (9). In our study, median value for the SOFA score was nine, and our results did not indicate a significant prediction performance of SOFA on mortality. As the previous studies have suggested, this may be due to the sepsis-specific design of SOFA score, which does not include mortality increasing parameters in COVID-19, such as age or comorbidity. Furthermore, as a limitation in our study, SOFA score was calculated only once within 48 h of ICU admission, and therefore further SOFA scores of patients were not included in the analyses.

APACHE-II is another scoring system used for mortality prediction within the first 24 h of ICU admission, together with

the presenting symptoms, laboratory results, and presence of additional acute and chronic diseases. The score ranges from 0 to 71, higher numbers indicating stronger expectations of mortality (10). Zou et al. (11) conducted a study with patients with COVID-19 and suggested that APACHE-II scores >17 are alarming for mortality and should be considered in treatment decisions. Chen et al. (12) evaluated the severity and mortality of COVID-19 pneumonia using APACHE-II, CURB-65, and pneumonia severity index, and reported all three scales as the viable options. In parallel, our results indicate a relationship between high APACHE-II scores and high mortality. Our APACHE-II median value was 19.5 (minimum-maximum 7-48), and 118 of the 144 patients did not survive. The median APACHE-II score of surviving patients was 14, whereas it was 22 for the exitus group. This was an expected result which could be explained by the severity of our patient group, the development of multiple organ failure, the high mean age (60+), and the high number of patients with comorbidity.

BCRSS provides a gradual approach to the management of patients with validated or predicted COVID-19 pneumonia. BCRSS is used for patients who present with COVID-19 pneumonia or describe symptoms going back >7 days. In these patients, four criteria are evaluated, and the algorithm presented suggestions based on the presence of ≤2 or >2 criteria. According to the algorithm, if more than two criteria are present, high-flow oxygen treatment (HFOT) or non-invasive mechanical ventilator (NIMV) are suggested. If more than two criteria are positive despite the NIMV and/or HFOT support, considering the age and comorbidities of the patient, decision to intubate may be made. Suggestions provided by the algorithm consist of eight layers. With every change in the patient's status and every new treatment provided, calculations could be remade, making BCRSS a dynamic and timely scale.

Even though BCRSS was, at first, used for determining the respiratory severity and guiding the patient management, it was also found to be useful for making decisions in two other areas (i.e., dexamethasone and tocilizumab treatments). Italian working group suggests treating patients with a BCRSS score of/higher than two with dexamethasone (13). Similarly, treating patients who have a BCRSS score of/higher than three with tocilizumab is suggested. The BCRSS score is based on an algorithm that provides a guide for many patient management issues, including the invasive/non-invasive respiratory support, prone positioning, treatment agents, and laboratory test orders. In Italy, in general, treatment decisions in emergency rooms, hospital services, and ICU were made through this scoring system, utilized by the clinician as frequently as preferred. For patients with COVID-19 pneumonia, for patients who describe symptoms going back at least seven days, and for patients who are polymerase chain reaction (PCR) (+) or whose PCR is inconclusive, all four test criteria are evaluated. These test criteria are applied on the algorithm, leading to a score from 0 to 8. The algorithm makes a treatment suggestion based on the score calculated. The scale was designed to be dynamic, to be consulted frequently and to provide new scores after each treatment (1). If the score is ≥4, the need for ICU admission and intubation should be considered. This scale, despite its apparent convenience, still has limited use since it is yet to be validated. However, the studies are being conducted for evaluating the use of BCRSS scores. For example, Ak et al. (14) analyzed ICU admission and mortality rates of all patients hospitalized with COVID-19 diagnosis, using BCRSS and qCSI. Authors report both scales to be viable options for this purpose (14). Similarly, Rodriguez-Nava et al. (15) compared different scales in terms of ICU admission and mortality prediction and suggest qCSI and BCRSS to be good indicators in this area. In parallel to this, in our study, BCRSS median value on ICU admission was four, and the BCRSS median value in the 48th hour was seven. The difference between the two values was statistically significant in terms of the mortality rates. The gradual scoring in BCRSS algorithm could be a useful guide for clinicians. Studies suggest that BCRSS could be used for making tocilizumab and Anakinra treatment choices (16,17). In our study, dexamethasone and methylprednisolone treatment is applied in pandemic services and intermediate care units, where patients are treated before ICU admission. There are studies suggesting a BCRSS score of three to be an indicator for evaluating the dexamethasone option (18). In our study, the majority of the patients received 1 mg/kg/day methylprednisolone or pulse methylprednisolone (250 mg/day for 3 days), and their treatment was continued with the same dosage of steroid or an increased dosage of pulse steroid (250-1,000 mg/day). It could be argued that, for patients in services, this scoring system could be used for determining the need for steroid treatment. Italian society of Infectious and tropical diseases suggests a BCRSS score of ≥3 for tocilizumab treatment (13). Based on this suggestion, Erden et al. (19) designed a study to compare BCRSS and other scales for Anakinra treatment decisions and reported the superiority of BCRSS, SOFA, and MuLBSTA scores to the H-score in the development of macrophage activation syndrome (19). In our study, we used BCRSS scores for predicting mortality. According to our results, BCRSS score calculated in the 48th hour was the best predictor.

Study Limitations

As limitations of our study, the design did not include a control group, and we haven't used BCRSS to apply steroid and

anti-cytokine treatments. The required laboratory tests for recalculating the SOFA scores were not fully ordered, resulting in a lack of data for evaluating daily increases/decreases in the SOFA score.

Conclusion

To conclude; our evaluations indicate that as the COVID-19 pandemic has been present for more than two years and as the patients still present severe symptoms due to additional variant viruses, the need for valid scoring systems will persist for not only triage purposes but also for the rational use of ventilators and ICU beds as well as for predicting the mortality. BCRSS score, specifically designed for COVID-19, is still not validated probably since the algorithm has yet not been tested on significant number of patients. Further studies may contribute to the validation of BCRSS for more reliable results.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Ethical Committee (2021.10.231).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Histopathological Evaluation of LAG-3, TIM-3 AND CD38 Levels in Meningiomas

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What is known on this subject?

Immune checkpoint molecules (ICM) regulate the immune system's response to different antigens.

What this study adds?

The relationship between meningiomas of different histopathological grades and ICM levels.

ABSTRACT

Objective: Meningiomas are the most common primary intracranial tumors in adults that account for 36% of primary tumors. Treatment options other than surgery and radiotherapy are necessary for meningioma. Immune checkpoint molecules (ICM) are modulators that regulate the proper response of the immune system. Lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin domain containing-3 (TIM-3), and the cluster of differentiation 38 (CD38) are known ICMs. This study hypothesized the relationship between meningiomas of different histopathological grades and the levels of these three ICMs. Additionally, the therapeutic potential of these molecules was investigated.

Material and Methods: This study re-evaluated 25 specimens diagnosed as meningioma. Tissues are classified according to LAG-3, TIM-3, and CD38 levels. Age, gender, surgery date, tumor type, and subtype, histopathologically malignant grade, radiological tumor size, and presence of edema were recorded in all patients. All data were statistically compared.

Results: This study included the specimens of 25 patients, of whom 9 were males and 16 were females. LAG-3 and CD38 levels were significantly higher in tumors bigger than 6 cm.

Conclusion: This study is the first to investigate LAG-3, TIM-3, and CD38 levels in meningiomas and found a significant correlation between LAG-3 levels and meningioma size. No significant correlation was found with other data. However, the number of patients in our study was insufficient. Therefore, larger patient groups may yield more significant results.

Keywords: Immune, checkpoint, histopathology, meningioma, molecules

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Introduction

Meningiomas are the most common primary intracranial tumors in adults that account for 36% of primary tumors (1). It is classified as grade 1, 2, and 3 according to histopathological features (2,3). Surgical resection is usually adequate in grade 1 meningiomas. However, the mean progression-free survival is 7 years in grade 2 tumors (atypical meningioma) and <3 years in grade 3 tumors (malignant meningioma). Of all meningiomas, 25-30% are grade 2 and 3% are grade 3 (3). Adjuvant radiotherapy is applied in these meningiomas; however, recurrence is often unavoidable (4), and treatment options other than surgery and radiotherapy are limited (5). Therefore, new and effective treatment methods are required.

Recently, the potential of immune checkpoint molecules (ICM) has been remarkable in meningioma treatment (2). ICM regulates the immune system's proper response to different antigens. The T-cell response is inhibited or stimulated by different molecules. Thus, the response of T-cells is regulated by a secondary signal after antigen recognition (6). Cancer cells use this way to evade the immune system. Tumors suppress the immune response by stimulating inhibitory ICMs and creating immune tolerance. Therefore, ICM modulation is considered a target in cancer immunotherapy for tumor activity suppression. These molecules include lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin domain containing-3 (TIM-3), and the cluster of differentiation 38 (CD38) (7). This study mainly hypothesized the relationship between meningiomas of different histopathological grades and the levels of these three ICMs. Additionally, the therapeutic potential of these molecules was investigated.

Material and Methods

This study was prospectively conducted after the approval decision of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Local Ethics Committee, dated 08.01.2018 and numbered 2018-01-07.

Tissue samples obtained from patients who were operated on for brain tumors in our center were used. The samples were fixed in paraffin. Patients with an adequate amount of stored tumor tissue that are histopathologically diagnosed as meningioma, with all ages and genders, who were on operated for the first time for the tumor, and did not receive chemotherapy or radiotherapy for the operated tumor were included in the study. Patients with different or suspicious tumor diagnoses were excluded from the study. Age, gender, surgery date, tumor type and subtype, histopathologically malignancy grade, radiological tumor size (8), and presence of edema were recorded in all patients.

Histopathological Examination

This study used meningioma tissue specimens that are obtained from a single center. Formalin-fixed and paraffin-embedded sections (4 µm) from the samples were used for immunohistochemistry (IHC) staining. Paraffin-embedded tissue sections were baked in a drying oven at 60°C for 1 h. Heat-mediated antigen retrieval was performed on LAG-3 slides. All slides were labeled and placed in a Benchmark XT system (Ventana Medical Systems, Tucson, AZ). Histopathological sections of typical and atypical meningiomas are in Figures 1A and B (Figure 1). After the slides had been treated with standard cell conditioning 1 solution for 60 min, primary antibody cell signaling LAG-3 [DANVERS MA-USA CST 15372S (KLON D2G40) 1/100, cell signaling TIM-3 KLONd5d5r (DANVERS MA -USA CST 45208S) 1/200, and CD38 cellmarque clone (SP149) ROCKLIN -CA-USA 1/100 dilution was applied, and the slides were incubated at 37°C for 1 h. An ultra view universal DAB detection and amplification kit (ROCHE, Ventana Tuscon Medical Systems] was used. Slides were counterstained with hematoxylin for 4 min and post counterstained with a bluing agent for 4 min. Slides were washed and then dehydrated in 70-100% reagent alcohol baths and then in xylene baths before coverslip application. The human normal tonsil was used as the positive control for LAG-3.

Histopathological Analysis

All IHC results were independently reviewed by a pathologist who was blinded from the clinical data. It was expressed in the cytoplasm of the lymphocytes with brown

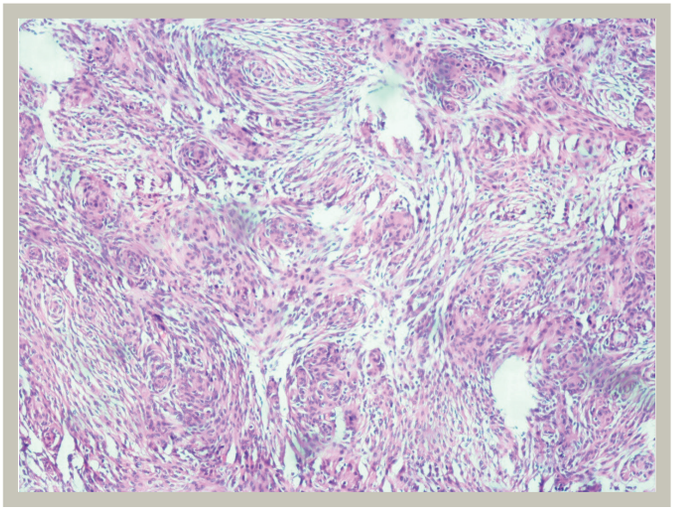

Figure 1A. Grade 1 meningothelial meningioma consisting of atypical meningothelial cells forming whorl structures (HEX100)

color. The number of lymphocytes was calculated in the microscope's field of vision on hematoxylin-stained sections, as described. Five randomly especial perivascular space-selected high-power fields (400×) were averaged in each case to calculate the positive cell percentage. LAG-3, TIM-3, and CD38 tumor-infiltrating lymphocytes (TILs) were evaluated in a tumor. The infiltrating intensity of TILs was assessed with a semiquantitative score from 1+ to 3+, with a score of 1+ that indicate a low TIL percentage (1-3 cell), 2+ a moderate percentage (3-6 cell), and 3+ a marked increased percentage (6 cell up) (Table 1) (9). The TILs were composed of mononuclear cells, including lymphocytes, macrophages, and plasma cells (Figure 2, 3, 4).

Statistical Analysis

Parametric tests were used without normality tests due to compliance with the Central Limit Theorem (10). Data analyses used mean and standard deviation, minimum and maximum values of features, and frequency and percentage values to define the categorical variables. The chi-square test statistic was used to evaluate the relationship between categorical descriptive statistics in meningioma LAG-3, TIM-3, and CD38 parameters. The statistical significance level of data was taken as $p<0.05$. The www.e-picos.com New York software and MedCalc statistical package program were used for data evaluation.

Table 1. Grading criteria according to LAG-3, TIM-3, CD38 levels

	Grade 1 (low)	Grade 2 (moderate)	Grade 3 (increase)
TILs	1-3	4-6	6+

LAG-3: Lymphocyte activation gene-3, TIM-3: T-cell immunoglobulin and mucin domain containing-3, CD38: Cluster of differentiation 38, TILs: Tumor-infiltrating lymphocytes

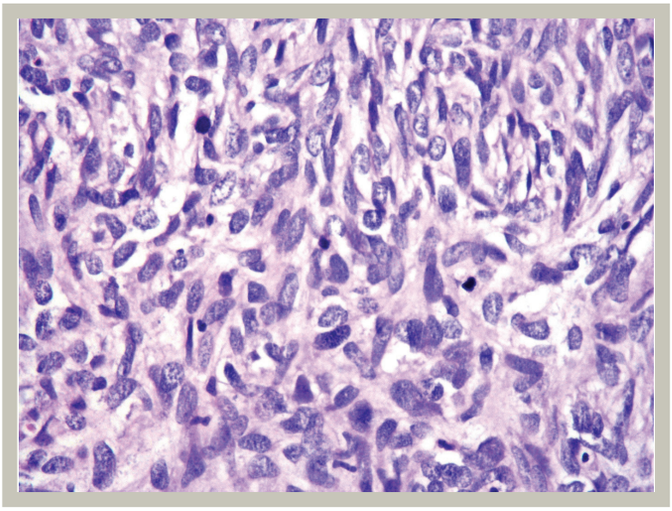

Figure 1B. Grade 2 atypical meningioma with atypical mitoses (HEX200)

Results

This study included specimens of 25 patients, of whom 9 were males and 16 were females. According to the lesion location, six were frontal, six were occipital, six were parietal, and seven were in the temporal lobe. No significant difference was found between the location and LAG-3, TIM-3, and CD38 levels. According to histopathological tumor subtypes, four atypical, 5 fibrosis, five transitional, 4 meningeal, and seven anaplastic types were determined. No significant difference was found between meningioma subtypes and LAG-3, TIM-

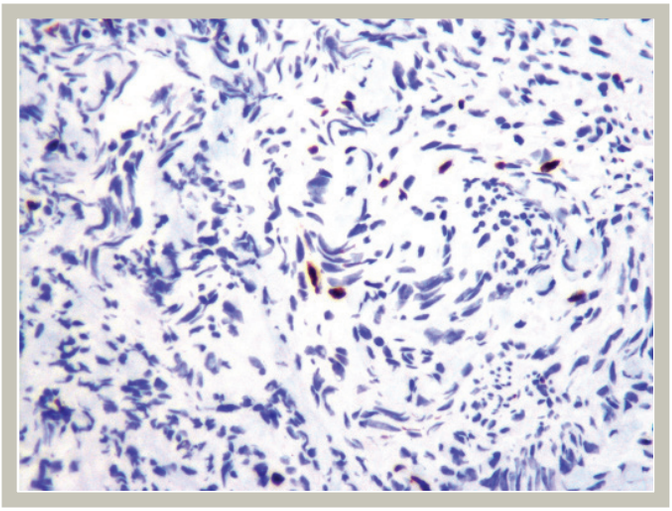

Figure 2A. LAG-3 grade 1, sparse cell collection (LAG-3X400)

LAG-3: Lymphocyte activation gene-3

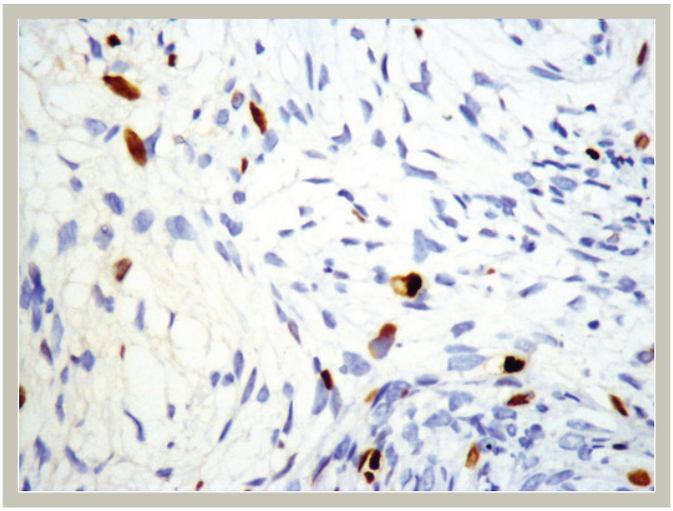

Figure 2B. LAG-3 grade 3 in the hotspot area (LAG-3X400)

LAG-3: Lymphocyte activation gene-3

3, and CD38 levels. The number of specimens according to tumor size revealed that ten were <3 cm, 9 were 3-6 cm, and 6 were >6 cm. LAG-3 and CD38 levels were significantly higher in tumors that are >6 cm in size ($p<0.01$). No significant difference was found between parenchymal invasion, bone invasion, and edema severity, and LAG-3, TIM-3, and CD38 levels. All findings are summarized in Table 2, 3, 4.

Discussion

Meningiomas are the most common primary intracranial tumors in adults (1). Treatment options are limited without surgery and radiotherapy (5). Therefore, studies are conducted for new and alternative treatments (2). Recently, a lot of work has been conducted on therapies that target the ICM. The cell types from which the meningioma originates are different from other cancers; however, the mechanisms for the immune system response are similar. This mechanism is regulated by ICMs, such as LAG-3, TIM-3, and CD38 (11).

ICM regulates the immune system's response to various antigens. The T-cell response is inhibited or stimulated by these molecules (6). Cancer cells use this method to avoid the immune response and suppress the immune response by activating inhibitory ICMs. Therefore, suppression of these molecules can be used in cancer immunotherapy (7).

Some of the ICM molecules are LAG-3, TIM-3, and CD38 (7). No study in the literature has examined the relationship between meningiomas and these ICMs. However, few studies

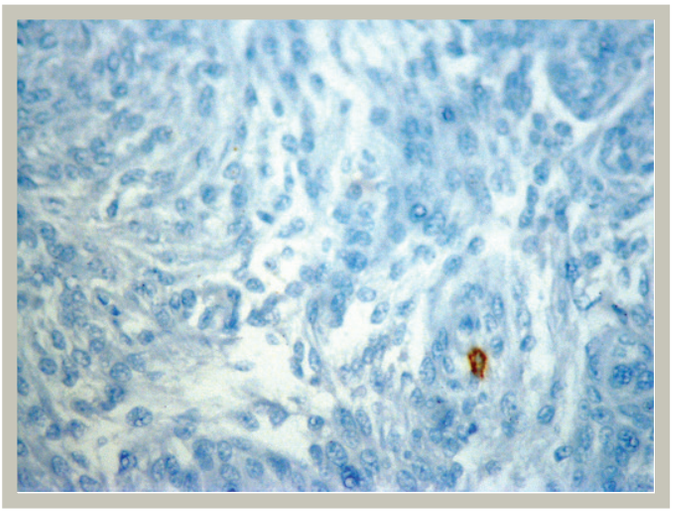

Figure 3A. TIM-3 grade 1, few sparse cell aggregates (TIM-3X400)

TIM-3: T-cell immunoglobulin and mucin domain containing-3

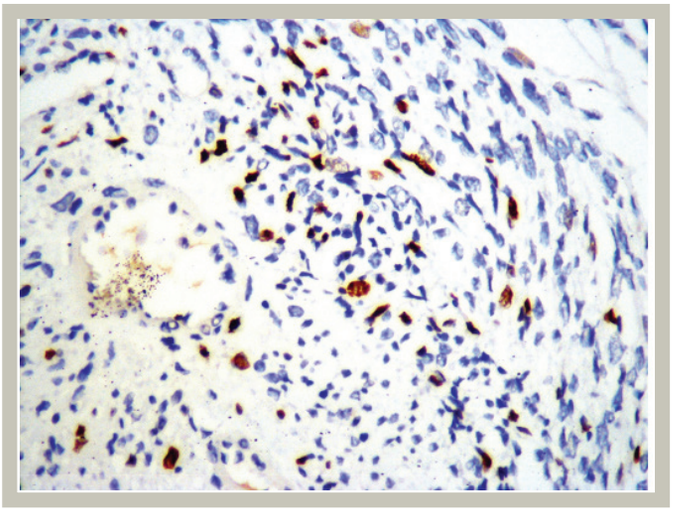

Figure 3B. Perivascular TIM-3 grade 3 in lymphocyte-rich meningioma tissue (TIM-3X400)

TIM-3: T-cell immunoglobulin and mucin domain containing-3

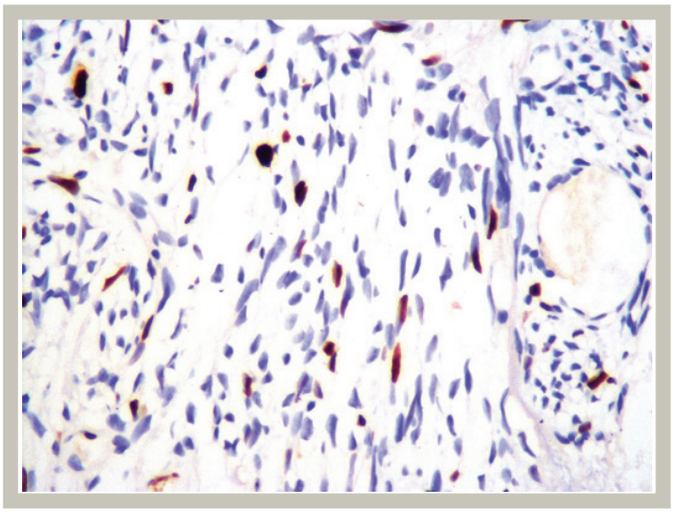

Figure 4A. CD38 grade 1 cells (CD38X400)

CD38: Cluster of differentiation 38

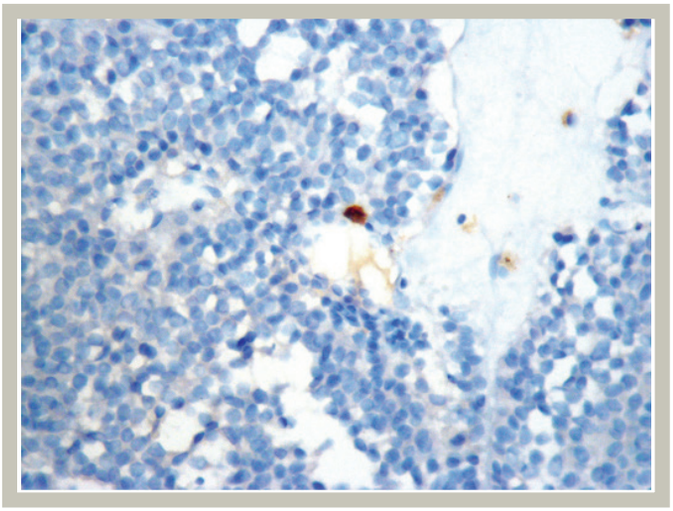

Figure 4B. CD38 grade 3 cells (CD38X400)

CD38: Cluster of differentiation 38

Table 2. Relationship between LAG-3 level and variables

n=25	LAG-3			
	1 n=10 n (%)	2 n=10 n (%)	3 n=5 n (%)	p value
Gender				
Female	8 (80)	7 (70)	4 (80)	0.85
Male	2 (20)	3 (30)	1 (20)	
Localization				
Frontal	2 (20)	2 (20)	2 (20)	0.63
Occipital	3 (30)	1 (10)	2 (40)	
Parietal	2 (20)	3 (30)	1 (20)	
Temporal	3 (30)	4 (40)	-	
Pathological subtype				
Atypical	1 (10)	1 (10)	2 (40)	0.5
Fibrosis	3 (30)	2 (20)	-	
Transitional	2 (20)	1 (10)	2 (40)	
Meningeal	1 (10)	3 (30)	-	
Malignant	3 (30)	3 (30)	1 (20)	
Size				
1 (<3 cm)	10 (100)	-	-	<0.001*
2 (3-6 cm)	-	8 (80)	1 (20)	
3 (>6 cm)	-	2 (20)	4 (80)	
Parenchymal invasion				
None	6 (60)	7 (70)	3 (60)	0.88
Yes	4 (40)	3 (30)	2 (40)	
Bone invasion				
None	8 (80)	8 (80)	4 (80)	1
Yes	2 (20)	2 (20)	1 (20)	
Degree of edema				
1- Minimal	3 (30)	2 (20)	-	0.65
2- Smaller than tumor size	3 (30)	5 (50)	3 (60)	
3- More than tumor size	4 (40)	3 (30)	2 (40)	

**The relationship between LAG-3 status and size is statistically significant (p<0.05). **Chi-square test statistics were used to evaluate the relationship between categorical variables. Considering the relationship between LAG-3 status and variables. LAG-3: Lymphocyte activation gene-3*

Table 3. Relationship between TIM-3 level and variables

n=25	TIM-3		
	1 n=19 n (%)	2 n=6 n (%)	p value
Gender			
Female	14 (73.7)	5 (83.3)	0.63
Male	5 (26.3)	1 (16.7)	
Localization			
Frontal	4 (21.1)	2 (33.3)	0.77
Occipital	5 (26.3)	1 (16.7)	
Parietal	4 (21.1)	2 (33.3)	
Temporal	6 (31.6)	1 (16.7)	
Pathological subtype			
Atypical	4 (21.1)	-	0.72
Fibrosis	4 (21.1)	1 (16.7)	
Transitional	3 (15.8)	2 (33.3)	
Meningeal	3 (15.8)	1 (16.7)	
Malignant	5 (26.3)	2 (33.3)	
Size			
1 (<3 cm)	9 (47.4)	1 (16.7)	0.19
2 (3-6 cm)	7 (36.8)	2 (33.3)	
3 (>6 cm)	3 (15.8)	3 (50)	
Parenchymal invasion			
None	12 (63.2)	4 (66.7)	0.88
Yes	7 (36.8)	2 (33.3)	
Bone invasion			
None	16 (84.2)	4 (66.7)	0.35
Yes	3 (15.8)	2 (33.3)	
Degree of edema			
1- Minimal	4 (21.1)	1 (16.7)	0.94
2- Smaller than tumor size	8 (42.1)	3 (50)	
3- More than tumor size	7 (36.8)	2 (33.3)	

***Chi-square test statistics were used to evaluate the relationship between categorical variables. Considering the relationship between TIM-3 Status and variables, there was no statistical significance (p>0.05). TIM-3: T-cell immunoglobulin and mucin domain containing-3*

have examined the relationship between Programmed death-ligand 1 (PDL1) and PDL2 of ICMs and meningiomas (2,12,13,14). Han et al. (2) reported that as the grade of meningiomas increased, PDL1 levels also increased with a negative effect on survival. Wang et al. (14) revealed that immunotherapy is more effective if PDL1 is inhibited in neurofibromatosis-related meningiomas. Proctor et al. (12) reported that PDL2 expression is higher in meningiomas compared to the normal cerebral cortex.

TIM-3 is a cell surface protein expressed from Th1 cells and suppresses the immune response by connecting to galectin-9 in T-cells (15). Models with solid tumors, such as melanoma, breast cancer, and colon cancers, showed an increased programmed cell death protein 1 level, which is a sign of T-cell reduction in tumor-infiltrating cells. These findings suggest that TIM-3 suppresses tumor death through the immune

Table 4. Relationship between CD38 level and variables

n=25	CD38			p value
	1 n=19 n (%)	2 n=5 n (%)	3 n=1 n (%)	
Gender				
Female	15 (78.9)	4 (80)	-	0.19
Male	4 (21.1)	1 (20)	1 (100)	
Localization				
Frontal	5 (26.3)	1 (20)	-	0.48
Occipital	6 (31.6)	-	-	
Parietal	4 (21.1)	2 (40)	-	
Temporal	4 (21.1)	2 (40)	1 (100)	
Pathological subtype				
Atypical	3 (15.8)	1 (20)	-	0.29
Fibrosis	5 (26.3)	-	-	
Transitional	4 (21.1)	1 (20)	-	
Meningeal	3 (15.8)	-	1 (100)	
Malignant	4 (21.1)	3 (60)	-	
Size				
1 (<3 cm)	8 (42.1)	2 (40)	-	0.04*
2 (3-6 cm)	9 (47.4)	-	-	
3 (>6 cm)	2 (10.5)	3 (60)	1 (100)	
Parenchymal invasion				
None	14 (73.7)	1 (20)	1 (100)	0.06
Yes	5 (26.3)	4 (80)	-	
Bone invasion				
None	15 (78.9)	4 (80)	1 (100)	0.88
Yes	4 (21.1)	1 (20)	-	
Degree of edema				
1- Minimal	5 (26.3)	-	-	0.16
2- Smaller than tumor size	9 (47.4)	1 (20)	1 (100)	
3- More than tumor size	5 (26.3)	4 (80)	-	

***Chi-square test statistics were used to evaluate the relationship between categorical variables. Considering the relationship between LAG-3 status and variables, *The relationship between LAG-3 status and size is statistically significant (p<0.05). CD38: Cluster of differentiation 38, LAG-3: Lymphocyte activation gene-3*

system by causing T-cell depletion, and the tumor relieved of the immune system. Therefore, TIM-3 may be a potential immune marker for cancer treatment. Galectins are previously reported to be associated with poor prognosis and metastasis in many cancer types (16). Recent studies with galectin 9 have shown its role as the main T-cell activity regulator, and T-cell activation is suppressed with galectin 9 infusion (17,18). Liu et al. (19) investigated the relationship of galectin 9 with the TIM-3 pathway and brain tumors. This study examined the lymphocytes in peripheral blood samples of patients with glioma and those normal and detected significantly increased galectin 9 and TIM-3 activity in the peripheral blood by TIL compared to the control group. No study has reported about TIM-3 level in meningiomas. Our study used IHC staining to evaluate TIM-3 expression in meningiomas and compared tumor histopathological grade, size, degree of edema, localization, parenchymal invasion, and bone invasion. No statistically significant difference was found between the TIM-3 level and these features. The small number of patients both prevented homogeneous distribution and affected the statistical results.

LAG-3 is also a membrane protein that is expressed on T-cells and inhibits T-cells by connecting to major histocompatibility complex class II receptors (20). Additionally, LAG-3 downregulates the immune system by regulating the regulatory T-cell functions (21). LAG-3 expression has been shown to increase tumor growth in many cancer types. Therefore, the LAG-3 protein in TILs is seen as a potential target in cancer therapy in the future (19). Our study evaluated LAG-3 expression in meningiomas using IHC staining and compared tumor histopathological grade, size, degree of edema, localization, parenchymal invasion, and bone invasion. No statistically significant difference was found between these features compared with the LAG-3 level, except for the tumor size. LAG-3 level was statistically higher in big-sized meningiomas.

CD38 is a type 2 membrane protein that regulates microglial activation (22,23) and many functions such as calcium mechanism, autophagy, and tumorigenesis (24). It catalyzes the synthesis of cyclic adenosine diphosphate-ribose, which increases intracellular calcium and kills stimulated cells by activating microglial cells (24). The literature reports no study that investigated the relationship between meningiomas and CD38. However, a study that investigated the relationship between CD38 levels and gliomas was conducted by Blacher et al. (24) and reported that approximately 30% of the glioma cell mass is formed by microglia and macrophage infiltration. In addition to its beneficial effects on microglial invasion, it also has harmful effects (24). Evidence showed that tumor-associated microglia and macrophages facilitate tumor invasion and progression (25,26,27,28,29). Therefore, CD38 inhibition is thought to decelerate glioma progression. Blacher et al. (24) reported that rhein tri-potassium salt (K-rhein), which provides microglial inhibition due to CD38

inhibition, slows glioblastoma progression. According to this, CD38 inhibition may reduce high-grade meningiomas, but the evidence is insufficient. Our study evaluated the CD38 expression in meningiomas using IHC staining and compared tumor histopathological grade, size, degree of edema, localization, parenchymal invasion, and bone invasion. No statistically significant difference was found between these features compared with CD38 level, except for the tumor size. CD38 level was statistically higher in big-sized meningiomas.

Conclusion

In conclusion, this study is the first to investigate LAG-3, TIM-3, and CD38 levels in meningiomas. Our study revealed a significant correlation between LAG-3 level and meningioma sizes. No significant correlation was found with other data. However, the number of patients in our study was insufficient. Therefore, larger patient groups may yield more significant results.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Local Ethics Committee, dated 08.01.2018 and numbered 2018-01-07.

Informed Consent: All patients signed informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.T., Data Collection or Processing: O.H., Analysis or Interpretation: U.E., C.T., Literature Search: U.E., C.O., Ö.G., Writing: O.H.

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

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Demographic Characteristics of Patients who Applied to the Emergency Service Green Area

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What is known on this subject?

The waiting times of patients are prolonged due to the intensity of services in the emergency department.

What this study adds?

Determined the peak hours of patients in the emergency department. Therefore, the waiting times of patients can be shortened with additional personnel reinforcement at the specified hours.

ABSTRACT

Objective: Emergency medical care is required at any time of the day, thus emergency services are available 24 h a day, 7 days a week. Additionally, emergency medicine is defined as the specialty that detects and treats the disease and injury that requires sudden medical intervention. The emergency service applications used a triage system to ensure that urgent and serious cases reach immediate medical intervention. The triage system in Turkey used a red, yellow, and green color-coding system.

Material and Methods: This retrospective and descriptive study was conducted by examining the computer-based records of all patients who applied to University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Emergency Service Green Field Polyclinics between May 1, 2020, and September 30, 2020.

Results: A total of 17,693 patients applied to the Emergency Service Green Area of University of Health Sciences Turkey, Başakşehir Çam and Sakura Hospital between May 1, 2020, and September 30, 2020, when the study was conducted. Of whom, 9,314 (52.8%) were females and 8,379 (47.2%) were males. The mean age of all patients was 36.3±12.8 years. Of whom, the average age of females was 36.3±12.9 years, whereas 36.2±12.7 years in males. The most common age range was 18-29 years, and the number of patients who applied was 6,452 (36.4%). Our study revealed that the most intensive hours were between 13:00-16:00 and 20:00-24:00.

Conclusion: Emergency services personnel should be planned according to the annual number of patients admitted to the emergency department of the hospital. Additionally, at certain times of the day, especially during the rush hours of the emergency services, the number of healthcare professionals, such as specialist physicians, research assistants, general practitioners, nurses, emergency medical technicians, medical secretaries, etc. should be increased.

Keywords: Emergency service, triage system, demographic features

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Introduction

Emergency medical care is needed at any time of the day, thus emergency services are available 24 h a day, 7 days a week (1). Additionally, emergency medicine is defined as the specialty that detects and treats diseases and injuries that require sudden medical intervention.

The Social Security Institution in Turkey defined emergency health practices as follows: These are situations that require medical intervention within the first 24 h from the beginning of the event in cases of sudden emerging diseases, injuries, and similar situations and is accepted as a risk of losing life and/or health integrity in case of urgent medical intervention or transfer to another health institution. However, the study conducted by the emergency medical assistants on 3,000 patients revealed that 62.3% of the total patient admissions were non-emergency situations (2).

In emergency service applications, a triage system is used to ensure that urgent and serious cases reach immediate medical intervention. In the hospital, which has the resources to intervene every patient, patients with non-urgent and urgent conditions that need medical intervention may wait longer (3).

In Turkey, the Ministry of Health Inpatient Health Facilities in the Application Procedures and Principles of Emergency Services for triage in determining the color codes on the following, and seeks to provide more efficient and effective services in the emergency departments. During the application, triage should be performed, using red, yellow, and green colors, depending on the urgency of health problems that require examination and medical and surgical intervention. The triage process needs a physician, emergency medical technician, nurse, health officer, and health personnel with similar qualifications.

The following are the color-coding in the triage:

- The red color code refers to patients with life-threatening conditions and needs immediate evaluation and treatment.

- The yellow color code refers to patients who can wait for a certain time compared to very urgent patients.

- The green color code refers to patients who present with non-urgent health problems and can undergo outpatient examinations and treatments.

This study aimed to organize and plan the most frequent application time for the green area in the emergency and the demographic characteristics of patients who applied to the emergency service to make the work of the green area more effective and efficient.

Material and Methods

This retrospective and the descriptive study examined the computer-based records of all patients who applied to University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Emergency Service Green Field Polyclinics between May 1, 2020, and September 30, 2020.

Our study retrospectively scanned the applications made to the green area between the dates determined in the Turkcell Hospital Information Management System, which is the computer-based system of the hospital, and the age, gender, and application hours of patients were obtained. Informed consent was obtained from the participants.

Inclusion criteria were determined as all patients older than 18 years of age who applied to the green area between the specified dates. Exclusion criteria were defined as missing data in the system and being younger than 18 years of age.

Institutional review board approval was obtained from the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethical Committee (number: 2021.09.185, subject number: KAEK/2021.09.185).

Statistical Analysis

The Statistical Package for Social Sciences for Windows 20.0 program was used for statistical analysis in the evaluation of obtained findings. Descriptive statistical methods (percentage, average, and standard deviation) were used to evaluate the study data, and the Pearson chi-square test was used to compare qualitative data. The independent samples t-test was used for the comparison of quantitative data in the case of two groups to compare the parameters between groups. The One-Way analysis of variance test was used to compare the parameters with normal distribution between groups in quantitative data in the case of more than two groups. Results were bilaterally evaluated at a 95% confidence interval and p values of <0.05 are considered significant (4).

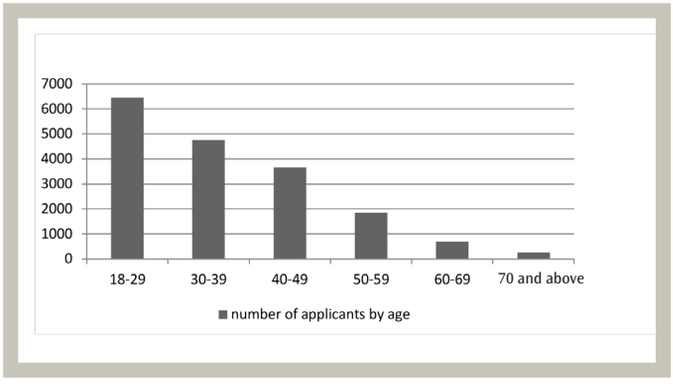
Results

The total number of patients who applied to the Emergency Service Green Area of University of Health Sciences Turkey, Başakşehir Çam and Sakura Hospital between May 1, 2020, and September 30, 2020, was 17,693, of whom 9,314 (52.8%) were females and 8,379 (47.2%) were males.

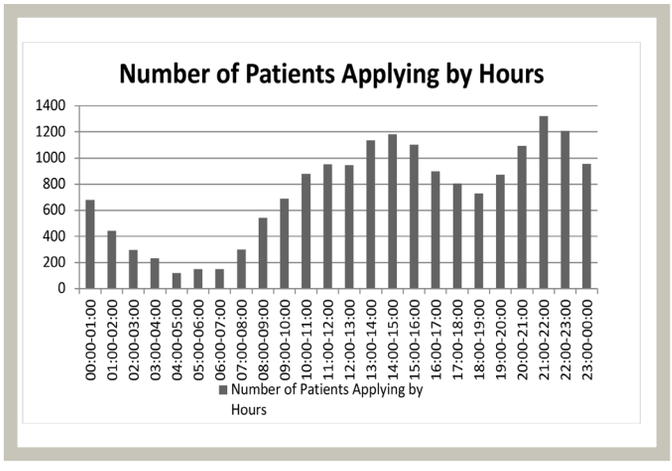
The average age of all patients who applied to the Emergency Service Green Area between the specified dates was 36.3 ± 12.8 years, of which the average age of females was 36.3 ± 12.9 years, whereas 36.2 ± 12.7 years in males.

The participants were grouped according to age as 18-29, 30-39, 40-49, 50-59, 60-69, and >70 years. The age range that most frequently applied to the Emergency Service Green Area was 18-29 years, which accounted for 6,452 (36.4%). The number of applications by age group is inversely proportional to the age; as age increases, the number of green area applicants gradually decreases. The least number of applicants to the green area was seen in the age group of 70 and over, accounting for 1.5% of all applicants (Graphic 1).

One of the most important factors that affect the number of patients who are admitted to the emergency department is the admission time. Many previous studies revealed a significantly decreased number of patients who present to the emergency department between 00:00 and 08:00. Our study revealed that the time with the least emergency service admission is between 05:00 and 07:00, with 301 (1.7%) patients. Additionally, the most frequent number of applicants peaks twice, which were between 13:00-16:00 and 20:00-24:00. The number of applications and percentages between these time zones were 3,422 (19.3%) and 4,579 (25.8%), respectively (Graphic 2).



Graphic 1. Number of patients who applied by age groups



Graphic 2. Number of patients who presented by hours

Discussion

The emergency medical service is the branch where the first intervention is performed in the prevention, diagnosis, treatment, and management of acute diseases or injuries in all age groups. Emergency services are an important unit within the hospital. The evaluation of all patients regardless of the branch, the uncertainty of applications and types, and more than one unit of evaluations (laboratory, imaging, etc.) are factors that affect the emergency service quality since some patients need to be immediately intervened.

In the T.C. Ministry of Health Statistics, the number of emergency department applicants is increasing annually. The number of patients who are admitted to the emergency department in 2010 was 74.2 million, 115 million in 2015, and 140 million in 2018 (5,6,7). University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Emergency Service had 17,693 people who applied to the green area in 5 months, with an increasing graphic monthly. The number of applications to the emergency room is gradually increasing in our country and worldwide. Therefore, the physical conditions of emergency services and the number of qualified personnel should be brought to a sufficient condition.

The rate of female patients who applied to University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Emergency Service Green Area was 52.8%, whereas 47.2% for males. Similarly, Edirne et al. (8) revealed 56.8% females and 43.2% males. Another study revealed similar rates of females and males who presented to the emergency service, wherein 56.5% were females and 43.5% were males (9).

The results of two studies revealed that patients who applied to the green areas were higher in females (9,10). A study conducted in the United States of America (USA) revealed no significant difference between genders in terms of urgency (11). Similar to the literature, the rate of females was higher in our study.

The majority of patients who applied to the Emergency Service Green Area were young population, wherein 6,452 (36.4%) patients were 18-29 years old. The age group that applies least to the green area is people who are 70 years old and over, with only 260 (1.5%) patients. In the USA, according to the National Hospital Ambulatory Medical Care Survey data, the most frequently admitted age group to the emergency department is between 25-44 and 45-64 years old (12).

Considering the application hours of patients, the number of patients decreased significantly between 00:00 and 08:00 hours. The number of patients who do not want to wait in the

conditions of the polyclinic and cannot get an appointment is increasing from 09:00 due to the application to the emergency department. A density mostly was observed between 13:00 and 16:00 although it remained stable on average during working hours. The number of patients who presented to the emergency department between 17:00 and 19:00 is significantly decreasing, probably due to the start of working hours and the traffic density in the city. The intensity of the emergency room significantly increases between 20:00 and 24:00 after the patients apply to the emergency service, which is the most accessible unit after completing their daily work. A study revealed a similar peak hour of emergency services to our study (13). A study conducted in the USA revealed that the most intensive time zone of emergency service applications was between 17:00 and 20:00, accounting for 64.7% of all emergency service applications (14).

Our study revealed that patients who applied to the emergency department were similar to the literature in all their characteristics.

Study Limitations

The most important limitation of our study is its retrospective design. Another limitation is the short period coverage due to the new establishment of the hospital.

Conclusion

With the development of emergency medicine worldwide and in our country, computer-aided national databases should be developed for patient information in all emergency services. With these databases, the necessary information can be easily analyzed and the quality of emergency medical service can be increased.

Emergency services personnel should be planned according to the annual number of patients who are admitted to the emergency department of the hospital. Additionally, at certain times of the day, especially during the rush hours of the emergency services, specialist physician, research assistant, general practitioner, nurse, emergency medical technician, medical secretary, etc. should be increased.

Since the emergency services are open 24 h a day, the working and resting hours of the physicians, nurses, and auxiliary health personnel in the emergency department should be sufficiently planned.

Finally, public awareness and education should be given to reduce the number of unnecessary and urgent emergency service applications. If all these results are taken into consideration and applied, the density in emergency services can be reduced. Additionally, providing services to situations that require real emergency intervention can be provided effectively and efficiently.

Ethics

Ethics Committee Approval: Institutional review board approval was obtained from the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethical Committee (number: 2021.09.185, subject number: KAEK/2021.09.185).

Informed Consent: Informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Bone Metastases of Endometrial Carcinoma: Report of Three Cases

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What is known on this subject?

Endometrial cancer is the sixth most common cancer in women worldwide and the 14th most common cancer overall. Endometrial cancer metastases to some parts of the body in a few ways. One of them is a hematogenous way. Bone metastasis occurs hematogenously and is a rare situation in literature. It has been reported 2-6%. Generally, bone metastasis occurs in the pelvic bone and spine.

What this study adds?

We presented three cases of bone metastasis in endometrial carcinoma. As we mentioned, bone metastases in endometrial carcinoma seldom occur. Due to this fact, these cases have significance for literature. These three cases' common point is bone metastases, while the process of each patient was different.

ABSTRACT

Presented herein are three patients with bone metastasis from endometrial cancer. Bone metastases were found in the pelvic bones of cases 1 and 3 and the spine of case 2. All cases had an endometrial biopsy. Cases 1 and 2 were diagnosed as low-grade endometrioid carcinoma and case 3 as high-grade endometrioid carcinoma. Cases 1 and 2 had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic-paraaortic lymph node dissection. Case 2 received 6 cycles of chemotherapy after the operation and had a postoperative recurrence in the left paraaortic area 11 months after the surgery. This case report emphasized the significance of evaluation of the bone metastasis in endometrial cancer.

Keywords: Endometrial cancer, bone metastasis, pelvic bone, spine

Introduction

Endometrial cancer is the sixth most common cancer in women worldwide (1) with hematogenous metastases to some body parts (2). Bone metastasis hematogenously occurs and is rarely reported in the literature (2), with an incidence report of 2-6% (3). Generally, bone metastasis occurs in the axial skeleton (4). Herein, presented three cases with endometrial cancer with bone metastases and overviewed in the literature.

Case Reports

Case 1

A 60-year-old postmenopausal and multigravida female patient had magnetic

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resonance imaging (MRI), which pointed out a large uterus and a mass lesion that covered the whole uterine cavity walls and cervix and continues through the cervix. The mass did not cross the uterine borders. Pathological lymph nodes were found in the right posterior side of the external iliac vessels and the left medial side of the internal iliac vessel. A 13 mm diameter metastatic bone lesion was found at the pubic symphysis level (Figure 1). At the immunohistochemical staining, tumor cells were 90% positive for estrogen and progesterone receptors. P53 was normal, which did not support the endometrial carcinoma with DNA mismatch-repair-mechanism defect. Ca125 increased at 67 U/mL. The patient had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omental sampling, intra-abdominal cytology, bilateral pelvic-paraaortic lymph node dissection, sentinel lymph node sampling, removal of the mass above the bladder, and repair of serosa above the bladder. Pathology showed a grade 2 metastatic endometrioid carcinoma. The myometrial invasion was 75%. The stromal involvement of the cervix was present. The lymphatic invasion was present, whereas the vascular was not. Peritoneal involvement above the bladder was observed. The peritoneal fluid was negative for malignancy. Additionally, 21 reactive lymph nodes were determined: 9 paraaortic lymph nodes, 1 left sentinel lymph node, 7 pelvic lymph nodes, 1 left pelvic lymph node, 1 left common lymph node, and 2 right common lymph nodes.

Case 2

A 63-year-old postmenopausal and multigravida female patient with MRI, showing a normal endometrium thickness according to age. Myomas were seen and the massive part of the tumor was located in the right adnexal and the right ovary, whereas the minor part was in the sinister and along the abdomen. Implants were seen in the upper abdomen and the larger one was in the Morrison pouch. No pathologic lymph nodes were observed. She had a debulking and bilateral pelvic-paraaortic lymph node dissection. The exploration revealed a 25 cm mass, which covered the whole abdomen and in the right ovary. Pathology showed that the tumor localization was the right and left ovary. Ovarian and endometrial cancers are not synchronous. Involvements include both ovarian surfaces, left uterine tube surface, and lymphovascular invasion. The omentum, the left uterine tube, and the left pelvic lymph nodes were involved. Peritoneal fluid was positive for malignancy. Additionally, 17 reactive lymph nodes and an implant in the left pelvis were observed. Endometrioid carcinoma grade 2 was diagnosed with chronic cervicitis, atrophic endometrium, and endometrial polyp. The patient received 6 cycles of chemotherapy for 4 months. After the chemotherapy, the last MRI revealed current pathological-sized lymphatic nodes in the left paraaortic area. Ca-125 was 13.2 U/mL. Bone metastasis occurred in the vertebrae after cancer recurrence (Figure 2). The last Ca-125 was 26.86 U/mL.

Case 3

A 60-year-old postmenopausal and multigravida woman applied to the hospital with a postmenopausal bleeding complaint. Endometrial biopsy indicated a malign tumor in the endometrium. Tumor cells were 90% positive for estrogen and progesterone receptor, and p53 was normal, which did not verify the endometrial carcinoma with DNA mismatch-repair-mechanism defect. The Papanicolaou test revealed cervicitis due to the presence of coccobacillus accordant with the flora change and malign atypical glandular cells. MRI showed a mass, which was full-layered and invaded the myometrium, reaching out the serosa and the cervix. The masses, which had equivalent characteristics with the uterine mass, were in the vagina, left ovary, and the right pubic bone (Figure 3). Ca125 was 120 U/mL. Positron emission tomography (PET) indicated a hypermetabolic increased uterine wall thickness. Slightly increased involvement was observed in the lymph nodes of the bilateral internal iliac area, which was diagnosed

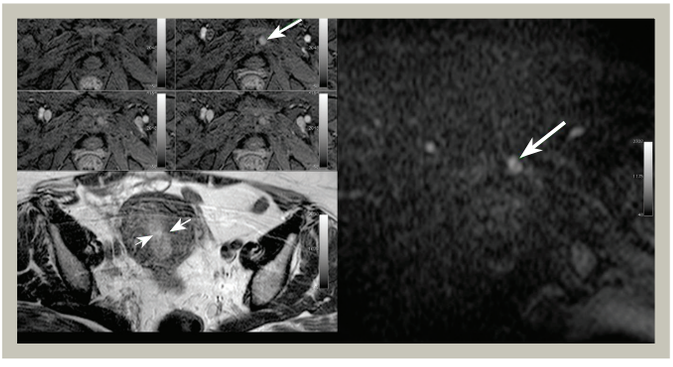

Figure 1. Long arrows indicate bone metastasis and short arrows indicate the endometrial carcinoma in the uterus

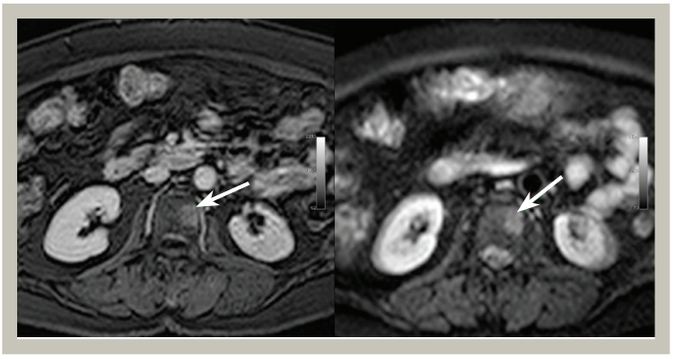

Figure 2. Vertebrae metastasis of a patient with recurrent endometrial cancer

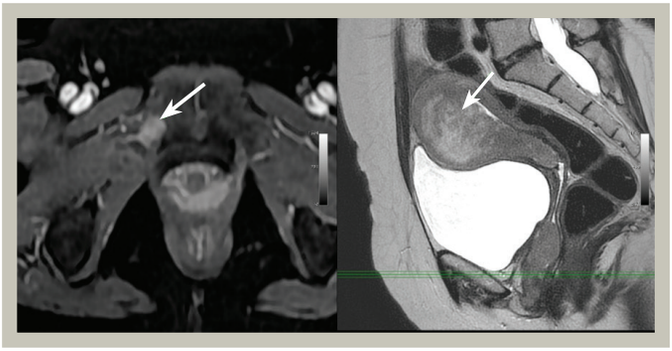

Figure 3. The left side of the picture shows bone metastasis in the right pubic bone. The right side of the picture shows endometrioid carcinoma in the uterus

as endometrioid carcinoma, grade 3. She also had a thyroid gland examination. Millimetric cystic areas and nodules with calcification were seen in the inferior pole of the right lobe. Except for the nodule, the parenchyma was homogeneous. No nodule was observed in the left lobe.

Discussion

This case report expressed bone metastasis in endometrial cancer. According to literature, bone metastasis is uncommon in endometrial cancer. Additionally, the spine and pelvic bones are mostly affected.

Despite the interaction between the increased Ca125 and lymph node involvement (5), case 2 had normal Ca125 values as reported. Bone metastasis, which is an extraperitoneal process, does not contribute to the Ca125 value because Ca125 rises as an intraperitoneal process consequence (5). Our data demonstrated that the Ca125 of cases with low-grade was lower than the case that has high-grade carcinoma.

The case with lymphovascular invasions can support that tumor cells enter the venous return directly and the systemic circulation indirectly (6). Cancer disseminates to the vertebrae and the pelvic bones by Batson's plexus and vertebral venous plexus (6,7,8). Here, case 2 had lymphovascular invasion and bone metastasis in the vertebrae. This bone metastasis can be considered to occur by Batson's plexus and vertebral venous plexus.

Single bone metastasis is infrequent in endometrial carcinoma, thus second primary malignancy should be underlined (9). Hence, other different tests should be performed in addition to the routine process, e.g., mammography, thyroid gland ultrasound scan, etc. (9). Herein, case 3, who has thyroid nodules, had a thyroid gland examination. Consequently, bone metastasis was found to primarily originate from endometrial carcinoma.

Moreover, MRI and PET were used to detect bone metastases. Bone metastases could be detected by different scanning methods, such as computed tomography and bone scan (10). The bone scanning might be performed, but MRI and PET were more advantageous to detect other metastatic structures.

Females with bone metastases in endometrial cancer had higher age at diagnosis (11). Particularly, 95% of cases are diagnosed after the age of 40 and in the postmenopausal process. The mean age of patients at diagnosis was 61 years, and they were all in the postmenopausal process.

Based on this report and other cases in the literature, bone metastasis should be considered in endometrial cancer diagnosis, especially symptoms of bone pain, to change the treatment methods and prognosis.

Ethics

Informed Consent: Patients have been informed before and after the research.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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