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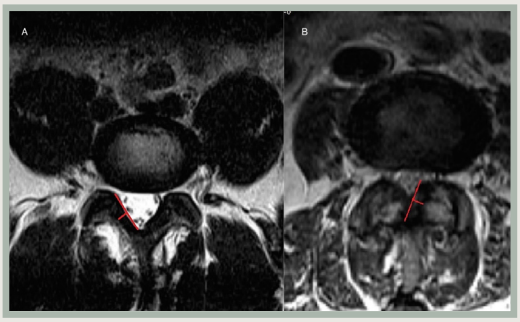

Figure 2. Left (A): axial T2-weighted MRI in a patient with isthmic spondylolisthesis showing that ligamentum flavum thickness is not increased and there is no facet degeneration in the adjacent segment. Right (B): axial T2-weighted MRI in a patient with degenerative spondylolisthesis showing that ligamentum flavum thickness is increased and there is facet degeneration in the adjacent segment

MRI: Magnetic resonance imaging

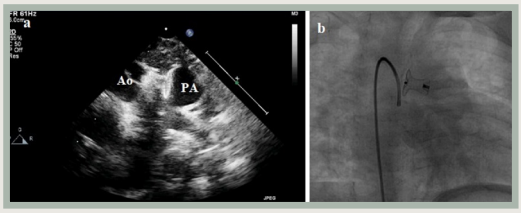

Figure 2. The transthoracic echocardiography (a) and catheter angiography (b) showed a good deployment of the device

Ao: Aorta, PA: Pulmonary artery

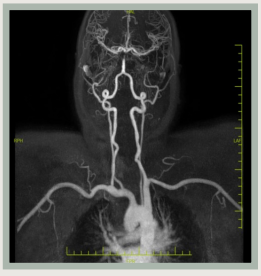

Figure 2. MRA

MRA: Magnetic resonance angiography

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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

E-ISSN: 2791-8823

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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.

Cam ve Sakura Medical Journal is currently indexed in J-Gate.

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Peer Review, Publication Ethics and Malpractice Statement

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of the editors, authors, or reviewers within the scope of COPE and ICMJE guidelines.

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Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

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.

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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

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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 („,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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Editorial

Dear Colleagues,

It is my great pleasure to be with you on the second issue of CSMJ this year. In this issue, you can read the article about COVID-19 infection in special patient groups that may allow you to evaluate high risk patients from different perspectives. The first original article in this issue includes evaluation and management of a rare congenital heart defect, aortapulmonary window. You can read the results of an experinced center in pediatric heart surgery. The second original article evaluates the role of combined use of D-dimer and neutrophil to lymphocit ratio in COVID-19 as coagulation and inflammation markers, hallmarks of pathophysiological changes in this devistating pandemic disease. The third article is about secondary bacterial infections in intubated COVID-19 patients in an adult intensive care unit. The last original article of this issue evaluated the level of degeneration in lumbar isthmic and degenerative spondylolisthesis by magnetic resonance imaging.

You can find an interesting lung cancer case report whose sialorrhea was treated with botulinum toxin injection into the salivary glands, as an promising therapy, for medical treatment resistant cases. In the second case report, you can read the endovascular treatment of Moya Moya disease.

I think that all these articles and case reports from different disciplines and centers may provide useful insights for your routine daily practice. We will continue to discuss different important topics in future issues of CSMJ with your support.

Best regards,

On Behalf of Deputy Editors, Associate Editors and Editorial Secretary

Merih Çetinkaya

Editor in Chief

Cam & Sakura Medical Journal

DOI: 10.4274/csmedj.galenos.2022.2022-11-3
Cam and Sakura Med J 2023;3(2):39-45

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COVID-19 in Special Patient Groups

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ABSTRACT

At the end of 2019, a new coronavirus was identified as the cause of many pneumonia cases in Wuhan, a city in China's Hubei Province. These cases spread rapidly, causing an epidemic throughout China, followed by increasing cases in other countries. In February 2020, the World Health Organization defined the definition of Coronavirus disease-2019 (COVID-19), which means 2019 coronavirus disease. The virus that causes COVID-19 is called severe acute respiratory syndrome-coronavirus-2. The rapidly expanding COVID-19 pandemic has affected all areas of daily life, including medical care. Although this epidemic significantly affected individuals from all parts of society, the clinical course, diagnosis, and treatment approaches may differ in some specific populations. The association of COVID-19 with various medical comorbidities and its impact on specific and vulnerable populations need to be addressed separately. This information will also assist in the management of COVID-19. The effects and the relationship of COVID-19 on comorbidities (chronic renal, diabetes mellitus, chronic liver, etc.) and special populations (pregnant, elderly, transplant patients, etc.) are comprehensively presented in the text.

Keywords: Chronic disease, comorbidity, COVID-19, special populations

Introduction

Pregnancy

The Coronavirus disease-2019 (COVID-19) pandemic (1) has many unknowns in terms of consequences for pregnant women. Complications and adverse events in pregnant women in infections caused by other coronaviruses, such as severe acute respiratory syndrome (SARS) and middle east respiratory syndrome, have led to careful evaluation of pregnant women against serious SARS-coronavirus-2 (CoV-2) infection.

Many physiological changes occur in the immune system, respiratory system, cardiovascular system, and coagulation pathway during pregnancy. These changes can have positive or negative effects on the course of COVID-19. While the impact of SARS-CoV-2 on pregnancy is not yet clear, collaborative, global studies are needed to determine the effects on implantation, fetal growth and development, delivery, and neonatal health. In addition to the direct effects of the disease, the restrictions caused by the pandemic negatively affect pregnant and maternal health by blocking access to reproductive health services and causing increased pressure on mental health and socio-economic deprivation.

Prevention, clinical manifestations, and diagnosis of COVID-19 are the same for pregnant and non-pregnant people, but there are some special considerations during pregnancy.

Pregnancy does not increase susceptibility to SARS-CoV-2 infection; however, it appears to worsen the clinical course of COVID-19 compared with women of reproductive age

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who are not pregnant. The risk of severe COVID-19 during pregnancy may be higher than that in the general population.

Vertical transmission is possible. Although congenital infection rates have been reported to be about 2 percent of maternal infections, well-documented cases of possible intrauterine transmission are rare. Severe neonatal disease is rare. Antenatal corticosteroid use for the threat of preterm labor is safe for the mother, and corticosteroid use may be beneficial for severe maternal disease.

Clinicians should be cautious about thromboprophylaxis and possible thromboembolic events in mothers with COVID-19. Asymptomatic COVID-19 may be common during pregnancy. The risk of developing preeclampsia is high even if the infection is asymptomatic (2).

Clinicians should be alert to the wider effects of the pandemic and ensure screening for mental health problems (3).

Anyone planning a pregnancy or who is pregnant or newly pregnant should be offered the COVID-19 vaccine as soon as possible rather than delaying vaccination after birth or breastfeeding (Class 1B). According to all available data, current SARS-CoV-2 vaccinations are safe for use before, during, and after pregnancy. The vaccine reduces the risk of developing COVID-19 and the likelihood of severe transmission if the disease develops (4).

Compared with uninfected pregnancies, pregnant women infected with COVID-19 do not have an increased risk of miscarriage or congenital anomalies.

Although the risk of preterm birth, cesarean delivery, and stillbirth appears to be increased, this risk appears to be limited to patients with severe or critical illnesses and third-trimester infections (5).

Geriatry

The susceptibility to infections increases in elderly individuals due to physiological and immunological disorders such as deterioration of mucosal barriers with aging, cellular and humoral immunity changes, and decreased antibody response to vaccines. Additionally, multiple chronic diseases in geriatric patients increase this susceptibility and cause infections to be more severe than those in young people.

Elderly individuals also have a high risk of mortality and morbidity in terms of COVID-19. Additionally, COVID-19 may present different symptoms and clinical findings in the elderly compared to young people. Although COVID-19 usually presents with symptoms such as fever, cough, weakness, anorexia, shortness of breath, myalgia, sore throat, loss of taste, and smell in young people, it has been reported that dyspnea is more common in the elderly (6,7). With aging, the fever response to infections decreases, and the cough reflex weakens (8). As in other infections, fever response may not be obtained in the elderly, symptoms may be milder, or non-specific findings may be seen in COVID-19. Symptoms and signs such as confusion, mental changes, decreased mobility, loss of appetite, and urinary/stool incontinence may be detected (9). Atypical presentation of COVID-19 in the elderly may cause a delay in diagnosis, detection at a later stage, and even death. Asymptomatic infection is also common in the elderly. The development of delirium in hospitalized elderly patients diagnosed with COVID-19 has been associated with increased mortality (10).

The treatment approach for COVID-19 in the elderly is the same as in younger patients. In addition to drug therapy, supportive treatments such as nutrition, exercise, and respiratory rehabilitation should be applied when necessary.

Human Immunodeficiency Virus Infection

The clinical features of COVID-19 appear the same in people with human immunodeficiency virus (HIV) as in the general population.

Among patients with well-controlled HIV infection under treatment, the majority remain asymptomatic (11). However, people with HIV are at risk for serious COVID-19 and complications. In several large observational studies, HIV infection has been associated with more severe COVID-19, higher hospitalization rates, higher rates of new infections after vaccination, and in some cases higher death rates from COVID-19 (12).

Among people with HIV, those who are older, have multiple comorbidities, have lower CD4-cell counts, and identify as Black or Hispanic are at the highest risk for adverse outcomes (13). Generally, the management of COVID-19 in patients with HIV is the same as in patients without HIV.

Rheumatological Diseases

The presence of a rheumatic disease alone may be associated with an increased risk of facing further complications from COVID-19, although the evidence is mixed (14).

Additionally, patients with various rheumatic diseases have a higher prevalence of various comorbidities such as advanced age, chronic lung and kidney disease, heart disease, hypertension, obesity and diabetes, which are risk factors for serious disease in COVID-19.

The clinical features of COVID-19 in patients with systemic rheumatic diseases are variable and do not differ from patients without these underlying diseases.

However, various rheumatic diseases may have clinical features that can mimic COVID-19, such as weakness, muscle pain, and fatigue. For patients with a current diagnosis of rheumatic disease, the clinician may need to differentiate the signs and symptoms of a disease flare from those of possible COVID-19 infection; therefore, the suspicion of possible COVID-19 infection should always be kept in mind.

Adjustments to medication regimens in patients with documented or probable COVID-19 should be individualized, with particular attention to the severity of the infection. Approaches are largely expert judgment, and temporary discontinuation of biological agents (e.g., anti-TNF inhibitors, IL-6 receptor inhibitors) is recommended. For most patients with COVID-19, hydroxychloroquine/chloroquine, sulfasalazine, methotrexate, leflunomide, immunosuppressants (e.g., mycophenolate, AZA), JAK inhibitors. However, where patients have active or organ-threatening rheumatic disease, their immunosuppressive therapy may need to be continued based on an individualized assessment (15).

The decision to continue these agents should be made with rheumatology, infectious diseases, and intensive care specialists involved in managing the patient's acute illness. Another exception to discontinuation of a particular agent may be where an antirheumatic therapeutic is also used for treating COVID-19. Additionally, patients receiving glucocorticoids should maintain the prescribed dose to prevent acute rheumatic disease exacerbation and complications of adrenal insufficiency associated with abrupt discontinuation of this drug (16).

There is limited evidence that COVID-19 infection has poor outcomes and subsequently adversely affects rheumatic disease in patients with rheumatic disease. The use of the vaccine is recommended for patients with rheumatic diseases.

Oncological Diseases

While the data is mixed, most studies suggest a higher risk of serious COVID-19 in adult patients with active cancer (17,18).

Improvements during prognosis are seen with advances in treating COVID-19 and early diagnosis (19).

The risk likely varies with the type and stage of cancer and the treatment received. In particular, hematological malignancies or lung cancer, advanced and/or progressive cancer, active chemotherapy treatment, advanced age, and comorbid conditions are risk factors for severe COVID-19 (20). Previous cancer is also a risk factor, but the risk is lower than that with active cancer (20).

Overall, COVID-19 disease management is similar to that in the general population. However, cancer is considered a risk factor for progression to severe COVID-19 infection, leading to faster and earlier initiation of available treatments.

For most cancer patients with COVID-19, chemotherapy, or immunotherapy should be discontinued, whether patients are symptomatic of COVID-19 or not. Generally, cancer treatment is continued when contagion-based measures can be discontinued. Institutional protocols usually determine the duration of such measures.

Diabetes Mellitus

People with diabetes are at high risk for COVID-19, and complications such as severe illness, need for hospitalization, need for intubation, and death may occur more frequently. Intensive care unit stays, long hospital stays, and death has been reported more frequently in patients with type 2 diabetes due to COVID-19 (21,22,23). Data on serious morbidity and mortality rates in patients with type 1 diabetes are less, but just as with other infections, patients with type 1 diabetes have an increased risk of COVID-19 compared with the healthy population.

The relationship between COVID-19 and diabetes is bilateral. COVID-19 can damage the pancreatic endocrine and exocrine systems with a cytokine storm. The observation of higher amylase levels in patients with severe COVID-19 infection than in mild cases supports this (24). It also stimulates hyperglycemia cytokine storm. COVID-19 cases with diabetes had higher levels of IL-6, C-reactive protein, and D-dimer than those without (25).

The role of hyperglycemia in severe disease in diabetic individuals is not fully understood. It is unclear whether hyperglycemia is a cause or consequence, as COVID-19 triggers an intense inflammatory response. As a matter of fact, there are studies reporting patients who develop newly diagnosed diabetes after COVID-19 (26). Newly diagnosed hyperglycemia may be due to critical illness or directly associated with beta cell damage from the virus or with the inflammatory response to the virus (27).

Whatever the cause, hyperglycemia indicates a poor prognosis. It has been determined that glycemic control and fluctuations in the first days of hospitalization determine the length of stay, need for intensive care, and mortality (28). Last previous HbA1c is associated with outcomes in both type 1 and type 2 diabetes and mortality, especially when HbA1c is >10% in COVID-19 disease (29).

Diabetic ketoacidosis, hyperosmolar coma, and severe insulin resistance can be seen in COVID-19 in people with known diabetes. The approach in managing patients should aim to prevent hypoglycemia, significant hyperglycemia, and ketoacidosis. Although using corticosteroids in addition to oxygen therapy reduces mortality, it can increase hyperglycemia, the need for insulin therapy, diabetic ketoacidosis, and hyperosmolar coma by increasing existing insulin resistance. The continuation of current insulin treatments, frequent blood glucose, and ketone monitoring are recommended in diabetic COVID-19 cases (30).

Chronic Lung Disease

Chronic lung diseases such as chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, interstitial lung disease, lung cancer, and sarcoidosis are associated with poor outcomes of COVID-19.

COPD: A meta-analysis stated that a previous history of COPD increases the risk of severe COVID-19 4-fold, and active smoking increases the risk of severe COVID-19 (31). COPD has been associated with a higher need for intensive care, invasive ventilation, and a higher risk of death in patients with COVID-19 (32,33). Patients with COPD presenting with new or increased respiratory symptoms, fever, or other COVID-19 symptoms should be tested for COVID-19, even if they are mild (34). It is recommended that patients with COPD continue to take all maintenance medications, such as bronchodilators and inhaled glucocorticoids, throughout the COVID-19 pandemic. There is insufficient evidence that inhaled glucocorticoids have an adverse effect on the course of COVID-19. Because of the risk of aerosolizing SARS-CoV-2 and increasing the spread of disease in patients receiving nebulized therapy, the risk of transmission should be minimized by avoiding using nebulizers in the presence of other people (34).

Asthma: In studies on the risk of COVID-19 in asthma patients, no increased risk of severe COVID-19 has been demonstrated in patients with well-controlled mild-to-moderate asthma. These patients are also not at risk for death associated with COVID-19. However, hospitalized people with severe asthma who have recently required oral corticosteroids are at an increased risk of death from COVID-19 (35). Patients with asthma are advised to continue taking the drugs they used during the pandemic, particularly inhaled corticosteroids.

Bronchiectasis: Patients with bronchiectasis may be more susceptible to COVID-19 than those without. COVID-19 patients with bronchiectasis have seen worse clinical outcomes, such as more severe clinical manifestations and death (36).

Interstitial lung disease: People with interstitial lung disease are at an increased risk of death from COVID-19, particularly if they are fibrotic. There is also an increased risk in older men and those with obesity or low lung function. For this reason, a diet is recommended for those who are overweight and have interstitial lung disease (34).

Sarcoidosis: Studies on patients with sarcoidosis have reported that the rate of COVID-19 is higher than that in the general population. It has been determined that sarcoidosis patients, especially those with lung and neurological involvement, are at a high risk for COVID-19 (37). The use of rituximab, especially in sarcoidosis patients, has been associated with an increased risk of COVID-19.

Chronic Renal Disease

In patients with chronic kidney disease, the susceptibility to infections is generally increased due to the deterioration of the immune system. Chronic kidney disease is also an independent risk factor for COVID-19-related mortality (38). High mortality in these patients may also be associated with advanced age and a high number of comorbidities. COVID-19 mortality has also increased in patients undergoing hemodialysis. The necessity of going to the dialysis center 3 times a week for hemodialysis patients, close contact with other patients and healthcare professionals increases the likelihood of having COVID-19 (39).

Comorbidities such as immunosuppressive drugs, advanced age, diabetes mellitus (DM), hypertension, and cardiovascular disease increase the risk of developing COVID-19 complications in kidney transplant patients (40).

It has been reported that acute kidney injury may develop in almost half of the hospitalized kidney transplant patients with COVID-19 (41). Simultaneously, the risk of mortality in kidney transplant COVID-19 patients has increased compared with the general population. It may be necessary to adjust the immunosuppressive agents used in kidney transplantation patients with COVID-19.

Chronic Liver Disease

It is unclear whether those with chronic liver disease are more susceptible to COVID-19. However, patients with chronic liver disease or those receiving immunosuppressive therapy may be at higher risk of serious illness for COVID-19.

Chronic hepatitis B (HBV) and hepatitis C (HCV): It is not known whether patients with chronic HBV and HCV are at a high risk of serious COVID-19. However, patients with chronic HBV or HCV-related cirrhosis have a poor prognosis (42).

There is no evidence that antiviral drugs used in chronic HBV or HCV have a negative effect on COVID-19. Therefore, patients with COVID-19, while using antiviral medication should not discontinue their antiviral therapy. HBV reactivation has been observed with glucocorticoids and tocilizumab are used for treating COVID-19. Therefore, when these treatments are to be administered, patients should be evaluated for HBV prophylaxis.

Non-alcoholic fatty liver disease: These patients have many risk factors, such as obesity and DM and therefore have increased mortality in COVID-19 and other respiratory diseases (43). These patients should be encouraged to change their lifestyle.

Alcoholic liver disease: Those with alcoholic liver disease are immunocompromised and more prone to infections. Additionally, most of these patients are accompanied by comorbidities such as obesity and metabolic syndrome. The restrictions and isolation applied during the pandemic period may also increase alcohol intake in these patients. For all these reasons, patients in this group are among the groups most affected by the COVID-19 pandemic and have a high risk of serious illness (43,44).

Autoimmune hepatitis: There is no need for discontinuation or dose adjustment of maintenance immunosuppressive therapy during the pandemic period in patients with autoimmune hepatitis. Medication adjustments may be necessary for patients with autoimmune hepatitis who experience COVID-19. There is no need to discontinue or adjust the dose of the immunosuppressive agent used in asymptomatic or mild COVID-19. In moderate or severe COVID-19, patients' previous history of relapse and risk of exacerbation should be evaluated. The dose of immunosuppressive drugs (e.g., azathioprine) can be reduced by 25-50%. Symptoms and daily liver enzymes should be monitored in hospitalized patients. If hospitalization is not required, liver enzymes need to be checked every 1-2 weeks, and if symptoms and enzymes are stable, follow-up needs to be done every 2-4 weeks. In cases of COVID-19-related neutropenia or lymphopenia, the dose of azathioprine or mycophenolate mofetil should be reduced and blood counts should be checked every 1-2 weeks (45).

Solid Organ Transplant

Solid organ transplant recipients may be at increased risk for coronavirus disease as they are immunocompromised and less likely to respond an adequate immune response to the vaccine. COVID-19 poses challenges for individuals who are solid organ transplant candidates or recipients and for the transplant process.

Donor-derived SARS-CoV-2 infection has been reported through lung transplantation, but not through non-lung transplantation (46).

Considering the risk of progression to severe disease and the potential to transmit SARS-CoV-2 to healthcare workers, all solid organ donors, and transplant candidates should be screened for COVID-19 with history, lung imaging, and microbiological testing.

After solid organ transplant, transplant recipients may be at risk of contracting infection, progressing to symptomatic infection, and/or developing more severe COVID-19.

The clinical manifestations of COVID-19 in solid organ transplant recipients are variable and generally similar to those observed in non-immunosuppressed patients. However, fever is less common.

The approach to diagnosis is similar to that in the general population. Clinicians are more sensitive to assessing and testing transplant recipients as transplant recipients may be missing signs and symptoms of COVID-19 and disease progression can be rapid (47).

The treatment approach (e.g., use of antivirals, supportive care) is similar to that for the general population. Attention should be paid to potential drug-drug interactions and their effects on the immunosuppressive regimen.

Adjustments for treating the immunosuppressive regimen must be individualized depending on the severity of the disease, the specific regimen used, the type of organ transplant, the post-transplant time, and the risk of acute allograft rejection. Some transplant recipients recover by reducing their dose of immunosuppressive therapy. Conversely, continued immunosuppression in some patients may increase the risk of uncontrolled infections.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.İ.S., Z.Y., H.K.K., Concept: A.İ.S., Z.Y., H.K.K., Data Collection or Processing: A.İ.S., Z.Y., H.K.K., Analysis or Interpretation: A.İ.S., Z.Y., H.K.K., Literature Search: A.İ.S., Z.Y., H.K.K., Writing: A.İ.S., Z.Y., H.K.K.

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

Financial Disclosure: The authors declared that this study received no financial support.

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Aortopulmonary Window: Classification, Associated Cardiac Anomalies, Treatment Options, and Clinical Outcome

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What is known on this subject?

Aortopulmonary window (APW) is a rare congenital heart defect. Symptoms depend on the size of the defect and associated anomalies. Treatment primarily involves surgical repair, with transcatheter closure reserved for select cases.

What this study adds?

The study highlights the importance of careful and systematic investigation for the detection of APW.

ABSTRACT

Objective: Aortopulmonary window (APW) is an uncommon congenital cardiac abnormality marked by a septation defect between the ascending aorta and pulmonary artery. This study aimed to define the clinical characteristics, diagnostic features, treatment strategies, and follow-up outcomes of pediatric patients diagnosed with APW.

Material and Methods: We retrospectively reviewed children diagnosed with APW from 2010 to 2023. Morphological APW typing of our patients was based on the classification that is settled by the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database Committee. The patients' demographic data, symptoms at admission, transthoracic echocardiography, cardiac computed tomography, management modalities, and follow-up data were evaluated.

Results: Twenty-five children were diagnosed with APW over the study period. Thirteen patients were male (52%), and the median age at presentation of the patients was three months (8 days-7.5 years). Two patients were diagnosed with coronary fistula by echocardiography at the first admission and were diagnosed with APW after catheterization. APW was detected in one patient while being operated on for large ventricular septal defect. According to the STS classification, 32% (n=8) of the patients were type III, 32% (n=8) were type I, 16% (n=4) were intermediate type, 12% (n=3) were type II, and 4% (n=1) were APW with aortic interruption. Associated cardiovascular malformations were in 76% (n=19) of the patients. Fifteen patients (60%) underwent surgery. Transcatheter closure of APW was performed in four patients (16%).

Conclusion: Detection of the APW requires careful and systematic investigation. Transcatheter closure can be performed in selected cases where the defect is suitable. Although rare, this defect, which can cause severe left-right shunting, should be kept in mind as a cause of pulmonary hypertension and unexplained cardiac dilation and should be investigated in patients whose cause cannot be determined.

Keywords: Aortopulmonary window, echocardiography, pulmonary hypertension, surgical treatment, transcatheter treatment

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Introduction

Aortopulmonary window (APW) is an infrequent congenital cardiac defect characterized by incomplete partitioning of the aortic and pulmonary artery walls, leading to communication between these two structures. The presence of two separate semilunar valves helps distinguish APW from truncus arteriosus (1). This cardiac anomaly is a rare occurrence, accounting for approximately 0.2-0.6% of all congenital heart defects (2). Previous studies have reported a higher incidence of this cardiac anomaly among males (1,2,3). However, findings have been observed, with some reports indicating a female predominance (4,5), while others suggest a comparable occurrence rate between males and females (6). APW is frequently accompanied by other congenital heart defects. These associated anomalies may include ventricular septal defect (VSD), tetralogy of Fallot, transposition of the great arteries, double-outlet right ventricle, aortic interruption, aortic atresia, and in rare instances, coronary abnormalities (4,6,7).

In APW, intercommunication between the aorta and pulmonary artery causes a left-to-right (systemic-to-pulmonary) shunt, with the degree of shunting dictating the clinical course of the disease.

Shunting from the aorta to the pulmonary artery considerably increases during the neonatal period when pulmonary vascular resistance decreases. This causes congestive heart failure, which manifests as tachypnea, tachycardia, irritability, exhaustion, sweating, poor feeding or failure to thrive. If left untreated, pulmonary vascular obstructive disease may ensue at an early age, which is irreversible. Hence, early closure of large APWs is imperative to avert heart failure or pulmonary vascular disease. While surgery remains the standard treatment of choice (6,8), transcatheter APW closure can be a suitable alternative for patients with adequate rims (9,10).

The main aim of this study was to delineate the clinical attributes, diagnostic features, therapeutic approaches, and follow-up of pediatric patients diagnosed with APW.

Material and Methods

This retrospective analysis examined 25 patients who received an APW diagnosis at our clinic between 2010 and 2023, ranging from 8 days to 7.5 years. Before conducting the investigation, all ethical standards were met in accordance with the Declaration of Helsinki, with approval obtained from the University of Health Sciences Turkey, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee (March 2022/2022.03.19). Patient data, including demographic information, admission symptoms, transthoracic echocardiography, cardiac computed tomography (CT), management approaches, and follow-up information, were retrospectively evaluated.

Our patient cohort's morphological APW typing was determined based on the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database Committee classification (11) modified version of Mori et al.'s (3) classification. This classification system includes five subtypes:

1. APW with interrupted aortic arch,

2. Type I (proximal) APW, located above the sinus of Valsalva with a small inferior rim,

3. Type II (distal) APW, located at the highest part of the ascending aorta with a well-formed inferior rim and a small superior rim,

4. Type III (complete defect of the aortopulmonary septum) APW involves most of the ascending aorta with minimal superior and inferior rims,

5. Intermediate-type APW exhibits adequate superior and inferior rims and is more amenable to transcatheter closure.

According to the occurrence of concomitant cardiovascular anomalies, the study population was divided into two groups: the isolated APW group (n=6) and the complex APW group (n=19). Management strategies for the patients included surgical or transcatheter closure of the defect or medical treatment for pulmonary hypertension (PH) in patients with negative vasoreactivity. The regular outpatient follow-up was conducted at 3-6 months intervals. Follow-up was defined as the period from presentation to the last admission or death. Of the total patient cohort, three patients were lost to follow-up, one died after the operation, and the remaining 21 completed the follow-up period.

Statistical Analysis

The statistical analyzes were carried out using the SPSS 25 program (SPSS Inc., Chicago, IL, USA). For categorical data, frequencies and percentages are shown. The median value and interquartile range for variables with non-normal distributions were used, whereas the mean and standard deviation were used for variables with normal distributions.

Results

Demographic and Clinical Characteristics

From 2010 to 2023, 25 patients were diagnosed with APW in our clinic. The median age at presentation was three

months (8 days-7.5 years) and the median weight was 4.25 kg (2.1-21 kg). Of the patients, 13 were male (52%) and 12 were female (48%), resulting in a male-to-female ratio of 1.08 to 1. Congestive heart failure was the most common presenting symptom observed in 12 patients (50%), while 11 patients (44%) had heart murmurs. Two patients with significant PH and a negative vasoreactivity test were asymptomatic at admission. Diagnostic evaluations included echocardiography, cardiac catheterization (54.2%), and cardiac CT (48%) (Figure 1). Table 1 provides further details of the patients with APW.

We could visualize the AP window by 2D echocardiography in 22 (88%) patients. Two patients were initially diagnosed with a coronary fistula but were later diagnosed with APW after catheterization. In one patient, APW was detected during surgery for large VSD. In 21 patients with APW, there was significant left-to-right shunting that led to left atrial and ventricular dilatation. In most cases (83.3%), except for four, severe PH was observed, with pulmonary pressure almost equivalent to systemic pressures. Pulsed-wave and color flow Doppler demonstrated negative diastolic flow in the descending aorta due to diastolic left-to-right shunting through the APW.

One patient (4%) had APW with aortic interruption, while type III APW was noted in 32% (n=8) of the patients, type I in 32% (n=8), intermediate type in 16% (n=4), and type II in 12% (n=3), as per the STS classification. In addition, a patient had a 15 mm wide APW between the descending aorta and the main pulmonary artery at the level of the left subclavian artery.

In the cohort under investigation, a substantial proportion (76%, n=19) of the patients presented with associated cardiovascular malformations. Within the subset of patients with complex APW, the most frequent co-occurring cardiovascular malformations included topsy-turvy heart in 4 cases (16%), atrial septal defect in 4 cases (16%), and VSD in 4 cases (16%). An interrupted aortic arch type A and patent ductus arteriosus was in one patient (4%) with complex APW. Notably, one male patient (4%) with complex APW type I presented with abnormal coronary anatomy, specifically an anomalous origin of right coronary artery originating from the pulmonary artery (ARCAPA). Three patients (12%) displayed a right aortic arch; of these, two had an aberrant left subclavian artery (ALSA). Finally, a 7.5-year-old male patient within the complex APW cohort had tetralogy of Fallot as an associated cardiac defect.

Patients who were diagnosed with a topsy-turvy heart had a recognizable rotational abnormality affecting their heart and major arteries. Atrioventricular and ventriculoarterial connections on the left-sided heart showed concordance, and atrial configurations showed the typical superior-inferior

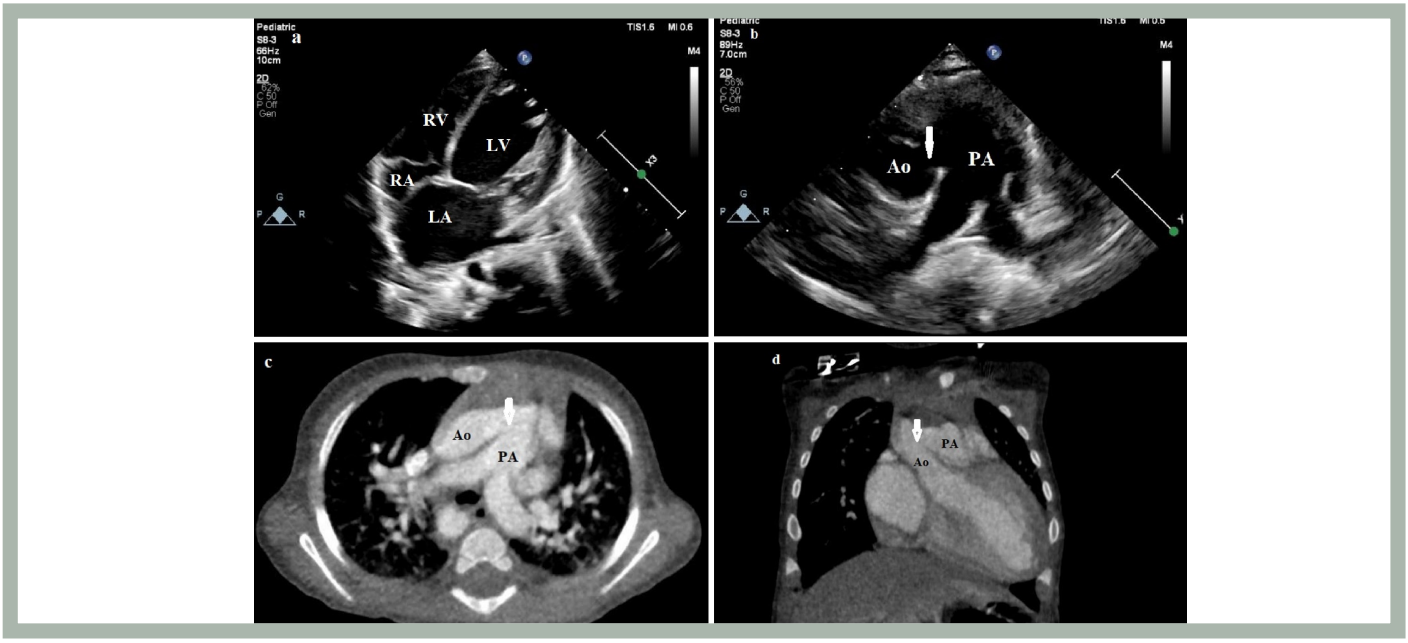

Figure 1. Echocardiography and computed tomography images of the patients with aortopulmonary window.
(a) Transthoracic echocardiography from apical four-chamber view shows enlarged left atrium (LA), and left ventricle (LV). (b) Transthoracic echocardiography from a parasternal short-axis view shows a wide defect between the ascending aorta (Ao) and the main pulmonary artery (PA) (white arrow). Computerized tomography shows a large aortopulmonary window (white arrow) in axial (c) and coronal (d) views.

RA: Right atrium, RV: Right ventricle

Table 1. Details of patients with aortopulmonary window

Patient	Age (month)	Weight (kg)	Symptom	Gender	Aortopulmonary window type	Concomitant cardiovascular anomalies	Management
1	3.5	4.5	Heart failure symptoms	M	III	Topsy-turvy heart	Surgery
2	4	3.8	Murmur	M	Intermediate type	Bicuspid aorta, right aortic arch, aberrant left subclavian artery	Transcatheter occlusion (ADO-I)
3	12	11	Murmur	F	I	Bicuspid aorta, aortic stenosis	Negative vasoreactivity
4	4	5	Heart failure symptoms	M	I	Left pulmonary artery stenosis	Surgery
5	3.5	21	None	F	Between the descending aorta and main pulmonary artery	Topsy-turvy heart	Negative vasoreactivity
6	15	6.5	Murmur	F	I	-	The decision of surgery was made. The patient lost to follow-up
7	6	5.3	Murmur	F	Intermediate type	Ventricular septal defect	Transcatheter occlusion (ADO-I)
8	72	18	Murmur	M	I	ARCAPA	Surgery
9	4	6.7	Heart failure symptoms	M	I	Ventricular septal defect	The decision of surgery was made. The patient lost to follow-up
10	5	5.5	Murmur	F	I	Right-sided aortic arch, aberrant left subclavian artery	Surgery
11	10 days	2.1	Murmur	F	Intermediate type	Atrial septal defect	Transcatheter occlusion (ADO-II)
12	8 days	2.3	Murmur	M	III	Atrial septal defect, a right-sided aortic arch, left persistent superior vena cava	Surgery
13	5	4	Heart failure symptoms	M	I	-	Surgery
14	2.5	3.7	Heart failure symptoms	M	II	-	Surgery
15	19 days	3	Heart failure symptoms	M	III	Topsy-turvy heart	Surgery
16	2.5	2.7	Murmur	M	I	Ventricular septal defect	Surgery
17	2	2.8	Heart failure symptoms	F	III	Atrial septal defect	Surgery
18	2	2.7	Heart failure symptoms	F	III	-	Surgery
19	20 days	3	Heart failure symptoms	F	III	Topsy-turvy heart	Surgery
20	8	8.3	Murmur	F	Intermediate type	-	Transcatheter occlusion (ADO-I)
21	90	20	None	M	II	Tetralogy of Fallot, absent left pulmonary artery	Negative vasoreactivity

Table 1. Continued

Patient	Age (month)	Weight (kg)	Symptom	Gender	Aortopulmonary window type	Concomitant cardiovascular anomalies	Management
22	20 days	3.5	Heart failure symptoms	M	III	Partial anomalous pulmonary venous return	The decision of surgery was made. The patient lost to follow-up
23	1	5	Heart failure symptoms	M	III	Ventricular septal defect	Surgery
24	1	3.4	Heart failure symptoms	F	APW with aortic interruption type A	Aortic interruption	Surgery
25	14 days	3	Murmur	F	I	-	Surgery

ADO: Amplatzer duct occluder, APW: Aortopulmonary window, ARCAPA: Anomalous origin of right coronary artery originating from the pulmonary artery, F: Female, M: Male

relationship of cardiac chambers. In addition, a significant connection was observed between the aorta and pulmonary artery (APW), which was associated with systemic pulmonary artery hypertension. Consistent with previous literature, all topsy-turvy heart cases were born to consanguineous parents, with two cases presenting as siblings. Among the patients analyzed, 23 out of 25 cases (92%) displayed no extracardial anomalies, while 8% of patients (two cases) demonstrated associated non-cardiac abnormalities, including Cornelia de Lange syndrome and tracheoesophageal fistula.

Management and Follow-up

Fifteen patients (60%) underwent surgery (patch repair of APW) at a median of 2.2 months (22 day-6 years) when they had a median weight of 3.6 kg (range, 2.7-18 kg). Among them, one male patient with abnormal coronary anatomy underwent reimplantation of ARCAPA during APW repair, and one patient with an interrupted aortic arch underwent patch augmentation of the aortic arch. A patient with esophageal compression resulting from an ALSA was successfully treated with ALSA transaction. Following surgical intervention, a patient diagnosed with a topsy-turvy heart manifested acute respiratory distress and left lung hyperinflation, leading to a rapid clinical deterioration. On the tenth postoperative day, venoarterial extracorporeal membrane oxygenation (ECMO) was initiated due to persistent respiratory failure. The patient of multiorgan failure and died on the 16th postoperative day, despite receiving six-day ECMO treatment (12). Transcatheter closure of APW was performed in four patients (16%) with aortopulmonary septal defects with adequate septal rims located at a safe distance from the aortic and pulmonary valves, coronary arteries, and pulmonary artery bifurcation at a median of 7.5 months (range: 4 months to 1.4 years) (Figure 2). No patient died during the intervention. Following a mean follow-up period of 33.6±28.3 months (4 months to 79 months), all patients remained asymptomatic without requiring medication. In three patients with large defects, cardiac catheterization indicated high pulmonary vascular resistance, and the pulmonary vasoreactivity test with nitric oxide and 100% oxygen inhalation was non-reactive. Consequently, medical PH treatment was initiated. However, three patients required surgical intervention but were not followed up.

Discussion

This study provides an analysis of the clinical and diagnostic features, treatment approaches, and consequences of 25 pediatric patients with APW from a tertiary cardiac center. The APW is characterized by a deficient septum between the pulmonary artery and ascending aorta. Previous research has linked this anomaly with a diverse range of other cardiac malformations, including interrupted aortic arch, VSDs, topsy-turvy heart, tetralogy of Fallot, transposition of the great arteries, and coronary anomalies (4,7,13,14). More than half of our patients demonstrated associated cardiovascular abnormalities in our study. Among patients with complex APW, topsy-turvy heart, atrial septal defect, and VSD were the most frequently observed associated conditions (50%). In the case reports we reviewed, rare cardiovascular abnormalities were identified in association with APW, including a right aortic arch with an aberrant origin of the left subclavian artery (15), an isolated origin of the left subclavian artery from the left pulmonary artery (16), total abnormal pulmonary venous return (17), a right pulmonary artery originating from the ascending aorta (8), and crisscross pulmonary arteries (18). We have not encountered such rare abnormalities in our patients. Aortic stenosis, bicuspid aortic valve, bilateral superior vena cava, partially aberrant pulmonary venous return, and ARCAPA are a few unique coexisting cardiovascular problems that we did notice.

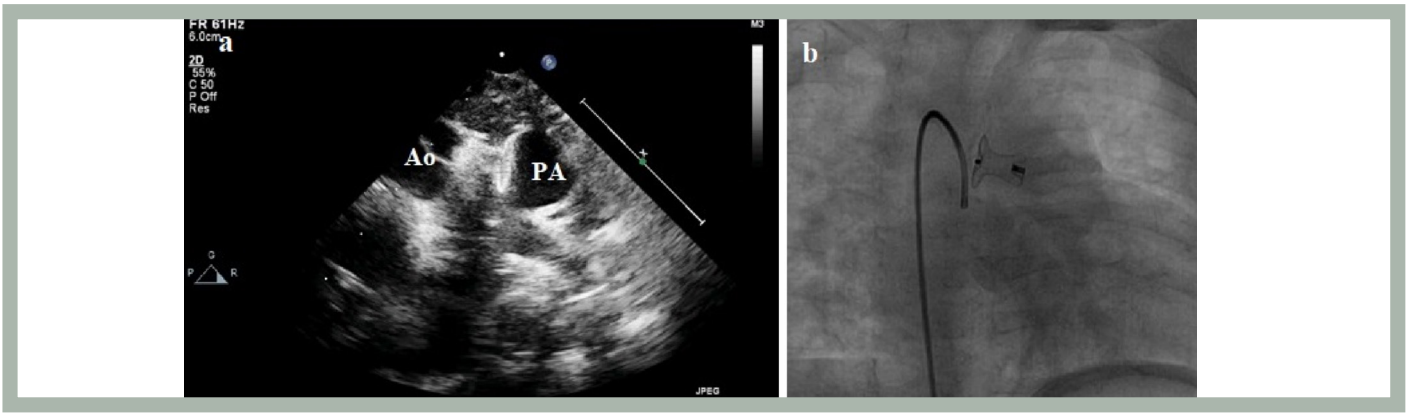

Figure 2. The transthoracic echocardiography (a) and catheter angiography (b) showed a good deployment of the device

Ao: Aorta, PA: Pulmonary artery

The clinical diagnosis of APW can be challenging in some cases and may require repeat echocardiography, diagnostic cardiac catheterization, or intraoperative assessment. Our study found that some patients were initially misdiagnosed but were later accurately diagnosed through further evaluation. One plausible explanation for the initial misdiagnosis of APW in a patient diagnosed during VSD surgery could be equalizing aortic and pulmonary pressure due to PH. Similarly, in two patients with a coronary fistula diagnosed during echocardiography, the small defect was mistaken for a fistula, and APW was only diagnosed during cardiac catheterization. In Kiran et al.'s (2) study, four patients were initially misdiagnosed with APW, and the factors contributing to this were analyzed. When there is unexplained heart failure, left heart dilatation due to a significant left-to-right shunt, and PH, an APW should be suspected. However, when the patient's clinical status and echocardiographic findings appear compatible, complex variants may be challenging to diagnose and easily overlooked. In addition to transthoracic echocardiography, this pathology can be demonstrated with the help of catheter or CT angiography and magnetic resonance imaging. Failure to diagnose APW patients can lead to irreversible obstructive changes in the pulmonary vascular bed, making the patient inoperable (19). In our cases, the late presentation of three patients with large defects (1 year, 3.5 years, and 7.5 years) highlights the importance of early detection and prompt intervention to avoid irreversible pulmonary obstructive changes, as all three had significant PH and negative vasoreactivity tests.

Important clinical factors in managing patients with APW include the size of the defect, the degree of left-to-right shunting into the pulmonary trunk, the presence of concurrent cardiovascular malformations, and the emergence of PH. Early closure is imperative given the potential for rapid onset of congestive heart failure owing to high pulmonary blood flow. The conventional approach to treating APW is surgical intervention, and several studies (4,5,6,8,13,20) have examined surgical outcomes in this context. However, transcatheter closure may serve as a viable alternative in cases with no associated cardiovascular lesions and adequate rims. In fact, several studies (9,10,21) have documented successful experiences with transcatheter occlusion of APW. It is of utmost importance to carefully assess the location and size of the defect as well as the amount of superior and inferior rims present to minimize the risk of device-related complications such as embolization, coronary artery blockage, and damage to great vessels and valves. Additionally, the type of defect plays a critical role in determining the feasibility of transcatheter closure, with intermediate-type defects being more amenable to this approach.

Study Limitations

We acknowledge that our study has several limitations. Retrospective reviews of patients with APW were performed at a single center, which limits the generalizability of our findings. Additionally, our study was limited by the middle follow-up period.

Conclusion

In patients with AP windows, the current preferred method of diagnosis is echocardiography. Accurate diagnosis necessitates a meticulous and systematic evaluation. Small defects associated cardiac anomalies, or PH may present a diagnostic challenge, and the misdiagnosis is possible. Transcatheter closure can be considered in appropriate cases with sufficient septal rims. Although rare, this defect can

cause severe left-right shunt, leading to PH and unexplained cardiac dilation. Therefore, it should be considered a possible cause and investigated in patients whose underlying causes cannot be determined.

Ethics

Ethics Committee Approval: All ethical standards were met in accordance with the Declaration of Helsinki, with approval obtained from the University of Health Sciences Turkey, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee (March 2022/2022.03.19).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.Y., S.H., Concept: F.S.Ş., Design: F.S.Ş., Data Collection or Processing: F.S.Ş., P.A., Analysis or Interpretation: E.Ö., İ.C.T., A.G., Literature Search: P.A., P.Ay., Writing: F.S.Ş.

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ORIGINAL ARTICLE

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Combined Use of D-dimer and NLR as a Prognostic Index in COVID-19

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What is known on this subject?

The reported mortality rate of coronavirus disease-2019 (COVID-19) patients has a wide range with the estimated rate of the World Health Organization being 3.4% in the world. Due to the heterogeneous clinical course, it is difficult to predict prognosis early on hospital admission, which can rapidly progress leading to high mortality.

What this study adds?

In this cross-sectional study, we aimed to investigate the combined use of D-dimer and neutrophil-to-lymphocyte ratio as coagulation and inflammation parameters, respectively, rather than a single parameter to predict mortality in COVID-19 patients.

ABSTRACT

Objective: We aimed to investigate the combined use of D-dimer and neutrophil-to-lymphocyte ratio (NLR) as a prognostic index-coronavirus disease (PRI-COVID) in COVID-19 patients to predict mortality.

Material and Methods: We included 152 COVID-19 patients in our cross-sectional study. The cut-off value of D-dimer to predict mortality was 1.07 µg/mL with a sensitivity of 68% and specificity of 80% [area under curve (AUC) ± SE: 0.752±0.05; positive predictive value (PPV) 39.5%, and negative predictive value (NPV) 92.7%; p<0.001]. Meanwhile, at a cut-off value of 3.83, the sensitivity and specificity of NLR in predicting mortality were 92% and 48.8%, respectively (AUC ± SE: 0.730±0.05; PPV: 26.1%; NPV: 96.9%; p<0.001). We categorized patients as low, moderate, and high risk using the PRI-COVID model (low risk: <1.07 D-dimer and <3.83 NLR; moderate risk: >1.07 D-dimer or >3.83 NLR; high risk: >1.07 D-dimer and NLR >3.83). High-risk PRI-COVID was associated with 6.37 times increased risk of death compared with the low/moderate risk group.

Results: Combined use of coagulation and inflammation parameters might can be associated with mortality.

Conclusion: Our results suggest that PRI-COVID is easy to assess and useful in predicting both 30-day and overall survival in patients with COVID-19.

Keywords: SARS-CoV-2 infection, D-dimer, fatal outcome, inflammation

Introduction

The reported mortality rate of coronavirus disease-2019 (COVID-19) patients has a wide range with the estimated rate of the World Health Organization (WHO) being 3.4% in the world (1). Due to the heterogeneous clinical course, it is difficult to predict the prognosis early on hospital admission, which can rapidly progress leading to high mortality. There is urgently needed for indexes consisting of clinical and laboratory parameters to predict the fatal progression of disease. As such, risk stratification would be critically lifesaving in

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terms of providing timely and successful management of this deadly disease. Although several parameters have been proposed as prognostic factors, limited data are available to evaluate the association between coagulation parameters and inflammation markers on mortality in COVID-19. Recently, increased D-dimer levels have been recognized in severe ill patients besides several biochemical and clinical features (2). Further, retrospective data and pooled analysis have shown that D-dimer has the potential to predict mortality (3,4). Despite available data indicating the prognostic role of D-dimer, a combined model rather than a single parameter would be more helpful.

Neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), a systemic inflammatory response (SIR) indicator, has been demonstrated to be a useful predictor of COVID-19. Elevated NLR results in a clinically increased level of NEUs and decreased level of LYMs, and has been proposed as a new biomarker for systemic inflammation. Recent studies showed that higher levels were associated with the severity of disease and could be an independent predictor of mortality in hospitalized patients (5,6). More effort needs to be given in analyzing the panel, including the prediction probability of NLR and D-dimer, which will provide a more personalized approach for the COVID-19 patients.

In this cross-sectional study, we aimed to investigate the combined use of D-dimer and NLR as coagulation and inflammation parameters, respectively, rather than a single parameter to predict mortality in COVID-19 patients.

Material and Methods

Study Design and Patients

In this single-center cross-sectional and observational study, 152 moderate to severe consecutively hospitalized patients (mean age 58.2±13.7 years; 64 female, 88 male) in University of Health Sciences Turkey, Yedikule Chest Disease and Thoracic Surgery Training and Research Hospital (tertiary care hospital in Turkey) with confirmed infection of severe acute respiratory syndrome coronavirus-2 by real-time reverse transcriptase-polymerase chainreaction of nasal and pharyngeal swab samples between 15 April 2020 and 1 December 2020 included. Patients' severity was defined according to WHO clinical management guidance of COVID-19 (7). The criterion for severe COVID-19 were percutaneous oxygen saturation (SpO_2) of lower than 90%, respiratory rates ≥30/min, the need for use of high-flow nasal cannula, or non-invasive mechanical ventilation using the biolevel positive airway pressure mode due to hypoxemia. Patients not reaching the criteria for severe COVID-19 and having pulmonary involvement associated with COVID-19 were considered non-severe. Patients who required mechanical ventilation and/or transfer to the intensive care unit for high-flow oxygen support were classified as critical. Classification according to computed tomography was conducted, evaluating the abnormalities as percent (%). Patients divided into groups mild (<%10), moderate (10-70%), severe (70%) (8).

Methods

This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval no: 2284). An informed consent form was signed by each subject included in the study.

NLR and D-dimer have been analyzed as markers of inflammation and coagulation, respectively. The combined model containing NLR and D-dimer has been named the predictive index for COVID-19 (PRI-COVID), and its role in predicting mortality has been investigated. Epidemiological and at the time of hospital admission and clinical data obtained from medical records, patient charts, and databases have been prospectively recorded. D-dimer levels were detected by Siemens BCSXP. All biochemical analyzes of the patients were performed in the biochemistry laboratory using the Beckman Coulter AU2700 device and Sysmex XT4000i devices. The D-dimer levels and hemogram blood samples were measured on admission to the hospital with the latex agglutination method.

Disease outcomes were interpreted as disease survivors and non-survivors obtained from computer-based national records. Receiver operator curve (ROC) and Cox regression analysis have been used to analyze critical values (optimal cut-off values associated with Youden index) and prognostic roles of combined use of D-dimer and NLR independent of other confounders.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) 13.0 for Windows 20 (IBM SPSS Inc., Chicago, IL). Categorical variables are presented as n (%), and normally distributed values are presented as mean ± standard deviation (SD). Multivariate Cox regression models were applied to determine independent risk factors predicting mortality. ROC analysis was applied to define the minimal optimal D-dimer and NLR level that predicted death, and cut-off value was evaluated according to the Youden index method. A statistical relative measure of Cox regression models was evaluated using the Akaike information criterion

and ROC curve analysis. Kaplan-Meier survival curves and log-rank tests were used to compare the time to death between those with elevated D-dimer and NLR levels and those without. The results are presented as hazard ratios (HRs) with 95% confidence interval. A p value <0.05 was considered significant.

Results

One hundred fifty-two hospitalized COVID-19 patients (mean age 58.2±13.7 years; 64 female, 88 male) were included in this study. There were more male patients in the cohort with similar mortality results to the females (p=0.40). Twenty (13%) patients were intubated. The mean length of stay was 9 (2-60) days. Sixteen deaths have occurred (10.5%) in 30-day period. Twenty-five patients (16.5%) have died in overall, while 127 (83.5%) patients survived. Median follow-up was 77 day (min 2-max 307 day). A hundred and four (68%) patients classified as severe and 48 (32%) patients considered as non-severe had mortality rates of 22% and 14%, respectively (p=0.25). Demographical features and clinical factors of survivors and non-survivors are shown in Table 1. The mean ± SD age of non-survived cases was 67.9±12.8 years, which is older than that of survived patients (<0.001). The most common pre-existing comorbidities were hypertension (HT) (41%), diabetes mellitus (30%), ischemic heart disease (21%), chronic obstructive pulmonary disease (COPD) (17%), and asthma (16.5%) in our cohort. Prevalence of comorbidities including COPD (HR: 2.74; p=0.019), HT (HR: 2.41; p=0.031), malignancy (HR: 4.83; p<0.001) was higher in non-survivors. A higher comorbidity index (HR: 1.54; p<0.001) was detected in non-survivors (Table 1).

Decreased resting arterial SpO_2 (HR: 0.92; p<0.001), abnormal radiologic pathology higher than 50% (HR: 3.47;

Table 1. Demographical features of patients with COVID-19

Variables	All population	Survival		Univariable regression			
		Survivors	Non-survivors	HR	95% CI		p
	n=152	n=127	n=25		Lower	Upper	
Age, years	58.2±13.7	56.3±13	67.9±12.8	1.07	1.03	1.10	<0.001*
Gender, n(%)							
Female	64 (42.1)	55 (43.3)	9 (36.0)	ref	-	-	-
Male	88 (57.9)	72 (56.7)	16 (64.0)	1.41	0.62	3.20	0.408
Weight, kg	81.4±17.1	83.3±17.2	71.8±13.2	0.96	0.94	0.99	0.003*
Height, cm	169±8.6	169.6±8.4	165.8±9.1	0.96	0.91	1.00	0.066
BMI, kg/m^2	28.4±5.2	28.8±5.3	26.2±4	0.91	0.83	0.99	0.022*
Obesity, n (%)	60 (39.5)	54 (42.5)	6 (24.0)	0.45	0.18	1.12	0.084
Smoke, n (%)							
Non-smoker	78 (51.7)	68 (54.0)	10 (40.0)	ref	-	-	-
Current smoker	15 (9.9)	12 (9.5)	3 (12.0)	1.60	0.44	5.82	0.475
Exsmoker	58 (38.4)	46 (36.5)	12 (48.0)	1.78	0.77	4.12	0.178
Smoke, pack/year	30 (0-150)	30 (0-150)	40 (0-125)	1.01	1.00	1.02	0.070
Comorbidity index	1 (0-7)	1 (0-6)	2 (0-7)	1.54	1.27	1.85	<0.001*
Asthma	25 (16.4)	21 (16.5)	4 (16.0)	0.95	0.32	2.76	0.920
COPD	26 (17.1)	18 (14.2)	8 (32.0)	2.74	1.18	6.34	0.019*
DM	46 (30.3)	36 (28.3)	10 (40.0)	1.57	0.70	3.49	0.270
HT	62 (40.8)	47 (37.0)	15 (60.0)	2.41	1.08	5.36	0.031*
IHD	32 (21.1)	26 (20.5)	6 (24.0)	1.12	0.45	2.82	0.803
CHF	14 (9.2)	10 (7.9)	4 (16.0)	1.83	0.63	5.34	0.266
CRF	4 (2.6)	3 (2.4)	1 (4.0)	1.37	0.19	10.13	0.758
Malignancy	15 (9.9)	8 (6.3)	7 (28.0)	4.83	2.00	11.63	<0.001*

*Numerical variables were shown as mean ± standard deviation or median (minimum-maximum). Categorical variables were expressed as numbers and percentages.*p<0.05 indicates statistical significance. HR: Hazard ratio, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension, IHD: Ischemic heart disease, CHF: Congestive heart failure, CRF: Chronic renal failure, BMI: Body mass index*

p=0.016), the need for intubation (HR: 24.39; p<0.001), and severe cases according to risk score (HR: 3.09; p=0.017) were detected as clinical risk factors associated with increased risk of mortality (Table 2). Furthermore, increased D-dimer (HR: 1.38; p<0.001) or NLR levels (HR: 1.09; p<0.001) and decreased LYM count (HR: 0.13; p<0.001) have been shown as laboratory abnormalities associated with increased risk of death in univariate analyzes (Table 3). The mean D-dimer and NLR levels across all patients with COVID-19 were 0.7 (0.2-6.2) and 4.5 (0.7-39.5), respectively.

Mortality-associated risk factors included the cox-regression model (Table 4). In the multivariate analysis, decreased SpO_2 (HR: 0.90; p<0.001), increased creatinine (HR: 3.11; p=0.005), and increased D-dimer (HR: 1.34; p=0.037) have been detected as independent predictors of mortality in model I (Table 4). When the laboratory parameters were included in model II (Table 4), decreased SpO_2 (HR: 0.92; p<0.001), increased D-dimer (HR:1.35; p=0.029) and NLR (HR: 1.07; p=0.005) have continued to be independent predictors of mortality. In model III (Table 4), D-dimer and NLR combination was tested to predict mortality with the pre-tested cut-off value in the ROC analysis. The optimum cut-off value of D-dimer to predict mortality was 1.07 µg/mL with a sensitivity of 68% and a specificity of 80% [area under curve (AUC) ± SE: 0.752±0.05]. ROC curve analysis for using NLR to predict mortality indicated an optimal cut-off >3.83 with a sensitivity of 92% and specificity of 48.8% [AUC ± SE: 0.730±0.05; positive predictive value (PPV): %26.1; negative predictive value: 96.9%; p<0.001]. We investigated the predictive accuracy of the combined model including

D-dimer and NLR. We were able to categorize patients as low, moderate, and high risk using the PRI-COVID model (low risk: <1.07 D-dimer and <3.83 NLR; moderate risk: >1.07 D-dimer or >3.83 NLR; high risk: >1.07 D-dimer and NLR >3.83). Model III was the best model to predict mortality independently (Figure 1). Patients with high-risk PRI-COVID had 6.37 times (HR: 6.37; p<0.001) increased risk of 30-day mortality and 5.82 times (HR: 5.82; p<0.001) increased risk of overall mortality when compared to low/moderate PRI-COVID patients (Figure 2).

Table 2. Clinical features with the comparisons between survivors and non-survivors

Variables	All population	Survival		Univariable regression			p
		Survivors	Non-survivors		95% CI		
	n=152	n=127	n=25	HR	Lower	Upper	
BMR, x10^3	1.4 (0.5-2.8)	1.5 (0.5-2.8)	1.3 (0.5-1.9)	1.00	1.00	1.00	0.088
ER, x10^3	1.8 (0.6-3.4)	1.8 (0.6-3.4)	1640 (0.6-2.3)	1.00	1.00	1.00	0.463
BT							
Mild	55 (36.2)	50 (39.4)	5 (20.0)	ref	-	-	-
Moderate	32 (21.1)	28 (22.0)	4 (16.0)	1.58	0.42	5.88	0.498
Severe	65 (42.8)	49 (38.6)	16 (64.0)	3.47	1.27	9.51	0.016*
Saturation	89.3±7.2	90.3±6	84.3±10.1	0.92	0.88	0.95	<0.001*
Clinical weight 1							
Non-severe	48 (31.6)	42 (33.1)	6 (24.0)	ref	-	-	-
Severe	42 (27.6)	41 (32.3)	1 (4.0)	0.19	0.02	1.61	0.129
Critical	62 (40.8)	44 (34.6)	18 (72.0)	3.09	1.22	7.82	0.017*
Clinical weight 2							
Non-severe	48 (31.6)	42 (33.1)	6 (24.0)	ref	-	-	-
Severe	104 (68.4)	85 (66.9)	19 (76.0)	1.71	0.68	4.30	0.250
ICU intubated	20 (13.2)	4 (3.1)	16 (64.0)	24.39	10.59	56.17	<0.001*
Length of stay in hospital	9 (2-60)	9 (2-45)	10 (2-60)	1.02	0.99	1.06	0.196

*Numerical variables were shown as mean ± standard deviation or median (min-max). Categorical variables were expressed as numbers and percentages. *p<0.05 indicates statistical significance. HR: Hazard ratio, CI: Confidence interval, CIT: Complaint initiation time, BMR: Basal met rate, ER: Energy requirement, ICU: Intensive care unit*

Discussion

The mortality rate in our cohort was 16.5% and was consistent with the results of previous studies (9,10). However, depending on the heterogeneous nature of the disease, the characteristics of the patients included, and the sample size, it appears that mortality rates can be in a wide range.

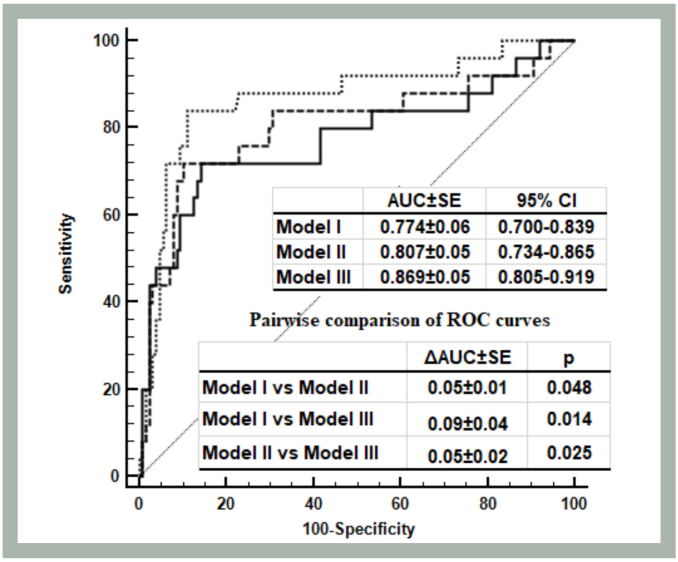

Figure 1. Receiver operator characteristic curve for D-dimer and NLR to predict deaths (comparisons of models)

NLR: Neutrophil-to-lymphocyte ratio, AUC: Area under curve, CI: Confidence interval

Excessive inflammation and platelet activation play a significant role in the development of prothrombotic states, which might play a role in the increased mortality of COVID-19. There is urgently needed for clinical and laboratory predictors of the progression of the disease toward severe and fatal forms. In earlier reports, several potential predictors have been revealed but none of the distinctive panels, rather than a single parameter, have emerged to be used sufficiently to predict prognosis. In this study, we showed that the combined model of D-dimer and NLR, called "PRI-COVID", can be used as a risk assessment index to more precisely predict prognosis with favorable sensitivity and specificity, rather than a single parameter in COVID-19.

In the retrospective study of Wang et al. (11), 119 middle-aged patients were included and having a comorbidity was exclusion criteria. Univariate and multivariate regression models were performed, and pri-covid was found to be a statistically significant predictor of mortality in COVID-19. Furthermore, the need for a larger study sample was emphasized in that study.

D-dimer has not been previously identified as a specific marker for viral pneumonia (12). However, increased D-dimer levels reported in COVID-19 patients in a wide range of 3.75 to 68% may simply reflect both thrombotic and fibrinolytic activities (13,14). Although different cut-off values were used in retrospective cohorts, non-survivors had significantly higher D-dimer levels (14,15,16), similar to the results of our study. D-dimer has been suggested as a potential marker for predicting in-hospital mortality, with an increased risk of

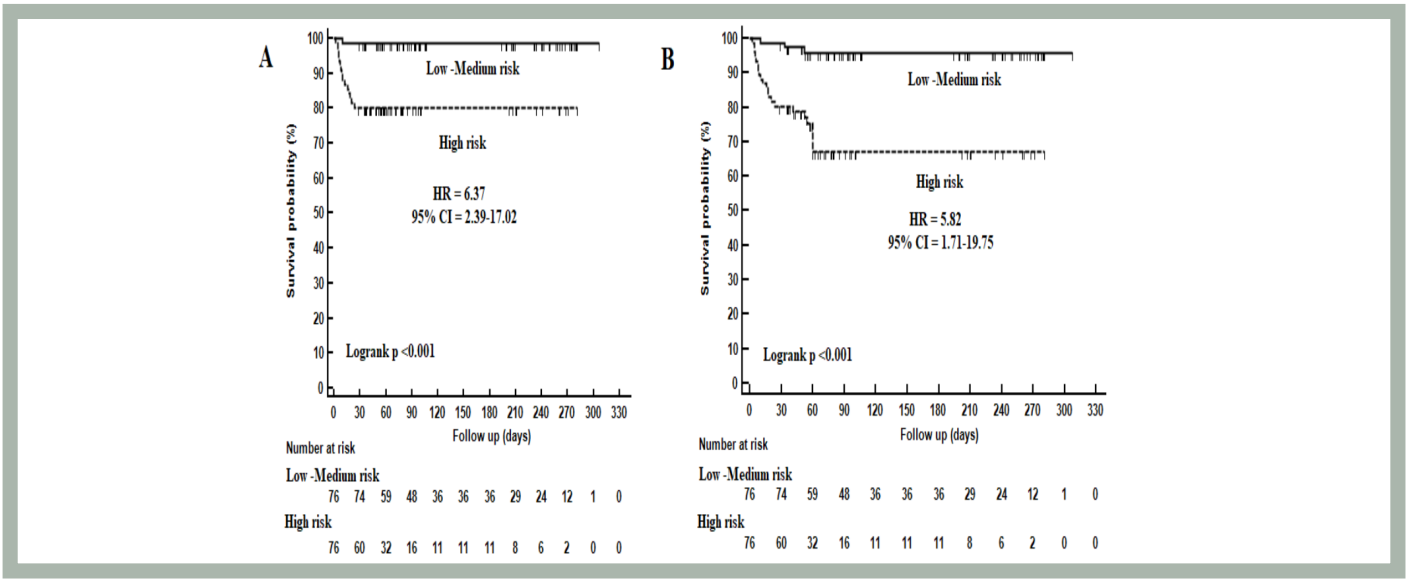

Figure 2. Kaplan-Meier survival curves for PRI-COVID (combined index with D-dimer and NLR) on admission. Comparisons of 30-day (A) and overall (B) mortality risk according to the PRI-COVID risk index

NLR: Neutrophil-to-lymphocyte ratio, HR: Hazard ratio, CI: Confidence interval, PRI-COVID: Predictive index for coronavirus disease

death even with D-dimer higher than 0.5 mg/L (adjusted HR: 1.75) in a large-scale study (17). Another retrospective study investigated optimal cut-off values for baseline D-dimer levels in 343 COVID-19 patients, which could also predict in-hospital mortality. D-dimer can predict in-hospital mortality with a cut-off value of 2.0 µg/mL, favorable sensitivity and specificity results (4) (92.3% and 83.3%, respectively), D-dimer might have an impact in predicting in-hospital mortality in patients with COVID-19 based on most retrospective analyses despite high heterogeneity and several limitations in the studies (3,4,18,19). There is no conclusive evidence that D-dimer plays an exact role in-hospital as well as in overall mortality, independent of other confounding factors, and that its use with markers of inflammation may lead to predict outcomes more precisely. In this cross-sectional study, our analysis indicates that D-dimer levels at admission can be useful for predicting both 30-day mortality and overall mortality. Increased D-dimer is associated with 1.38 times increased

Table 3. Laboratory results with the comparisons between survivors and non-survivors

Variables	All population	Survival		Univariable regression			
		Survivors	Non-survivors	HR	95% CI		p
	n=152	n=127	n=25		Lower	Upper	
CRP	66 (0.3-336)	57.3 (0.3-336)	102 (3.4-224)	1.00	1.00	1.01	0.119
D-dimer	0.7 (0.2-6.2)	0.6 (0.2-5.8)	1.3 (0.3-6.2)	1.38	1.10	1.72	<0.001*
Lymphocyte	1.2 (0.2-7.2)	1.3 (0.2-7.2)	0.7 (0.2-2.2)	0.13	0.05	0.38	<0.001*
LYM, %	17.4 (2.4-50.6)	18.7(3-50.6)	10 (2.4-46.6)	0.91	0.86	0.96	<0.001*
MPV	9.8±1	9.8±1	10.1±1.3	1.41	0.95	2.08	0.085
PDW	13.3±2.7	13.2±2.7	13.6±2.9	1.09	0.94	1.27	0.268
PLT	219.5 (97-487)	218 (97-487)	234 (103-476)	1.00	1.00	1.01	0.312
ALT	26 (3-616)	26 (3-616)	23 (3-184)	1.00	0.99	1.01	0.888
AST	34 (12-220)	33.5 (12-220)	35 (13-166)	1.01	1.00	1.02	0.277
Albumin	37.9±4.4	38.4±4.1	35.2±4.9	0.87	0.79	0.94	0.001*
e-GFR	92 (17-126)	93 (26-126)	76.5 (17-110)	0.97	0.96	0.99	<0.001*
CK	75 (15-2018)	73 (15-2018)	77 (25-1053)	1.00	1.00	1.00	0.152
Glucose	127 (63-724)	127 (63-516)	136 (73-724)	1.00	0.99	1.01	0.096
Urea	34 (12-124)	32 (12-109)	48 (15-124)	1.03	1.02	1.05	<0.001*
Creatinine	0.9 (0.4-3.3)	0.9 (0.5-2.3)	0.9 (0.4-3.3)	4.07	2.29	7.24	<0.001*
LDH	345 (128-1374)	327 (128-849)	386 (224-1374)	1.03	1.01	1.05	<0.001*
Uric acid	4.8 (2.2-13)	4.7 (2.3-13)	5.3 (2.2-12.5)	1.22	1.01	1.47	0.038*
Haematocrit	38.5±5	39±4.5	36±6.4	0.90	0.83	0.97	0.008*
Hemoglobin	12.9±1.8	13.1±1.6	11.9±2.3	0.72	0.58	0.90	0.004*
Troponin	2.7 (0-112.5)	2.3 (0-40)	13.9 (0-112.5)	1.03	1.02	1.05	<0.001*
Ferritin	321.9 (16-2000)	316.7 (16-2000)	492 (39-1500)	1.05	1.01	1.10	0.028*
Fibrinogen	547.5±181	548.7±184.6	541.0±163.8	1.00	1.00	1.00	0.955
Procalcitonin	0.07 (0.02-8.07)	0.06 (0.02-8.07)	0.19 (0.03-7.51)	1.27	1.03	1.57	0.023*
proBNP	129 (3-15432)	113 (3-12953)	2298.5 (81-15432)	1.04	1.01	1.08	<0.001*
PT (%)	96.1±15.4	97±14.6	90.9±19.3	0.98	0.96	1.00	0.081
aPTT	27.1±6.6	27.1±6.4	26.7±7.9	1.00	0.94	1.07	0.940
NLR	4.5 (0.7-39.5)	4.1 (0.7-30.2)	7.8 (0.9-39.5)	1.09	1.05	1.13	<0.001*

*Numerical variables were shown as mean ± standard deviation or median (minimum-maximum). Categorical variables were expressed as numbers and percentages.*p<0.05 indicates statistical significance. HR: Hazard ratio, CI: Confidence interval, CRP: C-reactive protein, PLT: Platelet, CK: Creatine kinase, LDH: Lactate dehydrogenase, PT: Prothrombine time, NLR: Neutrophil-to-lymphocyte ratio, LYM: Lymphocyte, MPV: Mean platelet volume, PDW: Platelet distribution width, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, e-GFR: Estimated glomerular filtration rate, PT: Prothrombin time, aPTT: Activated partial thromboplastin time*

risk of death with the optimum cut-off value of 1.07 µg/mL, which was reported in several variability in previous studies (14,15,16,17). It seems that when a D-dimer is used as a single marker, its contribution to predict mortality may be limited. Indeed, in a retrospective cohort study by Ye et al. (9), the peak value of the D-dimer.

Rather than baseline D-dimer value was shown to be associated with prognosis. Therefore, an easily applicable index model, as suggested in our study, could provide a potential field for more precise risk assessment.

The mechanisms underlying the increased D-dimer levels in COVID-19 are not clearly defined. Recent evidence indicates that sepsis-induced coagulopathy, evidence of disseminated intravascular coagulation (DIC) are not the only mechanisms responsible for increased D-dimer levels associated with severe COVID-19 patients (20). Importantly, increased pro-inflammatory cytokines have been shown in severe cases. Excessive inflammation and platelet activation might have crosstalk to the augmented effect of the procoagulant state in COVID-19 (21) while playing a significant role in the development of prothrombotic states, which result in increased mortality. Additionally, autopsy results have supported the fact that excessive NEU infiltration in capillaries leading to NEU extracellular traps can contribute to the thrombotic process (22). Increased inflammation and increased thrombosis might be associated (23). Furthermore, hypoxia also plays a role in the triggered procoagulant activity through the releasing of several cytokines. Based on increasing evidence, COVID-19 infection results in a prothrombotic state with an increased risk of venous thromboembolism (24). The anti-inflammatory effect of low-molecular-weight heparin (LMWH) has been reported in COVID-19 infection, which is characterized by the disregulation of the immune system response with increased pro-inflammatory. Furthermore, LMWH has recently been advised as a part of treatment care in hospitalized COVID-19 patients recently (2,14). However, the effect of systemic anticoagulation therapy on the reduced risk of mortality has not been well evaluated. It seems that hypercoagulability is in close association with an inflammatory response in COVID-19 and might behave as an additive effect on the disease outcomes.

White blood cell count, NEU-to-LYM-NLR, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio are indicators of the SIR that were investigated as useful predictors for poor outcomes of viral pneumonia in several studies previously (25,26). NLR has been suggested as a potential inflammatory marker in severe cases, but there is insufficient data on how efficiently can be used to predict mortality (5,10,27). The critical value of NLR was 3.83 in our cohort, which is reported in a wide range in previous studies

Table 4. **Independent risk factors predicting mortality**

Variables	Multivariable Cox regression			
	HR	95% CI		p
		Lower	Upper	
Model I				
Oxygen saturation	0.90	0.86	0.94	<0.001*
Creatinine	3.11	1.41	6.89	0.005*
D-dimer	1.34	1.02	1.76	0.037*
	-2 Log likelihood: 178.7; AIC: 239			
Model II				
Oxygen saturation	0.92	0.88	0.97	<0.001*
D-dimer	1.35	1.03	1.73	0.029*
NLR	1.07	1.02	1.11	0.005*
	-2 Log likelihood: 204.5; AIC: 224			
Model III				
Oxygen saturation	0.92	0.88	0.96	<0.001*
D-dimer and NLR combination				
Low-medium risk	Ref			
High risk	5.82	1.71	19.75	0.005*
	-2 Log likelihood: 204.2; AIC: 202			

**p<0.05 indicates statistical significance. HR: Hazard ratio, CI: Confidence interval, AIC: Akaike information criterion, NLR: Neutrophil-to-lymphocyte ratio*

(10,16,27) and slightly lower than the previously reported data (16,24) NLR has been detected as an independent risk factor for mortality in our cohort as in previous studies (5,6). Recently, each unit of NLR increase has been associated with a gradually increased risk of in-hospital mortality, especially in males (6). However, several factors such as body mass index, physical activity, smoking, alcohol consumption, and gender that may have an impact on NLR values limit the reliability of its use alone (28). Our results suggested that initial NLR by itself cannot have enough specificity to predict mortality with the poor PPV, which was also mentioned by Ye et al. (9).

NLR is an easy-to-obtain, inexpensive feasible marker reflecting the inflammatory response and might have an adjunct predictive power of D-dimer for patients with COVID-19. Thus, a combined model of D-dimer and NLR can more precisely determine the high risk of mortality.

Different assessment models, mostly based on machine learning models, have been developed for the best prediction analysis of mortality until now (29,30,31). Except for one recently published study (29), none of them included D-dimer although C-reactive protein, lactic dehydrogenase, and LYM count have been included as predictors.

Study Limitations

The limitation of our study was the single-center design, on the other hand, there were features to perform a stronger study. Our study sample consists of a population having comorbidities, so our results became more determinative. Furthermore, the larger sample size and the need for more studies on PRI-COVID emphasize the contributive features of our study.

Conclusion

Our prognostic model consisting of NLR and D-dimer could objectively predict critical cases more determinatively than single use of these factors to predict mortality in COVID-19 patients. These inexpensive and easily accessible biomarkers would provide the best model and would have significancy in predicting the mortality of COVID-19 patients with high differentiation ability. When we used a combined model including D-dimer and NLR, we could increase both specificity and sensitivity of predicting prognosis in this deadly disease. Thus, D-dimer and NLR have been used as a prognostic index named “PRI-COVID” to classify patients at hospital admission and this enables early detection of potential critical patients.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval no: 2284).

Informed Consent: An informed consent form was signed by each subject included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.P.Y., S.B., Concept: B.P.Y., D.G.H., C.A., Design: B.P.Y., C.A., Data Collection or Processing: B.P.Y., D.G.H., S.B., Analysis or Interpretation: B.P.Y., D.G.H., C.A., Literature Search: B.P.Y., D.G.H., S.B., Writing: B.P.Y., C.A.

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COVID-19-related Secondary Bacterial Infections in Intubated Critical Illness

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What is known on this subject?

Bacterial common pathogens are frequently seen in viral respiratory diseases like influenza, and they are a major source of morbidity and mortality, necessitating prompt identification and antibacterial treatment.

What this study adds?

Antibiotic-resistant microorganisms render humans more vulnerable to bacterial infections while also reducing our ability to fight off viral pandemics. Preventing drug resistance and avoiding needless antibiotic treatment are two strategies that should be implemented today to prepare for future pandemics.

ABSTRACT

Objective: The prevalence, occurrence, and characteristics of bacterial infection in individuals with severe acute respiratory syndrome coronavirus-2 is primarily unknown. In this research, we examined the effects of secondary bacterial infections (SBI), antibiotic use, and mortality on coronavirus disease-2019 (COVID-19) patients who were observed in intensive care units (ICU) when intubated.

Material and Methods: Between October 1, 2020 and February 1, 2021, patients who were monitored because of COVID-19 in adult ICUs at tertiary healthcare facilities were included in this retrospective research. The study included The study included a total of 170 individuals with acute respiratory distress syndrome and COVID-19 pneumonia.

Results: Antibiotics were given to 154 (90.58%) patients. While all SBI-positive patients received antibiotic treatment, 78 (45.88%) SBI-negative patients were also treated. In addition, SBI-positive patients had a higher mortality rate ($p<0.001$). Time-SBI was 3.13±2.42/days in patients with catheters, and it was shorter and statistically significantly different compared with patients without catheters ($p<0.03$). Blood culture growths were discovered in 24 (14.1%) of patients and were the most common.

Conclusion: Antibiotic-resistant microorganisms render humans more vulnerable to bacterial infections while also reducing our ability to fight viral pandemics. Preventing drug resistance and avoiding needless antibiotic treatment are two strategies that should be implemented today to prepare for future pandemics.

Keywords: ARDS, coronavirus, critical care medicine intubation, secondary bacterial infection

Introduction

In viral respiratory illnesses like influenza, bacterial common pathogens are commonly present and are a significant cause of fatalities and morbidity, needing timely detection and antibacterial treatment (1,2).

Uncertainty regarding the prevalence, incidence, and characteristics of bacterial infection in patients with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has emerged as a serious knowledge gap.

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Antibiotics are administered when bacterial co-infection cannot be ruled out if secondary bacterial infection (SBI) is present or probably present, even though they are useless for coronavirus disease-2019 (COVID-19) therapy. Some recommendations support the empirical use of antibiotics in severe COVID-19 patients due to the high mortality rate of patients with superinfection from bacteria throughout outbreaks of influenza (3,4). Nevertheless, misuse of antibiotics raises concerns about the risk of bacterial resistance.

In this research, we looked at how SBI, antibiotic use, and mortality impacted COVID-19 patients who were monitored in intensive care units (ICU) while intubated.

Material and Methods

Patients who underwent adult ICU follow-up because of COVID-19 between October 1, 2020 and February 1, 2021 in a tertiary healthcare center were included in this retrospective research. Following the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee's authorization for the study (ethical permission number: 2021-58, date: 14.04.2021), the records of patients admitted to the ICU within the specified periods were retrospectively scanned.

The following cases met the inclusion criteria for the study: 1) COVID-19 instances in whom polymerase chain reaction (PCR) testing confirmed the test; 2) acute respiratory distress syndrome (ARDS) patients identified using the Berlin criteria; and 3) intubated patients who were 18 years of age or older.

Criteria for exclusion: 1) patients under the age of 18 years; 2) patients without ARDS; 3) patients who are pregnant; 4) patients with concurrent malignancy; 5) patients with a history of transplantation of an organ and/or immunosuppression medication; 6) patients with a radiological diagnosis and a negative COVID-19 PCR test; the study included 170 ARDS patients who also had COVID-19 pneumonia (Figure 1).

Patient files and the hospital's computerized records were both used to obtain data on the patients. The patients' age, gender, concomitant disease status, and laboratory results on the day of admission to the ICU and the day of intubation were all studied. The Sequential Organ Failure Assessment Score (SOFA) and the Acute Physiology and Chronic Health Evaluation (APACHE) scores were also recorded at the time of admission to the ICU. The diagnosis of SBI was made by the infection expert after evaluating clinical deterioration, increases in C-reactive protein, procalcitonin, and white blood cell, and culture growths that appeared 48 h after the patients had been taken into the ICU. The moment when the diagnosis of SBI was made was accepted as the "Time of Secondary Bacterial Infection". All the research participants were COVID-19-infected patients who underwent follow-up and treatment in inpatient internal medicine, infection, and/or pulmonology. Patients who experienced clinical and laboratory deterioration within the first 48 h of ICU admission were deemed to have co-infections that originated outside the ICU (in the ward or during outpatient treatment), and they were therefore excluded from the research. Positive cultures that emerged due to contamination or colonization were disregarded immunomodulatory and immunosuppressive treatments were administered to the patients as follows: depending on the patient's condition, tocilizumab was given intravenously (iv) at a maximum dose of 800 mg at 8 mg/kg, and 400 or 800 mg. Anakinra was given to patients at a dose of 2-10 mg/kg/iv over the course of 7-10

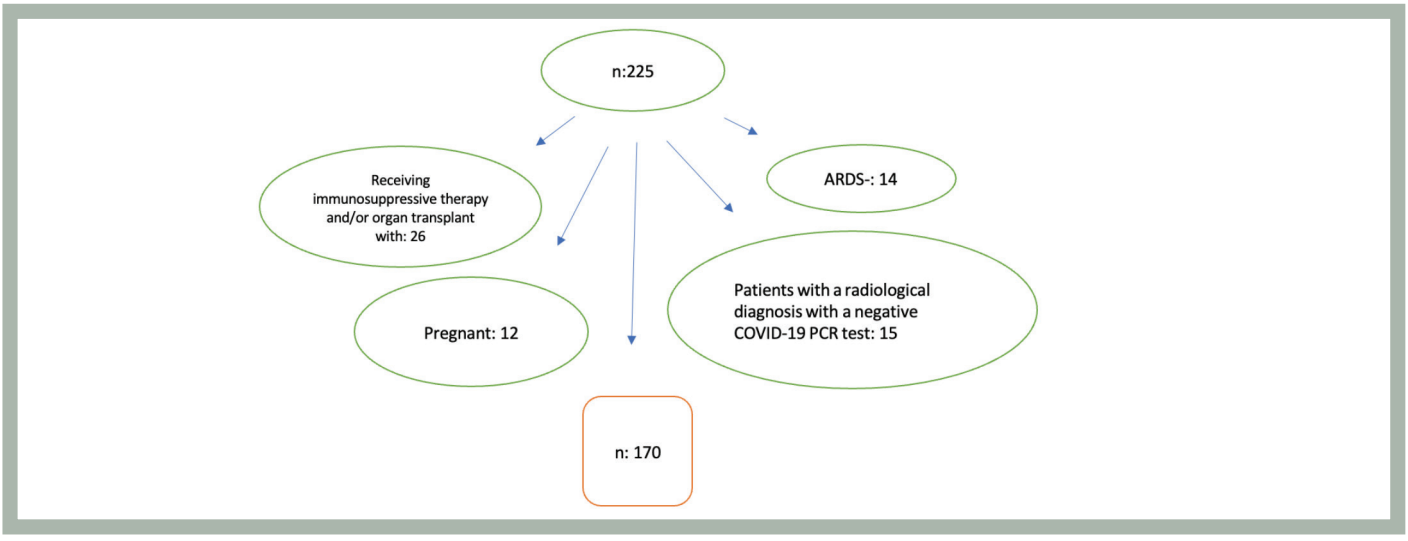

Figure 1. Flow chart

ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction

days, depending on their needs. The rheumatologist assessed the dosage and duration for each patient. iv immunoglobulin was administered at a total dose of 2 g/kg over the course of 2 days. Methylprednisolone pulse therapy was also given as 250 or 500 mg for 3-5 days, depending on the clinical condition of the patient. However, since these treatments were not used in all patients, the patients who used them were recorded.

Statistical Analysis

Using the SPSS tool, the study results were statistically evaluated. If the continuous data in one sample met the normal distribution, it was determined using the Kolmogorov-Smirnov test. In this study, quantitative data were expressed as the mean and standard deviation or median, depending on their distribution. The categorical variables were represented by percentages and numbers. The Mann-Whitney U test was used for continuous data that did not fit a normal distribution, whereas the Student's t-test was employed to compare the two groups. Using the chi-square test, categorical data from two groups were compared. Mortality was also assessed using logistic regression analysis.

Results

The study involved 170 patients. Two groups of patients were created based on their SBI status: those positive for SBI (SBI-positive) and those negative for SBI (SBI-negative).

Table 1. Demographic data of patients and laboratory results

n=170	All patients	SBI-negative n=93 (54.70%)	SBI-positive n=77 (45.29%)	p
Age	68.35±11.76	67.87±2.34	68.94±12.49	0.45
Glucose (mg/dL)	192±112.29	186.54±158.02	200.64±133.15	0.86
BUN (mg/dL)	79.3±63.09	85.94±71.97	71.30±49.62	0.25
Creatinine (mg/dL)	1.6±1.54	1.68±1.66	1.52±1.39	0.95
AST (U/L)	54.9±66.83	64.30±79.16	45.54±45.90	0.06
ALT (U/L)	47.31±75.76	55.82±94.099	37.05±40.59	0.28
LDH (U/L)	494.75±265.93	502.72±300.89	460.98±213.42	0.23
Fibrinogen (mg/dL)	59.3±174.35	573.45±188.40	618.48±153.32	0.17
D-dimer (µg FEU/mL)	3.03±4.15	3.09±4.13	2.97±4.2	0.34
Ferritin (ng/mL)	1440.12±1833.21	1557.02±2082.45	1298.67±1480.21	0.45
INR	1.19±0.68	1.23±0.88	1.14±0.36	0.34
WBC (10^9/L)	11.13±6.59	11.94±7.46	10.15±5.23	0.28
HB (10^9/L)	12.63±10.33	11.69±2.34	13.77±15.11	0.11
Platelet (10^9/L)	233.99±124.06	223.41±119.48	255.61±128.00	0.10
Lymphocyte (10^9/L)	0.98±1.13	0.88±0.79	1.04±1.43	0.94
Neutrophil (10^9/L)	9.48±6.14	10.10±7.4	8.73±4.60	0.59
CRP (mg/L)	135.06±93.31	127.58±9.26	145.12±103.77	0.47
PCT	2.86±9.57	3.22±12.11	2.42±4.98	0.99
Mechanic ventilation days	9.03±8.57	8.74±9.26	9.37±7.7	0.26
LOS in ICU/day	14.07±10.32	13.76±10.42	14.4±10.25	0.41
LOS in hospital/day	18.32±12.21	17.27±11.83	19.58±12.62	0.16
SOFA	9.96±2.62	9.66±2.46	10.32±2.72	0.23
APACHE	18.37±7.03	18.52±7.09	18.19±7.00	0.7
NLR	18.64±21.09	19.88±22.28	17.15±19.6	0.64
PLR	339.12±233.88	327.32±247.27	353.32±217.35	0.20
Mortality	126 (74.1%)	54 (31.8%)	72 (42.4%)	0.000
Antibiotic therapy	154 (90.58%)	78 (45.88%)	77 (45.29%)	0.002
The catheter's existence	123 (72.4%)	57(33.5 %)	66 (38.8%)	0.001

SBI-negative: Secondary bacterial infection negativity, SBI-positive: Secondary bacterial infection positivity, BUN: Blood urea nitrogen, AST: Aspartate transaminase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, WBC: White blood cell, HB: hemoglobin, PCT: Procalcitonin, CRP: C-reactive protein, SOFA: Sequential Organ Failure Assessment Score, APACHE: The Acute Physiology and Chronic Health Evaluation, LOS: Length of stay in ICU, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, INR: International normalised ratio

Table 1 summarizes the laboratory results and clinical features of these patients, and there was no statistical difference in the SOFA and APACHE scores between the two groups. Antibiotics were given to 154 (90.6%) of the patients. While all SBI-positive patients received antibiotic treatment, 78 (45.88%) SBI-negative patients were also treated. In addition, SBI-positive patients had a higher mortality rate ($p<0.001$). Table 2 summarizes the treatments used and the problems that occurred during ICU follow-up. In Table 3, the time of SBI (time-SBI) in patients with and without catheters is presented. Time-SBI was 3.13±2.42/days in patients with catheters, and it was shorter and statistically significantly different compared to patients without catheters ($p<0.03$).

Table 4 shows how culture growths were classified, with blood culture growths being discovered in 24 (14.1%) of patients and being the most common. In addition, in Table 4, 24 (14.1%) of the patients with SBI were informed that there was growth in the blood culture, that is, bacteremia. Catheter-related bloodstream infection was detected in 6 (3.53%) patients (5). In addition, SBI was found to predict mortality in binary logistic regression analysis ($p<0.001$) (Table 5).

Discussion

In this study, 77 (45.29%) of the COVID-19 patients followed in the ICU developed SBI-positive, and those with SBI-positive had a higher mortality rate. Time-SBI was also detected early in those who had a catheter. Bacterial infections aggravating viral diseases have been observed in earlier outbreaks and pandemics of viral respiratory diseases. Bacterial co-infection was recorded in up to 30% of critically ill individuals during the 2009 A (H1N1) influenza pandemic (2,6,7).

Based on studies on other coronaviruses, co-infections affect 11% of patients, with secondary infections being the most prevalent in the largest SARS-CoV-1 cohort (8) and bacterial infections having a negligible impact on Middle East respiratory syndrome (MERS) (9). Co-infection was noted

Table 2. Treatments and complications

All patients n=170	SBI-negative n=93 (54.70%)	SBI-positive n=77 (45.29%)	p
Male (n=91)	50 (54.9%)	41 (53.2%)	0.94
Female (n=79)	43 (46.2%)	36 (546.8%)	
Diabetic ketoacidosis	23 (12%)	16 (13.2)	0.89
Acute renal failure	51 (26.6%)	35 (28.9%)	0.64
Elevated liver enzymes	11 (5.7%)	8 (6.6%)	0.94
Deep vein thrombosis	2 (1%)	0 (0)	0.5
Pulmonary embolism	3 (2.5%)	3 (2.5%)	0.68
Tocilizumab	8 (4.2%)	7 (5.7%)	0.7
Anakinra	29 (15.1%)	13 (10.7%)	0.35
Plasmapheresis	16 (6.8%)	11 (9.1%)	0.97
IVIG	13 (6.8%)	6 (5%)	0.68
Methylprednisolone pulse therapy	76 (39.6%)	48 (39.7%)	0.98

SBI-negative: Secondary bacterial infection negativity, SBI-positive: Secondary bacterial infection positivity, IVIG: Intravenous immunoglobulin

Table 3. Time of secondary bacterial infection with and without central venous catheter

	Without catheterized group (n=11)	Catheterized group n=66)	p
The time of secondary bacteria infection/day	7.6±4.97	3.13±2.42	0.03

Table 4. Culture results

	n (%)
Blood culture	24 (14.1%)
Deep tracheal aspirate culture	18 (10.6%)
Urine culture	6 (3.5%)
Catheter culture	8 (4.7%)
Multiple growths	14 (8.2%)

Table 5. The logistic regression analysis of clinical and laboratory factors for predicting secondary bacterial infection

	Beta	OR	95% CI for EXP (B)		
			Lower	Upper	
APACHE	0.031	1.031	0.971	1.095	0.316
SOFA	-0.129	0.879	0.741	1.044	0.141
NLR	0.006	1.006	0.988	1.025	0.513
PLR	0.000	1.000	0.999	1.002	0.691
CRP	-0.001	0.999	0.994	1.004	0.717
PCT	-0.002	0.998	0.953	1.046	0.948
LOS in ICU	-0.027	0.974	0.889	1.066	0.563
Mechanic ventilation days	0.013	1.013	0.915	1.120	0.806
The catheter's existence	0.769	2.157	0.905	5.140	0.083
SBE	-2.189	0.112	0.039	0.320	0.000

APACHE: The Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment Score, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, CRP: C-reactive protein, PCT: Procalcitonin, LOS: Length of stay, ICU: Intensive care unit , CI: Confidence interval, OR: Odds ratio

in 3.5% [95% confidence interval (CI): 0.4-6.7%] of COVID-19 patients, and secondary infection was noted in 14.3% (95.5% CI: 9.6-18.9%) of COVID-19 patients, referring to a meta-analysis by Langford et al. (10). Over 70% of patients received antibiotic prescriptions, the majority of which were broad-spectrum antibiotics such as fluoroquinolones and cephalosporins of the third generation (10), although the overall risk of bacterial infections. SBI rates have been found to range between 5% and 30% in numerous cohort studies (11,12,13,14,15,16,17). SBI was found in 77 (45.29%) of the patients in our study, which was greater than the current rates.

Current recommendations are based on data from other viral pneumonia and lack randomized clinical trials on the use of empirical antibiotics in COVID-19 patients (18). In our study, all SBI-positive patients were given antibiotics, while 78 (45.88%) of SBI-negative patients and 154 (90.58%) of all patients were given antibiotics. In patients with COVID-19, drugs that inhibit the immune system are commonly used to reverse the immune system's irregular activation (19,20).

Secondary infection susceptibility is believed to be increased by a combination of virus and drug-induced immunosuppression. Furthermore, the finding of primarily *Streptococcus pneumonia* and *Staphylococcus aureus* (1) growths in hospitalized patients justify antibiotic treatment in patients with COVID-19. Rawson et al. (8) analyzed eighteen full-text reports of bacterial/fungal confections, of which nine (50%) were COVID-19, 5/18 (28%) SARS-1, 1/18 (6%) MERS, and 3/18 (17%) were about other coronaviruses. Although there is limited evidence for bacterial coinfection, it was reported that 62/806 (8%) of COVID-19 patients had bacterial/fungal co-infection at hospital admission and 1450/2010 (72%) received antimicrobial therapy. Patients who also had fungal or bacterial infections and broad-spectrum antibiotic usage were recorded in 89/815 (11%) of non-COVID-19 cases (8).

Clinicians still have trouble distinguishing between viral and bacterial infections. This diagnostic ambiguity has contributed to the well-acknowledged misuse of antibiotics in viral illness patients (21,22). Antibiotic use was shown to be extremely prevalent in our study. Broad-spectrum antibiotics weaken and impair the immune system's ability to manufacture antibodies (by decreasing gut bacteria). Furthermore, research shows that antibiotic use affects bile acid metabolism and triggers inflammatory reactions (23).

According to World Health Organization recommendations, antibiotic therapy or prophylaxis should be avoided in patients with mild COVID-19 symptoms or suspected or confirmed intermediate COVID-19 disease unless there is clinical evidence of bacterial infection (24).

Study Limitations

The study's limitations are that bacteria produced as a result of antibiotic treatments and patient culture growth were excluded from the data, and non-intubated patients were not included. In addition, the retrospective design of the study is another limitation of our study.

Conclusion

As a result, antibiotic-resistant microorganisms render humans more vulnerable to bacterial infections while also

reducing our ability to fight viral pandemics. Preventing drug resistance and avoiding needless antibiotic treatment are two strategies that should be implemented today to prepare for future pandemics.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee's authorization for the study (ethical permission number: 2021-58, date: 14.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.T., G.H.A., G.T., O.Ö., Concept: D.T., G.H.A., G.T., O.Ö., Design: D.T., G.H.A., G.T., O.Ö., Data Collection or Processing: D.T., G.H.A., G.T., O.Ö., Analysis or Interpretation: D.T., G.H.A., G.T., Literature Search: D.T., G.H.A., G.T., Writing: D.T., G.H.A., G.T.

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Magnetic Resonance Imaging Observations of Nearby Segment Deterioration in Isthmic and Degenerative Spondylolisthesis

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What is known on this subject?

Adjacent segments of degenerative spondylolisthesis exhibited more severe conditions in terms of disc space height, transverse area of the spinal dural sac, disc degeneration, and disc contour compared with ethmic spondylolisthesis.

What this study adds?

The study evaluated the level of degeneration in the neighboring upper and lower segments in lumbar isthmic and degenerative spondylolisthesis using magnetic resonance imaging.

ABSTRACT

Objective: The objective of the study was to evaluate the extent of deterioration in nearby upper and lower segments in lumbar isthmic and degenerative spondylolisthesis using magnetic resonance imaging (MRI).

Material and Methods: A retrospective evaluation was conducted on lumbar spine MRI scans of 51 individuals diagnosed with isthmic spondylolisthesis and 55 individuals diagnosed with degenerative spondylolisthesis. Adjacent intervertebral segments were evaluated for disc space height, thickness of ligamentum flavum, spinal dural sac transverse area, disc degeneration, facet hypertrophy, and disc contour.

Results: In all patients, both the upper segment (p=0.003) and lower segment (p=0.024) showed statistically significant differences between the two types of spondylolisthesis. Additionally, at the L4-L5 level (between the fourth and fifth lumbar vertebrae), there was a significant difference for the upper segment (p=0.005). There were statistically significant differences between the two types in the spinal dural sac transverse area in all patients for the upper segment (p=0.004), disc degeneration in all patients for the upper segment (p=0.003), disc contour in all patients for the upper segment (p=0.014), and L4-L5 level spondylolisthesis for the upper segment (p=0.021).

Conclusion: Disc space height measurements, spinal dual sac transverse area, disc degeneration, and disc contour were all worse in adjacent segments of degenerative spondylolisthesis compared with isthmic spondylolisthesis.

Keywords: Adjacent segment, degenerative spondylolisthesis, isthmic spondylolisthesis, lumbar vertebrae, magnetic resonance imaging

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Introduction

Spondylolisthesis was first described by Herbiniaux (1) in 1782. Spondylolisthesis is characterized by a shift in the uppermost part of the vertebral body as opposed to the lower part. Wiltse et al. (2) categorized spondylolisthesis into five classifications: congenital, isthmic, degenerative, traumatic, and pathological. Wiltse and Rothman (3) further distinguished the postsurgical type from the pathological type, resulting in a total of six distinct types of spondylolisthesis.

The degenerative and isthmic types are the most common forms of spondylolisthesis. The pathophysiology of spondylolisthesis is distinct in the degenerative and isthmic types. The effect of spondylolisthesis on adjacent segments is also distinguished between degenerative and isthmic types. The difference in degeneration in adjacent segments of degenerative and ithmic spondylolisthesis may also necessitate different surgical approaches for these pathologies. This study aimed to assess the level of degeneration in the neighboring upper and lower segments in cases of degenerative and ethmic spondylolisthesis using magnetic resonance imaging (MRI).

Material and Methods

Subjects

A retrospective evaluation was conducted on MRI scans of the lumbar spine in 51 individuals diagnosed with isthmic spondylolisthesis, and 55 individuals diagnosed with degenerative spondylolisthesis. These images were obtained from the Neurosurgery Department, Balıkesir University Faculty of Medicine, Balıkesir, Turkey. The inclusion criteria for the study were patients experiencing symptoms such as claudication, radiating pain, or low back pain leading them to undergo lumbar spine MRI. Individuals who had previously undergone lumbar surgery, had a vertebral fracture, or displayed spondylolisthesis in multiple segments or both types of spondylolisthesis were excluded from the study. This retrospective study was approved by the Clinical Research Ethics Committee, Balıkesir University Faculty of Medicine, Balıkesir, Turkey (decision no. 2023/64 and date: 10/05/2023).

Magnetic Resonance Imaging

We acquired sagittal T1-weighted images (repetition time/echo time msec: 758/12) and sagittal T2-weighted images (repetition time/echo time msec: 4,667/112) as part of the imaging process using Siemens Avanto 1.5T MRI (Siemens, Munich, Germany) and Philips Achieva 1.5T MRI (Philips, The Netherlands). The acquired images had a thickness of 4 mm, with matrix dimensions of 168×512 for T1-weighted images and 180×512 for T2-weighted images.

Measurements

(a) Degree of Spondylolisthesis at the Index Level

The severity of spondylolisthesis was determined using the Meyerding System, which classifies degrees of translational displacement into grades 1 to 5 (4). These degrees of translational displacement were obtained from T2-weighted sagittal MRIs. Computed tomography of the lumbar spine was also used to verify the type of spondylolisthesis. Only patients with grade 1 Meyerding classification were included in this study, excluding Meyerding grades 2-5.

(b) Disc Space Height at the Superior and Inferior Adjacent Levels

The Farfan index was used to measure disc heights. To reduce errors, disc heights were determined from both the posterior and anterior regions of the disc space in sagittal T2-weighted images. The sum of these measurements was then divided by the anteroposterior diameters of the discs (5).

(c) Thickness of Ligamentum Flavum at the Superior and Inferior Adjacent Levels

The thickness of the ligamentum flavum was assessed using axial T1-weighted images at the midpoint of its length (6). This determined whether the interlaminar space had narrowed as the spinal motion segment lost height secondary to degeneration. In addition, we observed whether the ligamentum had folded into the spinal canal and thickened.

(d) Spinal Dual Sac Transverse Area at the Superior and Inferior Adjacent Levels

Lumbar spinal stenosis is characterized by the narrowing or constriction of the spinal canal, nerve root canal, or intervertebral foramina. The transverse area of the spinal dual sac was employed as an indicator for predicting canal stenosis. The cross-sectional area of the vertebral canal was measured at both the upper and lower adjacent levels.

(e) Degeneration of the Discs in the Neighboring Upper and Lower Levels

The severity of degeneration in the neighboring upper and lower intervertebral discs was assessed using the Pfirrmann et al. (7) grading system. In this classification method, the degree of degeneration was assessed using sagittal T2-weighted images. The grades were defined as follows: grade 1 indicated a normal shape with a distinct intact annulus and nucleus pulposus; grade 2 denoted an irregular shape of the nucleus pulposus with a horizontal band and reduced differentiation

between the nucleus pulposus and the annulus; grade 3 indicated an indistinct separation between the annulus and the diverse nucleus pulposus, which remained recognizable; grade 4 indicated a heterogeneous nucleus pulposus with annulus rupture, low signal intensity, and a decrease in disc height; and grade 5 represented similar characteristics as grade 4 but with the collapsed intervertebral space.

(f) Facet Hypertrophy at the Superior and Inferior Adjacent Levels

Facet hypertrophy was described as degeneration and enlargement of the facet joints. A normal facet joint was classified as F0. When the inferior articular process was hypertrophied, this was classified as F1. The hypertrophied superior articular process was classified as F2. When both the inferior and superior articular processes were hypertrophied, they were classified as F3 (8,9,10).

(g) Changes in the Disc Contour at the Superior and Inferior Adjacent Levels

The description of disc contour changes was categorized on a nominal scale as follows: 0 indicated a normal contour, 1 represented a bulge, 2 denoted a focal protrusion, 3 indicated a broad-based protrusion, and 4 indicated an extrusion.

Statistical Analysis

The data are reported as the mean ± standard error of the mean. Statistical analysis was conducted using the Number Cruncher Statistical System (NCSS 2007) software (NCSS LLC, Kaysville, Utah, USA). One-Way ANOVA was employed to assess significant differences between the means of two or more independent groups. The Mann-Whitney U test was used when comparing differences between two independent groups with either ordinal or non-normally distributed continuous variables. Tukey's honest significant difference test was conducted to identify significantly different means. Student's t-test was used to evaluate significant differences between two sets of data. Wilcoxon signed-rank test was employed for comparing two related or matched samples. A p value below 0.05 was considered statistically significant.

Results

The study included 51 instances of ithmic spondylolisthesis and 55 cases of degenerative spondylolisthesis. The patients were 22.6% (n=24) male and 77.4% (n=82) female, with the average age for the isthmic type being 54.82 years of age ±12.29 years (range, 19 to 77 years of age) and the average age for the degenerative type being 59.60 years of age ±14.08 years (range, 42 to 82 years of age). For the isthmic type, 12 were (23.5%) men and 39 were (76.5%) women; there were three (5.9%) cases at the L3-L4 level, 18 (35.3%) cases at the L4-L5 level, and 30 (58.8%) cases at the L5-S1 (fifth lumbar and first sacral vertebrae) level. For the degenerative type, 12 were (21.8%) men and 43 were (78.2%) women; there were 1 (1.8%) cases at the L1-L2 level, 7 (12.7%) cases at the L2-L3 level, 8 (14.5%) cases at the L3-L4 level, 22 (40.0%) cases at the L4-L5 level, and 17 (31.0%) cases at the L5-S1 level. In the case of isthmic spondylolisthesis, 72 adjacent superior and inferior segments were observed, with 51 adjacent superior segments and 21 adjacent inferior segments. In contrast, in degenerative spondylolisthesis, there were 92 adjacent superior and inferior segments, consisting of 54 adjacent superior segments and 38 adjacent inferior segments. Specifically, at the L4-L5 level, isthmic spondylolisthesis exhibited 18 adjacent superior and 18 adjacent inferior segments, while degenerative spondylolisthesis showed 22 adjacent superior and 22 adjacent inferior segments. Complete details can be found in Tables 1, 2, 3, 4.

Degrees of Translation

The Meyerding system for determining the severity of spondylolisthesis was used to measure the translational displacement. Only patients with grade 1 Meyerding classification were included in this study, excluding Meyerding grades 2-5 from the statistical analysis.

Disc Space Height at the Superior and Inferior Adjacent Levels (Figure 1)

In midsagittal-T2-weighted MRI, the Farfan index was employed to measure disc heights. The obtained values for patients with isthmic and degenerative spondylolistheses were 0.46±0.12 and 0.39±0.12, respectively, for the upper segment. For the lower segment, the values were 0.52±0.15 for isthmic spondylolisthesis and 0.42±0.16 for degenerative spondylolisthesis. The values obtained for L4-L5 level spondylolisthesis for the degenerative and isthmic types were 0.48±0.10 and 0.37±0.12 for the upper segment and 0.54±0.15 and 0.47±0.18 for the lower segment, respectively. Significant statistical differences were noted between the two types of spondylolisthesis, both for the lower segment (p=0.024) and the upper segment (p=0.003). In individuals experiencing spondylolisthesis specifically at the L4-L5 level, statistical significance was found for the upper segments (p=0.005). There were no statistically significant differences between the two types of spondylolisthesis for the lower segment in patients with L4-L5 levels spondylolisthesis (p=0.172).

Table 1. Superior adjacent intervertebral levels in all patients for disc space height, thickness of ligamentum flavum, spinal dural sac area, disc degeneration, facet hypertrophy, and disc contour

Superior adjacent level of all patients (n=105)	Isthmic (n=51) Mean ± SD	Degenerative (n=54) Mean ± SD	p
Disc space height	0.46±0.12	0.39±0.12	[a]0.003**
Right lig flavum thickness (mm)	3.54±1.16	3.84±1.47	[a]0.250
Left ligamentum flavum thickness (mm)	4.10±1.22	3.82±1.16	[a]0.240
Spinal dural sac transverse area (mm^2)	144.74±48.11	117.26±47.93	[a]0.004**
Disc degeneration	2.69±0.73	3.09±0.73	[d]0.003**
Facet hypertrophy	1.02±1.12	1.41±1.14	[d]0.059
Disc contour	1.25±0.84	1.80±1.16	[d]0.014*

*[a]Student's t-test, [d]Mann-Whitney U test, *p<0.05, **p<0.01, SD: Standard deviation*

Table 2. Inferior adjacent intervertebral levels in all patients for disc space height, thickness of ligamentum flavum, spinal dural sac area, disc degeneration, facet hypertrophy, and disc contour

Lower adjacent level of all patients (lower n=59)	Defect (+) (n=21) Mean ± SD	Defect (-) (n=38) Mean ± SD	p
Disc space height	0.52±0.15	0.42±0.16	[a]0.024*
Right ligamentum flavum thickness (mm)	3.19±1.08	3.65±1.11	[a]0.136
Left ligamentum flavum thickness (mm)	3.81±1.43	3.94±1.49	[a]0.757
Spinal dural sac transverse area (mm^2)	122.8±34.25	131.16±47.34	[a]0.480
Disc degeneration	2.95±0.74	3.13±0.96	[d]0.430
Facet hypertrophy	1.19±1.17	1.47±1.27	[d]0.405
Disc contour	1.57±0.93	1.66±1.12	[d]0.899

*[a]Student's t-test, [d]Mann-Whitney U test, *p<0.05, SD: Standard deviation*

Table 3. Superior adjacent intervertebral levels in all patients with L4-L5 level spondylolisthesis for disc space height, thickness of ligamentum flavum, spinal dural sac area, disc degeneration, facet hypertrophy, and disc contour

Upper (L3-L4) intervertebral level of isthmic and degenerative L4-L5 spondylolisthesis (n=40)	Defect (+) (n=18) Mean ± SD	Defect (-) (n=22) Mean ± SD	p
Disc space height	0.48±0.10	0.37±0.12	[a]0.005**
Right ligamentum flavum thickness (mm)	3.57±1.30	4.26±1.41	[a]0.121
Left ligamentum flavum thickness (mm)	4.10±1.28	4.29±1.04	[a]0.661
Spinal dural sac transverse area (mm^2)	128.47±45.33	101.68±39.99	[a]0.054
Disc degeneration	2.72±0.89	3.18±0.59	[d]0.059
Facet hypertrophy	1.11±1.32	1.55±1.22	[d]0.288
Disc contour	1.00±0.69	1.68±1.09	[d]0.021*

*[a]Student's t-test, [d]Mann-Whitney U test, *p<0.05, **p<0.01, SD: Standard deviation*

The Thickness of the Ligamentum Flavum at the Neighboring Upper and Lower Levels (Figure 2)

No statistically significant differences were found between the two types of spondylolisthesis for the right ligamentum flavum values, both in the lower segment (p=0.136) and the upper segment (p=0.250). Likewise, in individuals with spondylolisthesis specifically at the L4-L5 level, no statistically significant difference was found for the right ligamentum flavum values in both the lower segment (p=0.093) and the upper segment (p=0.121).

In terms of the left ligamentum flavum values, there were no statistically significant differences between the two types of spondylolisthesis in all patients, both in the upper segment (p=0.240) and lower segment (p=0.757). Likewise, among

Table 4. **Inferior adjacent intervertebral levels in all patients with L4-L5 level spondylolisthesis for disc space height, thickness of ligamentum flavum, spinal dural sac area, disc degeneration, facet hypertrophy, and disc contour**

Lower (L5-S1) intervertebral level of isthmic and degenerative L4-L5 spondylolisthesis (n=40)	Defect (+) (n=18) Mean ± SD	Defect (-) (n=22) Mean ± SD	p
Disc space height	0.54±0.15	0.47±0.18	[a]**0.172**
Right ligamentum flavum thickness (mm)	3.12±1.14	3.75±1.15	[a]**0.093**
Left ligamentum flavum thickness (mm)	3.64±1.00	4.23±1.64	[a]**0.177**
Spinal dural sac transverse area (mm²)	116.71±32.70	140.36±43.20	[a]**0.063**
Disc degeneration	2.89±0.76	2.09±1.06	[d]**0.503**
Facet hypertrophy	1.11±1.18	1.18±1.14	[d]**0.849**
Disc contour	1.61±0.98	1.64±1.22	[d]**0.944**

[a]Student's t-test, [d]Mann-Whitney U test, SD: Standard deviation

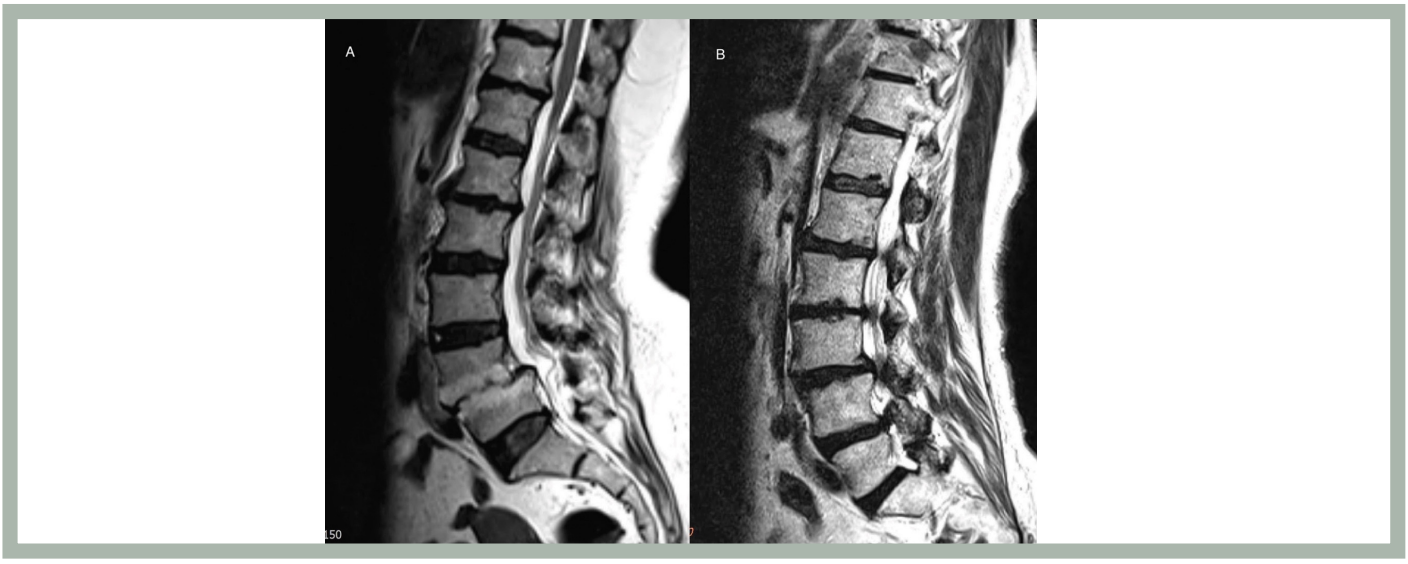

Figure 1. Left (A): midsagittal T2-weighted MRI in a patient with isthmic spondylolisthesis showing that disc space height is not decreased in adjacent segments and showing also grade 3 disc degeneration in the upper adjacent segment and grade 2 disc degeneration in the lower adjacent segment. Right (B): midsagittal T2-weighted MRI in a patient with degenerative spondylolisthesis showing that disc space height is decreased significantly in adjacent segments and showing also grade 4 disc degeneration in the upper adjacent segment and grade 3 disc degeneration in the lower adjacent segment

MRI: Magnetic resonance imaging

patients with L4-L5 level spondylolisthesis, no statistically significant difference was observed for the left ligamentum flavum values in both the upper segment (p=0.661) and lower segment (p=0.177).

The Cross-sectional Area of the Dural Sac at the Neighboring Upper and Lower Levels (Figure 3)

For measurements obtained regarding the cross-sectional area of the dural sac, the measurements obtained for patients with isthmic spondylolisthesis were 144.74±48.11 mm², while for those with degenerative spondylolisthesis, the measurements were 117.26±47.93 mm² for the upper segment. For the lower segment, the values were 122.8±34.25 mm² for isthmic spondylolisthesis and 131.16±47.34 mm² for degenerative spondylolisthesis.

Among individuals diagnosed with spondylolisthesis specifically at the L4-L5 level, the measurements for the isthmic type were 128.47±45.33 mm² for the upper segment and 116.71±32.70 mm² for the lower segment. The values were 101.68±39.99 mm² for the upper segment and 140.36±43.20 mm² for the lower segment in patients with the degenerative type.

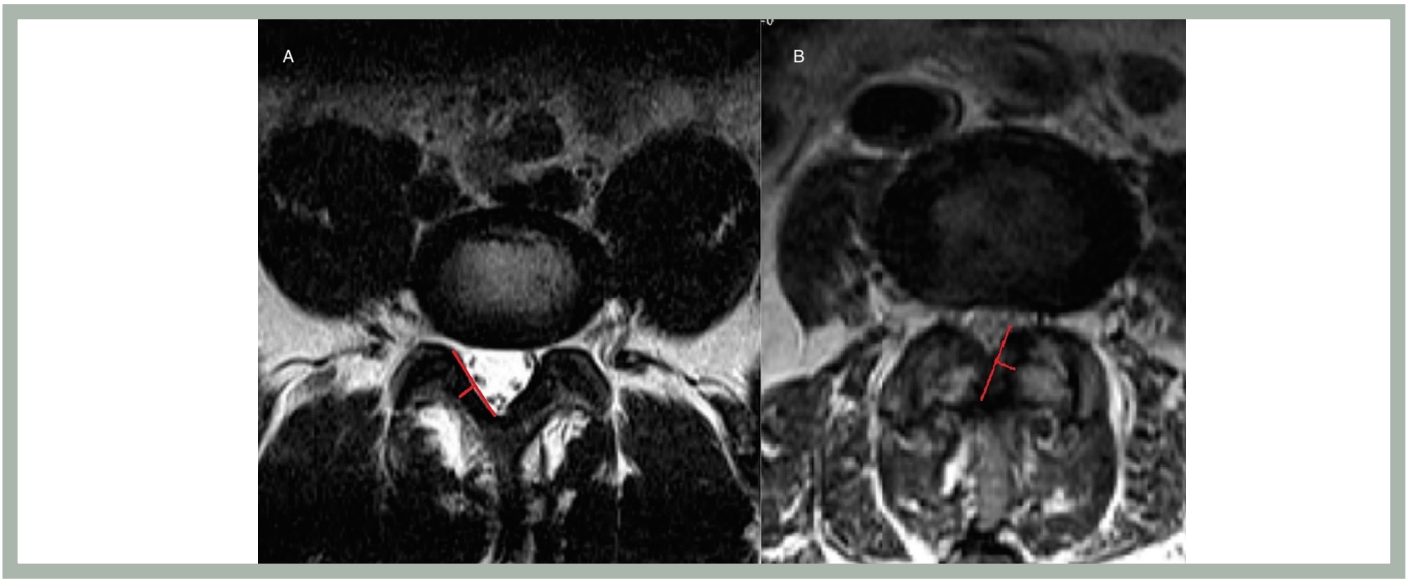

Figure 2. Left (A): axial T2-weighted MRI in a patient with isthmic spondylolisthesis showing that ligamentum flavum thickness is not increased and there is no facet degeneration in the adjacent segment. Right (B): axial T2-weighted MRI in a patient with degenerative spondylolisthesis showing that ligamentum flavum thickness is increased and there is facet degeneration in the adjacent segment

MRI: Magnetic resonance imaging

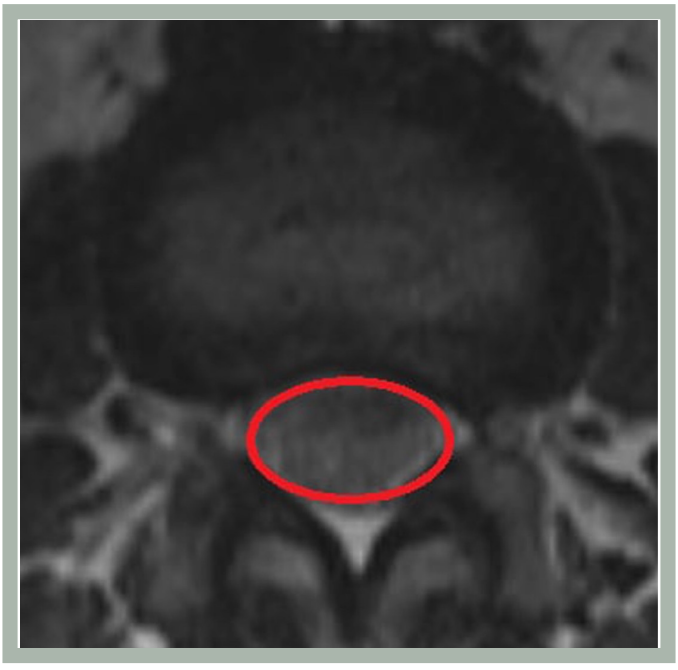

Figure 3. Axial T2-weighted MRI in a patient showing spinal dural sac area at the level of the disc

MRI: Magnetic resonance imaging

Statistical significance was found between the two types of spondylolisthesis in all patients for the upper segments (p=0.004). However, no statistical significance was observed between the two types of spondylolisthesis in all patients for the lower segment (p=0.480), in patients with L4-L5 level spondylolisthesis for the upper segment (p=0.054), and in patients with L4-L5 level spondylolisthesis for the lower segment (p=0.063).

Degenerative Changes in the Discs at the Neighboring Upper and Lower Levels

The disc degeneration values obtained in all patients for the degenerative and isthmic types were 3.09±0.73 and 2.69±0.73 for the upper segment and 3.13±0.96 and 2.95±0.74 for the lower segment, respectively. The values obtained for L4-L5 spondylolisthesis for the degenerative and isthmic types of spondylolisthesis were 3.18±0.59 and 2.72±0.89 for the upper segment and 2.09±1.06 and 2.89±0.76 for the lower segment, respectively. Statistically significant differences were determined between the two types of spondylolisthesis in all patients for the upper segment (p=0.003). There were no statistically significant differences identified between the two types of spondylolisthesis in all patients for the lower segment (p=0.430), in patients with spondylolisthesis at the L4-L5 level for the upper segment (p=0.059), and in patients with spondylolisthesis at the L4-L5 level for the lower segment (p=0.503).

Facet Hypertrophy at the Superior and Inferior Adjacent Levels (Figure 4)

The values obtained for facet hypertrophy in all patients with the degenerative and isthmic types of spondylolisthesis were 1.41±1.14 and 1.02±1.12 for the upper segment and 1.47±1.27 and 1.19±1.17 for the lower segment, respectively.

In individuals diagnosed with spondylolisthesis specifically at the L4-L5 level, the values for the degenerative and isthmic types were 1.18±1.14 and 1.11±1.18 for the lower segment and 1.55±1.22 and 1.11±1.32 for the upper segment, respectively. However, there were no statistically significant differences observed between the two types of spondylolisthesis in all patients for the upper segment (p=0.059), in all patients for the lower segment (p=0.405), in patients with L4-L5 level spondylolisthesis for the upper segment (p=0.288), and in patients with L4-L5 level spondylolisthesis for the lower segment (p=0.849).

Changes in the Disc Contour at the Superior and Inferior Adjacent Levels (Figure 5)

The disc contour values obtained in all patients for the degenerative and isthmic types of spondylolisthesis were 1.66±1.12 and 1.57±0.93 for the lower segment and 1.80±1.16 and 1.25±0.84 for the upper segment, respectively. The values obtained for L4-L5 level spondylolisthesis for the degenerative and isthmic types were 1.64±1.22 and 1.61±0.98 for the lower segment and 1.68±1.09 and 1.00±0.69 for the upper segment, respectively. Statistical significance was observed between the two types of spondylolisthesis in all patients for the upper segment (p=0.014) and in patients with L4-L5 level spondylolisthesis for the upper segment (p=0.021). No statistically significant differences were found between the two types of spondylolisthesis in all patients for the lower segment (p=0.899) and in patients with L4-L5 level spondylolisthesis for the lower segment (p=0.944).

Discussion

The degenerative and isthmic types of spondylolisthesis are the prevailing forms. These types differ in their causes, mechanisms of development, natural progression, and treatment approaches. The ethmic type is characterized by a fibrous loss in the ethmic region of the posterior arch, leading to forward protrusion of the upper vertebral body and separation from the neural arch on the anterior surface. This type is primarily caused by repetitive anterior and posterior bending, often associated with stress fractures resulting from extension. It is frequently observed between the fifth lumbar (L5) and the first sacral (S1) vertebrae, and it tends to occur more frequently in men. In adults, the lesion can lead to instability and degenerative changes that can cause nerve compression, neurological symptoms, and severe pain and often require surgical intervention. Conversely, the degenerative type of spondylolisthesis arises from degenerative alterations and instability in the lumbar area, leading to the enlargement of bones and soft tissues (11). This type presents with back pain and neurological symptoms (12). The degenerative type frequently between the fourth and fifth lumbar vertebrae and has a higher incidence rate in men.

Both isthmic and degenerative spondylolisthesis exhibit a progressive degenerative process as individuals age. However, they can be distinguished by their underlying causes, pathogenesis, and natural progression. The factors causing the degenerative and isthmic types of spondylolisthesis, and the spondylolisthesis itself, produce some changes in

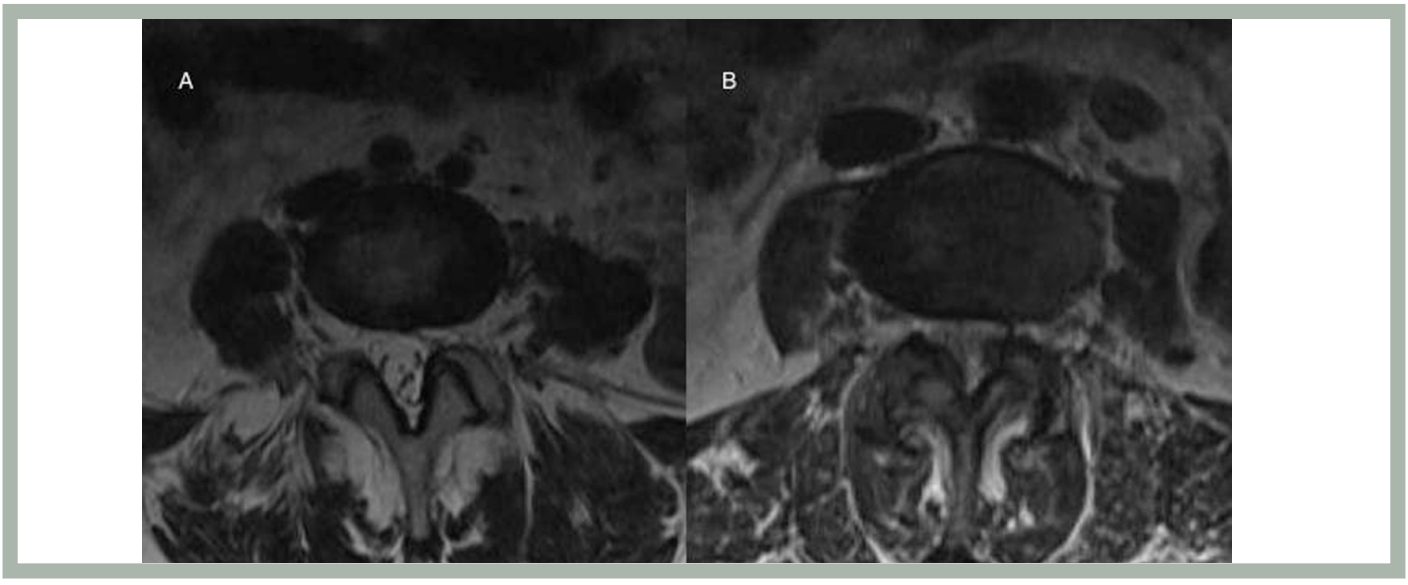

Figure 4. Left (A): axial T2-weighted MRI in a patient with isthmic spondylolisthesis showing mild facet hypertrophy. Right (B): axial T2-weighted MRI in a patient with degenerative spondylolisthesis showing severe facet hypertrophy

MRI: Magnetic resonance imaging

adjacent segments. The adjacent segments of degenerative and isthmic spondylolisthesis exhibit distinct characteristics in terms of degeneration and pathogenesis. However, there is limited research on the degenerative features of these adjacent segments in both types of spondylolisthesis. Jeong et al. (13) conducted a study using plain radiographs and MRI to evaluate the extent of degenerative changes and related factors in the lesion segments and their adjacent superior and inferior segments. They discovered that high-intensity zone lesions were more common in the superior segment above the lesion in islamic spondylolisthesis than in the degenerative type. Another study by Saleem et al. (14) investigated the relationship between various aspects of lumbar degenerative disc disease, MRI findings, and symptomatology. They found that the most commonly affected lumbar discs associated with degeneration leading to herniation and stenosis were L4-L5 and L5-S1, which could be attributed to long-standing degeneration and changes in disc resilience. Wan examined the biomechanical effects of interspinous spacer (X-stop) implantation on the area of the implant area and adjacent segments through computed tomography scanning (15). The study showed that X-stop implantation effectively expanded the dimensions of stenotic spinal segments but had minimal immediate biomechanical impact on the adjacent superior and inferior levels. In our present study, we examined MRI images of the affected segment as well as the neighboring upper and lower segments in both isthmic and degenerative spondylolisthesis cases to evaluate the level of degeneration in the adjacent segments.

Limited research has been conducted on the measurement of disc height in the adjacent upper and lower segments in cases of degenerative and ethmic spondylolisthesis using MRI. In our studydisc space height was higher in the adjacent upper and lower segments of ithmic spondylolisthesis compared with the adjacent upper and lower segments of degenerative spondylolisthesis. This difference was statistically significant

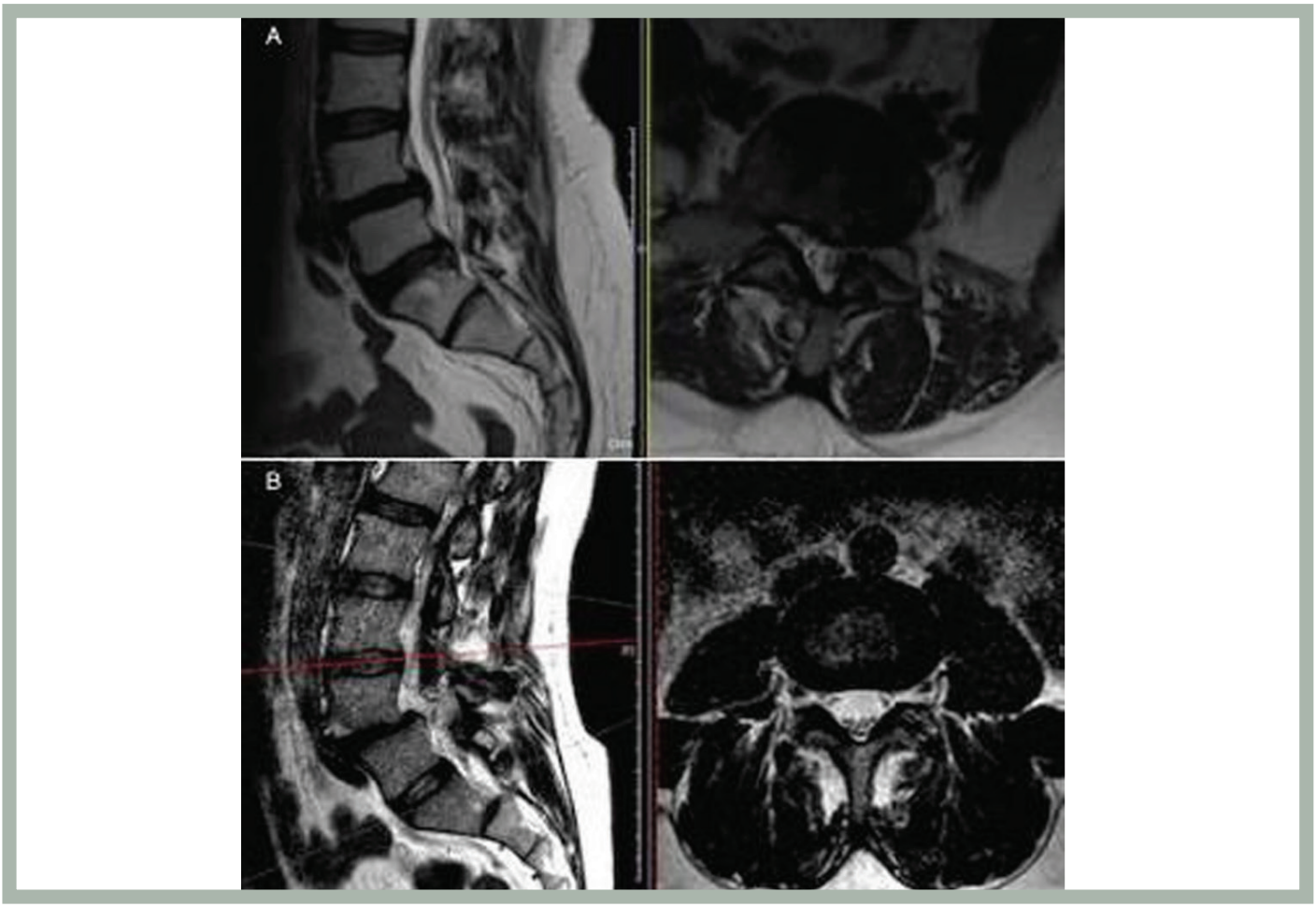

Figure 5. Upper figures (A): T2-weighted MRI in a patient with degenerative spondylolisthesis showing grade 4 disc herniation in the adjacent segment. Lower figures (B): T2-weighted MRI in a patient with isthmic spondylolisthesis showing no disc herniation in the adjacent segment

MRI: Magnetic resonance imaging

between the two types of spondylolisthesis in all patients for the upper segment (p=0.003), in all patients for the lower segment (p=0.024), and in patients with L4-L5 level spondylolisthesis for the upper segment (p=0.005). Loss of disc space height means more degeneration; however, our data show that there is less degeneration in the adjacent upper and lower segments with isthmic spondylolisthesis compared with the adjacent upper and lower segments with degenerative spondylolisthesis.

The enlargement of the ligamentum flavum can reduce the posterior diameter of the spinal canal. However, in our study, we did not find any statistically significant differences in ligamentum flavum hypertrophy between the two types of spondylolisthesis in all patients, specifically in the adjacent upper and lower segments.

The narrowing of the cross-sectional area of the dural sac is an important sign of degeneration in the lumbar spine. In our study, statistical significance was observed between the two categories of spondylolisthesis in all patients for the upper segments (p=0.004). These data show that there is less degeneration in the adjacent upper segment with isthmic spondylolisthesis compared with the adjacent upper segment with degenerative spondylolisthesis.

Limited studies have investigated intervertebral disc degeneration in the neighboring upper and lower segments of islamic and degenerative spondylolisthesis using MRI. Our study revealed significant differences between the two types of spondylolisthesis in all patients regarding the upper segments (p=0.003). We observed that the adjacent upper and lower segments of isthmic spondylolisthesis exhibited lesser disc degeneration compared with the adjacent upper and lower segments of degenerative spondylolisthesis.

Facet hypertrophy refers to the enlargement of one or more facet joints, which play a crucial role in connecting the spinal vertebrae and enabling movement and flexibility. This enlargement typically occurs as a natural response of the body's healing mechanisms. To compensate, the body promotes the growth of bone tissue in the joints. However, this reaction leads to increased joint size and puts additional pressure on the surrounding areas. In some cases, facet hypertrophy can even result in the joints exerting pressure on the spinal nerves. In our study, we discovered that there was no statistically significant distinction in facet hypertrophy between the two types of spondylolisthesis in all patients, particularly in the neighboring upper and lower segments.

Changes in the disc contour are also important signs of degeneration. Our study shows that there are statistically significant changes in the disc contour between the two types of spondylolisthesis in all patients for the upper segment (p=0.014) and in patients with L4-L5 level spondylolisthesis for the upper segment (p=0.021). These data show less degeneration in the adjacent upper segment with isthmic spondylolisthesis compared with the adjacent upper segment with degenerative spondylolisthesis.

Disc space height measurements, the cross-sectional area of the dural sac, disc degeneration, and alterations in disc contour exhibit less favorable results in the neighboring segments of degenerative spondylolisthesis in contrast to the adjacent segments of isthmic spondylolisthesis. This difference can be attributed to the prolonged duration of degenerative changes affecting all segments of the lumbar spine in degenerative spondylolisthesis. Such effects may contribute to the occurrence of spondylolisthesis in one segment and subsequent degeneration in the surrounding segments. The increased degeneration observed in adjacent segments of degenerative spondylolisthesis may necessitate the need for decompression and instrumentation across a larger number of spinal levels. Using the analyzed parameters as a predictor of further degeneration may be a subject for future investigation. Also, a new MRI classification of the adjacent levels and available treatment options are topics for further investigation.

Study Limitations

The relationship between demographic factors and the degenerative process was not studied, and this is a limitation of this study.

Conclusion

Due to different etiopathogenesis, degeneration appears quite different in the two types of spondylolisthesis. Degenerative spondylolisthesis progresses throughout all segments of the spine. The greater instability in islamic spondylolisthesis plays a role in the degeneration of the other segments. disc space height measurements, spinal dual sac transverse area, disc degeneration, disc contour, modic change, and Schmorl's node appear worse in adjacent segments of degenerative spondylolisthesis compared with isthmic spondylolisthesis.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Clinical Research Ethics Committee, Balıkesir University Faculty of Medicine, Balıkesir, Turkey (decision no. 2023/64 and date: 10/05/2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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CSMJ

Ultrasound-guided Botulinum Toxin Injection into the Salivary Glands for Treating Sialorrhea in a Case of Small-cell Lung Cancer

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What is known on this subject?

In cases resistant to medical treatment, botulinum toxin application with ultrasound guidance to the salivary glands appears to be an effective and safe method.

What this study adds?

Since this method is known for increased saliva, more studies are needed for this subject. Our case will add expert experience to the literature.

ABSTRACT

Sialorrhea or excessive drooling is an important problem known as saliva spillage from the mouth. Drooling may accompany many diseases, especially chronic neurological diseases and other chronic diseases. A 57-year-old female patient presented with a complaint of drooling that started after concurrent chemotherapy and radiotherapy due to small-cell lung cancer. The patient's complaints were significantly reduced with an ultrasound-guided botulinum toxin injection into the salivary glands.

Keywords: Sialorrhea, botulinum toxin, treatment, lung cancer

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Introduction

Sialorrhea is a clinical condition that occurs when saliva cannot be swallowed because of an increase in saliva secretion or a dysfunction in the coordination of the oral phase of the swallowing mechanism. Mental retardation and cerebral palsy in children, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and stroke in adults are the most common causes. Rare causes include oral inflammation (tooth, gum), drug adverse effects (clozapine, risperidone), gastroesophageal reflux, toxin exposure (mercury), and oral anatomical disorders (macroglossie). There are different treatment options ranging from conservative methods such as regulating eating habits, exercise, and intraoral devices to invasive methods such as botulinum toxin (BTX) application, radiotherapy (RT), and surgery (1).

Here we present a patient who was recently diagnosed with small cell lung cancer and underwent chemotherapy (CT), RT, and later developed sialorrhea that impaired the quality of daily life. The patient's complaints were significantly reduced with BTX, which we applied under ultrasound guidance as a treatment.

Case Report

A 57-year-old female patient presented with a complaint of increased saliva secretion. During the annual control of the patient

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who had tuberculosis 22 years ago, a mass was detected in the right bronchus and lung after the examination and tests performed in January 2020 with the complaint of influenza infection. After biopsy, she was diagnosed with small cell carcinoma. The patient gave a complete response to therapy after concurrent CT and RT (cisplatin + TNL 28 frc, 64.4 Gy). Then intensity modulated RT + image guided RT + volumetric modulated arc RT and linear accelerator technology were planned for the treatment.

Her habits are smoking (50 years*1 pack/day) and alcohol consumption socially.

She had a history of meningitis, breast fibroadenoma, operated myoma, and helicobacter pylori treatment. Currently, follow-up and treatments are performed by the gastroenterology clinic due to the problem of gastroesophageal reflux.

In the control fluorodeoxyglucose positron emission tomography (PET) examination, it was reported that the right hilar/paratracheal cardinal hypermetabolic mass and lymphadenopathy were not observed compared with pre-treatment PET. A grade II esophageal reaction was determined according to the Radiation Therapy Oncology Group acute radiation morbidity criteria. Electromyography was evaluated as normal.

When medical treatments (such as amitriptyline, propranolol, tropicamide) did not benefit, it was planned to administer 100 U of botulinum toxin type A (Botox® 100 U) under ultrasound guidance. Botox® 100 U was diluted with 2 cc of saline solution. Anesthesia was not used, and the area to be treated was cleaned locally. Under ultrasound guidance with a dental needle, BTX was performed on both parotid (35 U + 35 U) and submandibular glands (15 U + 15 U). There were no complications after the application. It was observed that there was a significant difference between the global impression of change scale (GICS) score before the application and the GICS score one week after the application (before: -3, after: +2).

Discussion

Although thoracic RT for lung cancer is generally well tolerated, acute esophagitis is the most prominent symptom during this treatment period. The RT technique and the radiation dose exposed by the esophagus are important factors in the incidence of esophageal toxicity. When 1/3 of the esophagus takes 60 Gy, the risk of complications in 5 years is 5%. The relationship with sialorrhea has been reported in conditions such as gastroesophageal reflux, esophagitis, and loss of motility (2,3). In this study, diagnosed with small cell lung cancer, 64.4-Gy RT were applied and then a grade II esophageal reaction was detected.

BTX application to salivary glands is a treatment option used for treating sialorrhea in PD, ALS, pseudobulbar, and bulbar palsy. In a placebo-controlled, randomized, double-blind study, they concluded that BTX application provides level I evidence for treating chronic sialorrhea. In this study, 184 patients (three groups; placebo-75 U-100 U BTX) were included. While the injection was performed in 104 (56.5%) of the patients with ultrasound guidance, the rest was done using anatomical landmarks. Most patients had PD (70.7%), and the remainder had stroke and traumatic brain injury. Dry mouth (5.4% and 2.7% of patients) and dysphagia (2.7% and 0% of patients) were seen as side effects in the 75 U and 100 U groups depending on the application (4). We applied 100 U in this study with ultrasound-guided BTX injection. In this study, the GICS score was +2 at the end of the first week and no adverse effects were identified. In another study, most of the cases were PD and ALS, and an ultrasound-guided BTX injection was applied to the parotid and submandibular glands to reduce saliva secretion. 100 U of BTX was used for each patient and diluted with 4 mL of normal saline. A local hematoma in the left submandibular area, which was the application site, was observed in one patient, and a non-severe dysphagia was observed in another patient. All patients started to feel the effects of the treatment one week after the application, and the activity lasted for an average of 4.5 months (3 months-9 months) (5). Because of the study, BTX applied to pathothyroid and submandibular glands under ultrasound guidance was found to be safe and effective. In this study, we diluted 100 U of BTX with 2 mL of normal saline. We used a dental needle and applied it to several different points in the gland. There were no local complications after the application. The effect started a week after the application.

RT and surgical procedures that can be applied to the parotid and submandibular glands should be the last choices to be considered in order to reduce salivary secretion (6).

As a result; increased salivary secretion may accompany chronic diseases, especially chronic neurological diseases. In cases resistant to medical treatment, BTX application with ultrasound guidance to the salivary glands appears to be an effective and safe method. Comparative studies are needed on this subject.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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CASE REPORT

81

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CSMJ

Moyamoya Case with Stenting for Basilar Stenosis

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What is known on this subject?

Surgical or endovascular interventions can be used in Moyamoya patients with recurrent progressive ischemic events and decreased cerebral perfusion.

What this study adds?

Endovascular treatment, as in Moyamoya disease, is a life-saving treatment option that is successfully applied in many diseases that cause severe cerebrovascular stenosis.

ABSTRACT

Moyamoya disease is a chronic, progressive hereditary disease characterized by narrowing of the vascular lumen because of hypertrophy of smooth muscles in the walls of the arteries that form the circle of Willis. Cerebral vessels may be encountered in bleeding and occlusion clinics. Although it is seen as predominant in Asian races, cases have been reported worldwide. Although its etiopathogenesis is not clear, genetics, some infectious agents, and autoimmune mechanisms are blamed. The gold standard in diagnosis is digital subtraction angiography. Surgical or endovascular interventions can be used in patients with recurrent progressive ischemic events and decreased cerebral perfusion. Here we present a 43-year-old Moyamoya patient who presented with posterior system findings and had a stent implantation with critical stenosis in the basilar artery.

Keywords: Moyamoya, stroke, basilar artery, stenosis, stent

Introduction

Moyamoya disease (MMD) is a progressive cerebrovascular disease characterized by narrowing of the lumen because of hypertrophy of smooth muscles in the vascular wall in the terminal part of the intracranial arteries (1). An increase in the collateral circulation in the leptomeningeal vessels is observed due to a decrease in brain perfusion. Because this vascular structure was likened to cigaret smoke by Suzuki and Takaku (2), who first described the disease in 1969 in cerebral angiographies, the disease was named "Moyamoya", which means cigaret smoke in Japanese. In Japan, where the number of cases is the highest, the annual prevalence is 3 in 100,000. The disease can be seen in children and adults and shows a bimodal course. It is two times more common in women than in men. It may present with intracerebral hemorrhage and stroke. Digital subtraction angiography (DSA) is the gold standard for diagnosis. Providing revascularization is important in treatment (3,4). Here, the clinical and radiological findings of the patient who

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presented with severe cognitive impairment and posterior system stroke findings were discussed.

Case Report

A 43-year-old female patient presented with complaints of diplopia and impaired speech. In her family history, it was learned that her mother died at the age of 30 due to intracranial hemorrhage. In her neurological examination, she was consciously cooperatively oriented, speech dysarthric, with inner gaze limited in the right eye, and horizontal nystagmus in the left eye was observed in the left eye. She had no motor or sensory impairment. In the laboratory examination, low-density lipoprotein was 160 mg/dL (0-100 mg/dL), and no significant pathology was observed in other blood tests. Computed tomography of the brain was normal. In diffusion magnetic resonance imaging (MRI), acute infarction was seen in the left half of the pons (Figure 1a, b). Her electrocardiography was in normal sinus rhythm, and her arrival blood pressure was measured as 150/100 mmHg. His treatment was arranged as acetyl salicylic acid (ASA) 100 mg/day + clopidogrel 75 mg + enoxaparin sodium 0.6 mL 2x1 subcutaneously. In the transthoracic electrocardiogram, the ejection fraction was 60% and no intracardiac mass/thrombus was detected. The thromophilia panel and vasculitis markers (such as protein C, protein S, antithrombin 3, factor 5 Leiden mutation, prothrombin 2 gene mutation, antinuclear antibody, complement levels, and other vasculitis markers) were normal. In cranial and cervical MR angiography, no flow was observed in both internal carotid arteries (ICA), and approximately 50% stenosis was observed in the distal of the basilar artery (Figure 2). In DSA, it was found that bilateral ICAs were occluded, and critical stenosis of up to 80% was in the distal part of the basilar artery. It was observed that cerebral circulation was provided through the vertebrobasilar system and leptomeningeal vessels (Figure 3a, b, c). On the 3rd and 7th days of the patient's hospitalization, diffusion MRIs taken due to clinical progression revealed new acute infarct areas in the right half of the pons, right temporal lobe, and centrum semiovale level. In his new neurological examination, consciousness was confused, and taking a single command, she had left hemiparesis (3/5). After the patient's clinical progression, it was decided to stent the basilar artery. The pre-procedure treatment was adjusted as ASA 100 mg/day + ticagrelor 120 mg/day. Under general anesthesia, first angioplasty and then a stent of the appropriate diameter were placed in the spleen in the distal part of the basilar artery (Figure 4). The mini-mental test score performed on the 5th day after the stent was found to be 27/30. Clinically, the patient who had no deficits other than -5/5 in left muscle strength was admitted to the neurology outpatient clinic under ASA 100 mg/day + clopidogrel 75 mg/day and was discharged. Of note, informed consent was signed by the patient for this report.

Discussion

Although the etiopathogenesis of MMD remains uncertain, MMD has been observed in the family in 7-12% of the cases, suggesting that autosomal dominant inheritance plays a

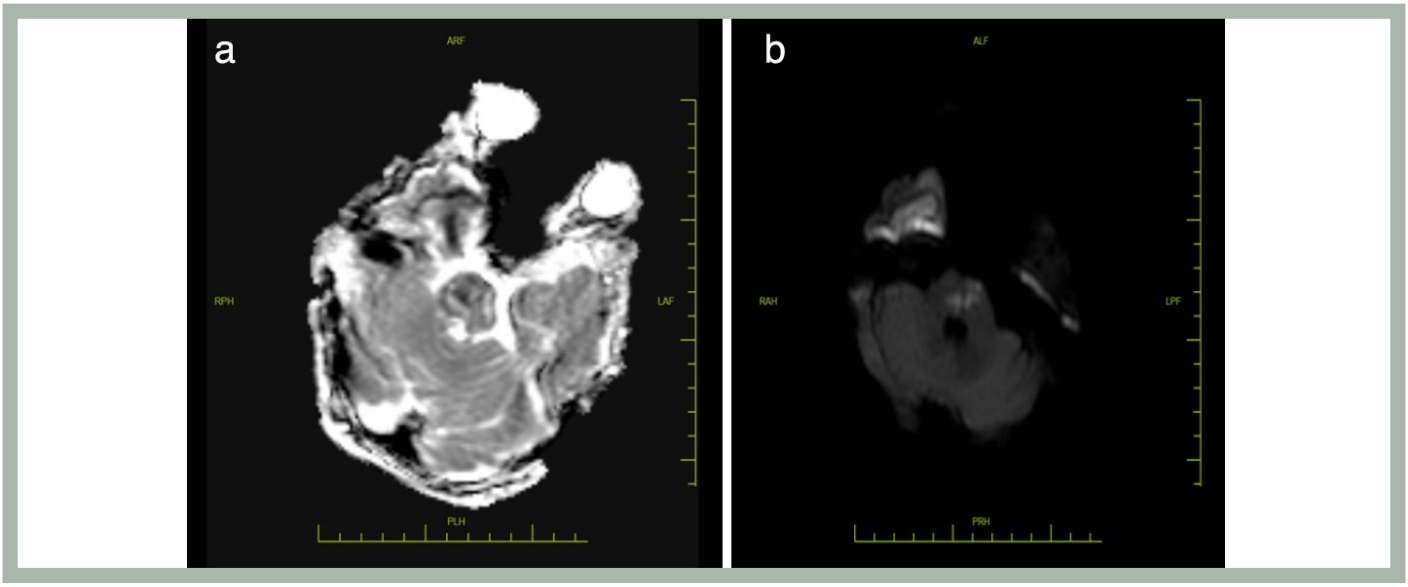

Figure 1. (a, b) ADC-DWI

ADC: Apparent diffusion coefficient, DWI: Diffusion weighted imaging

role in the transmission of the disease (5,6). Studies suggest that the disease may be associated with the *HLA DQB1*, *B51* genes and 3, 6, 8 and 17 chromosomes (7,8). Considering that the mother of our patient died at the age of 30 due to sudden intracerebral hemorrhage, we had cranial and cervical angiomas in two children of our patient, considering the risk of possible MMD genetic transmission. We found no significant pathology in imaging. We did not perform genetic analysis either. In addition, studies have shown that infectious agents and autoimmunity are effective in pathogenesis (9,10). The presence of hypothyroidism in the history of our patient may suggest this possibility. Studies have shown fibrocellular initial thickening in the affected vessels, proliferation in smooth muscle cells, increased elastin accumulation, and dilated, thin-walled, non-muscular collateral vessels in the subarachnoid space (11). Microaneurysms can often occur as a result of weakening of the vascular media layer. Approximately 25% of individuals diagnosed with MMD may have stenosis in the proximal part of the posterior cerebral arteries (12). Our patient had severe stenosis in the distal part of the basilar artery. MMD may present with migraine-like, medical treatment-resistant, recurrent headaches. Our patient had long-lasting migraine-like headaches. The clinic may differ in children and adults. Ischemia is more prominent in children and bleeding in adults (13,14). It manifests mostly as transient ischemic attacks in children. Hemorrhages may occur in intracerebral, intraventricular, subarachnoid, and subdural areas because of rupture of small microaneurysms and dilated vessels in the posterior circulation (14,15).

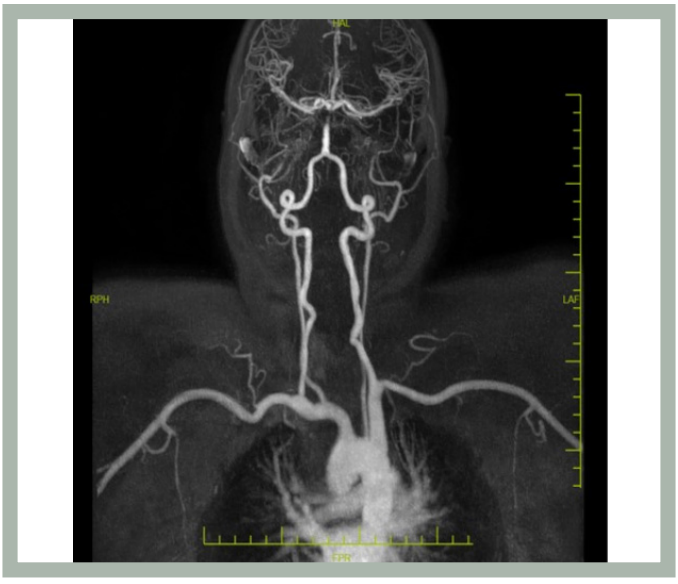

Figure 2. MRA

MRA: Magnetic resonance angiography

In MMD, the specificity of MRI has been reported as 100% and its sensitivity as 73%. When MRI-angiography is included, the sensitivity reaches 92% (16). On MRI, it is observed that the flow areas decrease in the terminal part of the middle cerebral artery, and the flow areas increase due to perforating vessels in the basal ganglion localization (17). The gold standard in diagnosis is DSA. With DSA, stenosis in the distal of the cerebral arteries, increased collateral network ofleptomeningalleptomeningeal arteries, and vascularization near the basal ganglia are observed. In our case, while no flow was observed in both ICAs, it was observed that the circulation of the anterior system was provided from the relative system

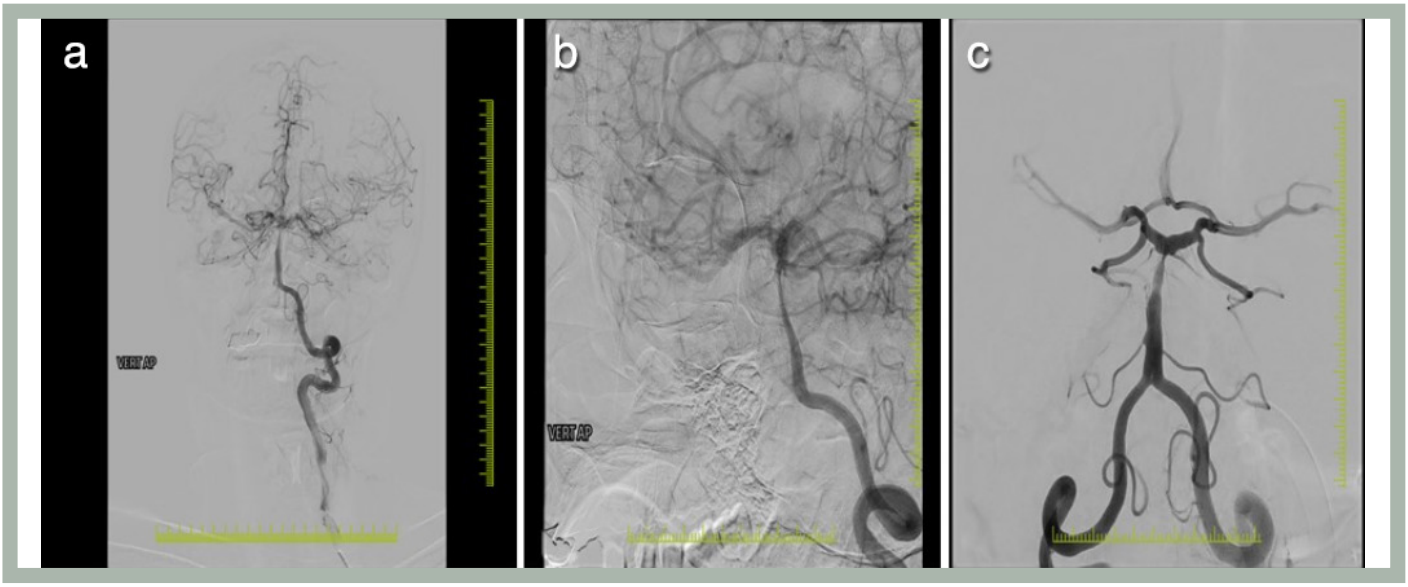

Figure 3. (a, b, c) DSA-before the procedure

DSA: Digital subtraction angiography

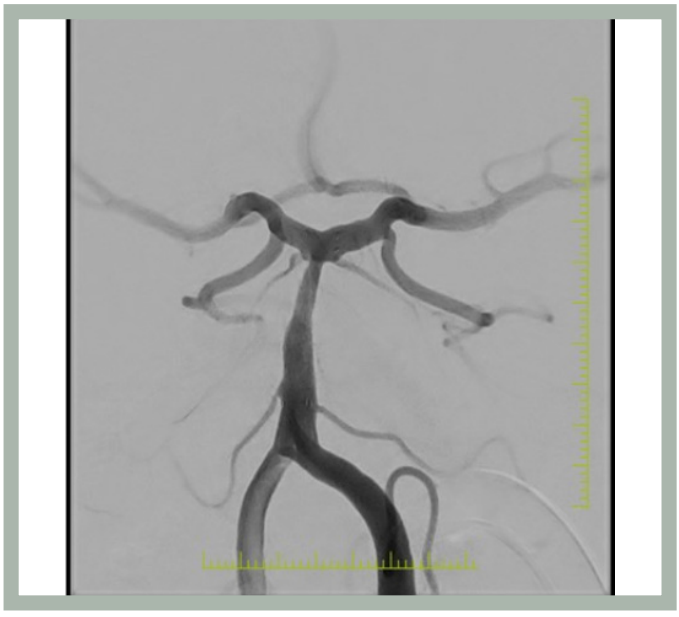

Figure 4. DSA-after the procedure

DSA: Digital subtraction angiography

through the Willis polygon and that the superior basilar artery was severely narrowed distally.

There is no definitive treatment for MMD, and the purpose of treatment is to minimize the ischemic process and reduce the risk of bleeding. Steroids, anticoagulants, antiaggregants, and vasodilators can be used in medical treatment, but their efficacy is controversial (3). Our patient continued to have ischemic attacks under dual antiaggregant and anticoagulant therapy. Some studies have shown the positive effects of the calcium channel blockers used in resistant headaches and the reduction in the frequency and severity of transient ischemic attacks (13). Endovascular and surgical treatment options are also used in addition to medical treatment. Few reports have been published detailing endovascular approaches to MMD (18). The stent-assisted angioplasty procedure, which is advantageous due to its less invasiveness, is technically suitable and safe for the treatment of selected patients with intracranial atherosclerotic stenosis. Endovascular embolization of intracranial aneurysms accompanying MMD is also possible. In our patient, time was gained by delaying the development of new collateral network formation in the anterior circulation with the basilar artery stenting strategy. Surgical interventions to increase cerebral blood flow are used in patients with recurrent progressive ischemic events and reduced cerebral circulation network. Surgical approaches can be applied under direct, indirect, or combined techniques. In the direct surgical approach, bypass of the superficial temporal or middle meningeal artery with the distal parts of the middle cerebral artery or anterior cerebral artery and anastomoses of the occipital artery with the posterior cerebral artery are options (19,20). Dura, temporal muscle, and galea can be used in indirect surgical techniques; thus, it is aimed to induce spontaneous angiogenesis with peduncle tissue (21). The incidence of stroke in the first five years after surgery is almost below 5%. Recurrent episodes of stroke and early onset of the disease are poor prognostic factors. Morbidity is more than 70% in untreated patients (16,22). Progressive course can be seen in patients whose early diagnosis is delayed and appropriate treatment cannot be provided, and due to this situation, irreversible cortical atrophy and mental retardation can be observed in patients. Our patient had recurrent ischemic attacks, cognitive loss, and impaired consciousness. Increasing brain perfusion was achieved by stenting the basilar artery with endovascular treatment. After this treatment, it was observed that the neurological deficit was almost completely resolved and the cognitive loss completely regressed.

As a result, endovascular treatment, as in MMD, is a life-saving treatment option that is successfully applied in many diseases that cause severe cerebrovascular stenosis.

Ethics

Informed Consent: Informed consent was signed by the patient for this report.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K., U.D., T.G., M.C., Concept: Ö.K., U.D., T.G., M.C., Design: M.Ç., Data Collection or Processing: K.T., A.Ö., Literature Search: K.T., A.Ö., M.Ç., Writing: K.T., A.Ö., M.Ç.

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

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