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INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2023;14(50)

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Journal's History

Journal's Previous Name	Parallel Title	ISSN	Years
Mustafa Kemal Üniversitesi Tıp Fakültesi Dergisi	Medical Journal of Mustafa Kemal University	1308-7185	2010-2014
Mustafa Kemal Üniversitesi Tıp Dergisi	Medical Journal of Mustafa Kemal University	2149-3103	2015-2022

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INDEXED BY

TUBITAK TR INDEX

Türkish Medline

Turkish Citation Index

DOAJ

Index Copernicus World of Journals

The Journal is committed to practice the publication ethics and takes all possible measures against any publication malpractices.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Interdisciplinary Medical Journal

Volume 14, Issue 50, 2023

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INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2023;14(50)

ABOUT

Interdisciplinary Medical Journal is an open access scientific journal, which publishes original contributions in clinical disciplines pertaining to human medicine. In this context, the Journal publishes original research, case reports and reviews based on clinical studies having interdisciplinary approach on medicine. The Journal is official publication of Hatay Mustafa Kemal University, Faculty of Medicine. The manuscript evaluation is based on the principles of blind peer-review process. It is published online three times a year on April, August, and December. The communication, review and publication language of the Journal is English. Manuscripts submitted for publication in the journal should be prepared in accordance with research and publication ethics. All manuscripts should be submitted by online system of the Journal. All manuscripts submitted to the Journal are screened in terms of originality.

Focus & Scope

Interdisciplinary medicine can be defined as "an interdisciplinary approach that relies on health professionals from different disciplines, along with the patient, working collaboratively as a team. The most effective teams share responsibilities and promote role interdependence while respecting individual members' experience and autonomy.

By supporting the interdisciplinary research on medicine, The Journal aims to;

Publish original contributions from different scientific disciplines through the advisory board covering a wide range of clinical medical disciplines,

Offer all its content freely available without charge to the user or his/her institution, to make research freely available to the public, and to support a greater global exchange of knowledge,

By permitting authors to enter into separate, additional contractual arrangements for the non-exclusive distribution of the journal's published version of the work (e.g., post it to an institutional repository or publish it in a book), to lead productive exchanges, as well as earlier and greater citation of published work.

Subject areas include, but are not restricted to the **clinical studies** of the following fields:

First Aid and Emergency Medicine

Family Medicine

Public Health and Preventive Medicine

Internal Diseases

General Surgery

Gynecology and Obstetrics

Ear, Nose and Throat Diseases

Eye Diseases

Orthopedics and Traumatology

Radiology and Radiodiagnostics

Anesthesia and Intensive Care Medicine

Adolescent Diseases

Childhood Diseases

Multisystem Diseases

Physical Medicine and Rehabilitation

Forensic Medicine

Mental Health and Diseases

Cardiovascular System Diseases

Nervous System Diseases

Neurosurgery

Respiratory System Diseases

Infectious Diseases

Occupational Diseases

Nuclear Medicine

Oncological Diseases

Sports Medicine

Genetic Diseases

Medical Pathology

The journal covers all relevant branches in **clinical medicine** specialties of the topics mentioned above.

Audience

Academicians, specialist physicians and research assistants in surgical and non-surgical medical disciplines and general practitioners.

Abstracting and Indexing

Interdisciplinary Medical Journal is indexed by TÜBITAK TR Index, Turkish Medline, Turkish Citation Index, DOAJ and Index Copernicus World of Journals

Editorial Policy

The editorial and publication processes of the journal are shaped in accordance with the guidelines of The International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of

Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).

Peer-Review Policy

Initial Manuscript Evaluation

For consideration, all manuscripts should be submitted by online system of The Journal at https://dergipark.org.tr/en/pub/interdiscip. The whole editorial process of The Journal is done via online submission system and can be documented in case of a conflict or objection.

The suitability of papers for publication in The Journal is decided by the editorial policy of the editorial board.

Editor-in-Chief is fully authorized for reviewing process, which is processed in the order of submission to The Journal.

Editor-in-Chief assigns either one of the Co-Editors or himself in order to perform initial assessment. Then, the assignee conducts initial pre-refereeing checks to ensure the article is legible, complete, correctly formatted, original, within the scope of The Journal, in the style of a scientific article and written in clear language.

Ethical Declaration

The Journal is committed to practice the publication ethics and takes all possible measures against any publication malpractices.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.Identifying information, including names, initials, or autopsy numbers of the patients/deceased should not be exposed in written descriptions or photographs in no ways. Identifying details should be omitted if they are not essential. Informed consent should be obtained in human studies and it should be stated in the manuscript.

Human and Animal Rights: For the experimental, clinical and drug human studies, approval by ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 2013, www.wma.net) are required. In experimental animal studies, the authors should indicate that the procedures followed were by animal rights (Guide for the care and use of laboratory animals, https://nap.nationalacademies.org/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals), and they should obtain animal ethics committee approval. The Ethics Committee approval document should be submitted to the The Bulletin of Legal Medicine together with the manuscript.

The approval of the ethics committee, statement on the adherence to international guidelines mentioned above and that the patient's informed consent is obtained should be indicated in the Method section and is required for case reports whenever data/media used could reveal the identity of the patient. The declaration of the conflict of interest between authors, institutions, acknowledgement of any financial or material support, aid is mandatory for authors submitting a manuscript, and the statement should appear at the end of the manuscript. Reviewers are required to report if any potential conflict of interest exists between the reviewer and authors, institutions.

For persons under 18 years of age, please provide a consent form that includes both parents' signatures or of the person's legal guardian or supervisor.

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2013. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Check for Plagiarism

The Journal is a member of Crosscheck, and all manuscripts are screened by Crosscheck in terms of originality. If serious issues are identified concerning the manuscript, the assignee will notify the corresponding author as part of our standard procedure. No action is required from you unless specifically requested for very serious concerns.

Any article that has problems with any of the above criteria may be rejected at this stage. Manuscripts rejected at this stage typically are not in line with the focus and scopes of the journal. Essays that pass through this stage are then entered into the peer review process.

Manuscript Files

This journal follows a double-blind reviewing procedure. Authors are therefore requested to submit; a blinded manuscript, and a separate title page file.

You may download full manuscript and blinded manuscript templates by following the links on Journal's homepage.

1) Blinded Manuscript File: This is the blinded manuscript file that will be presented to the reviewers. The main text of the article, beginning from Abstract till References (including tables, figures or diagrams) should be in this file. The file must not contain any mention of the authors' names or

initials or the institution at which the study was done, ethical committee or acknowledgements. Self-identifying citations and references in the article text should be avoided.

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After assigned, the reviewers are invited to participate the review process via a notification email. The email invitation to reviewers will contain all necessary information about the manuscript. The reviewers are asked to log into the journal web site to indicate whether they will undertake the review or not, as well as to access the submission and to record their review and recommendation.

Automated email reminders are sent to the reviewer when the reviewer does not respond to a review request within 15 days. The typical period of time allowed for reviews is 4 weeks but note that it can be modified during the editorial process.

Peer Review Reports

Reviewers make one of the following recommendations to the Editors: accept submission, minor revision, major revision, decline submission. Additionally, reviewers are asked to provide significant commentary for authors and are also provided space to make comments intended solely for the editors. Reviewers are not asked or expected to make any copyediting comments.

If both reviewers agree on acceptance or rejection, the decision stands.

Occasionally, we receive contradicting Reviewers' reports and need to ask for a third reviewer, which does delay the process. When their opinions are poles apart, then the Associate Editor takes a further process to decide acceptance or rejection of that paper. For the further process, Associate Editors request an emergency review by another advisory board member. Associate Editors may take a further process for the manuscript of which reviewing process is overdue.

If a paper is not suitable for publication it will be returned to the author with a statement of reasons for rejection. The author may appeal if he or she believes an erroneous or unfair judgment has been made. A letter to the Editor-in-Chief presenting reasons why the decision should be reconsidered will be subjected to due consideration.

After review, the author is notified by email for revision in accord with suggestions made by the reviewers and the Editor.

At the completion of each round of the peer review process, the submitter receives a formal letter from the Editor that includes notes from the Peer Reviewers.

When authors make revisions to their article in response to the referees' comments, they are asked to submit a list of changes and any replies for transmission to the referees. The author must upload the revised manuscript to the online system within 4 weeks; otherwise, the author will be notified that the paper will be considered withdrawn.

The revised version is usually returned to at least one of the original referees who is then asked whether the revisions are satisfactory. If the referees remain dissatisfied, the paper can be referred to the advisory board of the journal for further consideration.

The assignee then, will check if the manuscript is revised as suggested by editorial members and proceed to the next step. If the assignee finds the revisions satisfying, then he or she will record the decision to accomplish the review process and reach final decision.

Decision Making Process

Based upon two or more reviewers' reports, the Co-Editors are responsible for making the decision regarding acceptance or rejection each essay and for communicating this decision to the submitter. At the completion of the peer review process, each submitter receives a formal letter from the Editors that includes notes from the Peer Reviewers.

The final decision by Editor-in-Chief is usually completed within 2 months from the time of the paper submission.

Authors are notified by e-mail when a manuscript has or has not been accepted for publication. Proofs of accepted manuscripts are sent to the author for correction within 4 weeks after acceptance. They should be proofread carefully according to the instructions attached and returned within the considered period. Authors will be charged for major corrections to their proofs.

For 2020, average days required to complete the review process is 120 days, whereas average days that pass till publication is 180 days.

Publication Frequency

Interdisciplinary Medical Journal publishes three issues online in April, August and December. The communication, review and publication language of the Journal is English.

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Author Guide

Dear author,

Thank you for your interest in submitting your manuscript to Interdisciplinary Medical Journal for editing and publication consideration. In order to facilitate preparation and submission of your manuscript, we have prepared this guideline explaining basic points that should be taken into account when preparing the paper.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines.

2. Where available, DOIs for the references list have been provided.

3. During the online submission, I undertake to enter the names of all the authors in the manuscript, their positions, ORCID ID*** information and the contact details of the responsible author.

*** The publication of ORCID ID information of all authors is mandatory by TUBITAK ULAKBIM Index.

4. By 2020, in accordance with the TR Directory Rules, the authors have to submit an official letter with an Ethical Commission report or equivalent for the works requiring ethics committee permission.

5. Blinded manuscript file to be sent to the reviewer,

6. Title page, A separate title page file containing article title; academic titles, areas of expertise, affiliations, and e-mail addresses each author; contact address of the corresponding author, disclaimer, financial resources of the study, information on whether there is a conflict of interest, article title, short title, thanks and authorship contribution.

7. The author agreement form has been signed by the corresponding author and prepared for submission.

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8. Blinded manuscript file and title page file are in the Microsoft Word file format.

Writing Rules

In order to prevent waste of effort and time, and to evaluate the manuscript drafts you send to Interdisciplinary Medical Journal, you must use Interdisciplinary Medical Journal templates, which you can download to your computer using the links on the journal homepage, and which contain explanations for the writing rules in the comments section.

The Journal is official publication of Hatay Mustafa Kemal University, Faculty of Medicine. It is an open access scientific journal, being published three times a year and peer reviewed. The Journal aims to publish original contributions based on clinical studies having interdisciplinary approach on medicine. The publication language of the journal is English.

Subject areas include, but are not restricted to the **clinical studies** of the following fields: first aid and emergency medicine, family medicine, public health and preventive medicine, internal diseases, general surgery, gynecology and obstetrics, ear, nose and throat diseases, eye diseases, orthopedics and traumatology, radiology and radiodiagnostics, anesthesia and intensive care medicine, adolescent diseases, childhood diseases, multisystem diseases, physical medicine and rehabilitation, forensic medicine, mental health and diseases, cardiovascular system diseases, nervous system diseases, neurosurgery, respiratory system diseases, infectious diseases, occupational diseases, nuclear medicine, oncological diseases, sports medicine, genetic diseases, medical pathology.

The journal covers all relevant branches in **clinical medicine** specialties of the topics mentioned above.

Audience

Academicians, specialist physicians and research assistants in surgical and non-surgical medical disciplines and general practitioners.

Manuscript Preparation

All manuscripts which will be published in the journal must be in accordance with research and publication ethics. All authors should have contributed to the article directly either academically or scientifically. Presentations at congresses or in symposia are accepted only if they were not published in whole in congress or symposium booklets and should be mentioned as a footnote.

Manuscripts are received with the explicit understanding that they have not been published in whole or in part elsewhere, that they are not under simultaneous consideration by any other publication. Direct quotations, tables, or illustrations that have appeared in copyrighted material must be accompanied by written permission for their use from the copyright owner and authors. All articles are subject to review by the editors and referees.

Process of Peer Review

The journal utilizes a standard online site (https://dergipark.org.tr/en/pub/interdiscip), supported by Tubitak Ulakbim, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration of publication to the journal, the journal manager and editorial staff review the submission to assure all required components as outlined in this Guide for Authors are included. The manuscript is then assigned to one of the co-editors (either the editor in chief or an associate editor) who directs and oversees the peer-review process. The co-editor then reviews the submission for relevance, content and quality. Those submissions deemed appropriate for consideration of publication are then assigned to at least two peer reviewers. In order for a manuscript to be considered for publication, it must be original and significant, providing a contribution to research and importance to field. In general, there should be no flaws in the specific procedures used in performance of the study, or in the logic used for the interpretation of the data. It is important that the results of the study support its conclusions, and that there are no errors in reference to prior work (or no exclusions of pertinent references). Where appropriate, confirmation of regulatory review (such as institutional review board approval) must be present. The validity of the statistics used (often including a justification of a sample size) to analyze data is necessary, and the data presented in the figures and tables should be reflective of the results presented and adequate to justify the study conclusions. In general, the manuscript length and quality of the writing are important to ensure its quality.

When the editor has a full complement of reviews completed, the editor reviews the comments and recommendations, and a decision regarding the suitability for publication of the manuscript is made. Acceptance is based on significance, and originality of the material submitted. If the article is accepted for publication, it may be subject to editorial revisions to aid clarity and understanding without changing the data presented.

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

About the scientific language to be used in writing your manuscript

In line with the recommendation of the international directories we applied to increase the scientific effectiveness of our journal and enrich its content, our Editorial Board has decided that the studies to be published in English. So, the manuscripts sent to our journal are subject to English language control and revision.

Our experience from previous articles has shown that most of the articles prepared in English need to be improved in terms of fluent readability and intelligibility, as well as scientific and technical examination. Most of the manuscripts should undergo a comprehensive review and revision process in terms of language, before they were included in the review stage.

Therefore, we recommend that you receive professional English editing and proofreading services before submitting your manuscript to our journal, although it is not mandatory.

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By uploading the revised English full text of your manuscript to our Journal system by ensuring that English Editing and Proofreading is carried out by a local or foreign professional, you may minimize the possibility of rejection due to translation errors.

Use of first person

In addition, it is necessary to make the necessary checks and revisions in terms of language of your work and to ensure integrity in terms of language and time use throughout the entire article.

Expressions such as ... "Our study, in our study, we, we did, we found, we aimed, I did, I found, I think ... etc." should be revised as follows;

- In this study, ... it was found/determined/... or
- In this study ... it was aimed to ...

Names made up of single word should not be abbreviated.

Instead of,

- Hypertension (HT) is one of the most ...

Throughout the manuscript, you should use;

- Hypertension is one of the most ...

Instead of,

- Rituximab (RTX) is an IgG1 kappa chimeric monoclonal

Throughout the manuscript, you should use;

• Rituximab is an ...

Numbers should always be used to indicate statistics, age and measurements (including time as in the 3 weeks example). In specifying the others, only the numbers one to nine should be written in letters. (Numbers between 1-10 should be written with letters, except for the date and number of cases)

For example;

• In 2 studies, ...

Should be replaced with;

• In two studies ...

For example;

• ... perivascular lymphotic infiltration in only 10 percent and fibrosis in 7 percent of the patients,

Should be replaced with;

• ... perivascular lymphotic infiltration in only 10% of patients ... in 7% of patients ...

Prejudiced expressions should be avoided in expressions other than classical textbook knowledge, which has been verified by dozens of studies and has become the industry standard in the literature.

• determined to be high

Should be replaced with;

• ... was found to be high.

Or throughout the entire manuscript;

• found to be significantly higher ...

If diametrically opposite findings are mentioned among the studies mentioned in the Discussion section, it should be stated as "... a significant relationship was found / observed / reported", rather than "a significant relationship was determined" etc.

• While no significant relationship was determined between blood pressure and disease severity (26,27), a strong relationship was determined in some studies (28,29).

Should be replaced with;

While no significant relationship was observed between blood pressure and disease severity (26,27), it was reported that a strong relationship was found in some studies (28,29).

General Principles

The text of articles reporting original research should be divided into Introduction, Method, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

Sections of the manuscript

Article title

The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Information about the study design could be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Please avoid capitalizing all letters of the title and capitalize only the capital letter of first word of the title, proper nouns, proper adjectives. Other words and conjunctions (e.g., and, but, both, or, either, neither, nor, besides, however, nevertheless, otherwise, so, therefore, still, yet, though etc.) should be in small letters. No abbreviations or acronyms should be used within the titles.

Short title

You should add a running title not exceeding 40 characters to be placed at the header of the inner pages.

Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical method), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not overinterpret findings. Please, do not cite figures, tables or references in the abstract.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. All the articles submitted to the journal require to include abstract in English. Abstracts of original articles should not exceed 250 words.

Keywords

Three to six words or determinative groups of words should be written below the abstract. Abbreviations should not be used as keywords. Keywords in English should be chosen from MESH (Medical Subject Headings http://www.nlm.nih.gov/mesh) index. Abbreviations cannot be used as keywords, but instead they should be written explicitly. Letters that do not exist in Latin alphabet (e.g., alpha, beta, delta etc.) should be used with their pronunciation.

Examples: carbon monoxide, firearms, sexual abuse, oral mucosa

Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Method

The guiding principle of the Method section should be clarity about how and why a study was done in a particular way. The Method section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results.

The authors should clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), autopsied persons, including eligibility and exclusion criteria and a description of the source population.

In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the method section.

The Method section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Identifying information, including names, initials, or autopsy numbers of the patients/deceased should not be exposed in written descriptions or photographs in no ways. Identifying details should be omitted if they are not essential.

Informed consent should be obtained in human studies, and it should be stated in the manuscript.

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Statistical Analysis

The authors should describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. They should define statistical terms, abbreviations, symbols and should specify the statistical software package(s) and versions used.

Results

You should present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Please, do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Method Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

You should give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. You should restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Please, use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.” Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

Discussion

It is useful to begin the discussion by briefly summarizing the main findings and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular,

distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted but label them clearly.

In-text Citations and References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press". Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Laws (e.g., penal code), statutes and regulations are not scientific writings. In addition to being published on the official gazette, since it is published on various internet sites, a reference number should not be given to laws, statutes and regulations. If it is to be cited within the text, the law could be cited by specifying the number of the law, the date and number of publications in the official gazette (e.g., A Review of Article 5 of the Turkish Criminal Penal Code No. 5237). They should not be numbered within the text, or in the reference list.

To minimize citation errors, references can be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Reference list should be numbered consecutively in the order in which they are first mentioned in the text. Roman numerals should be avoided. Identify references in text, tables, and legends by Arabic numerals (1, 2, 3 ... 9, 0) in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals).

If you refer to a work more than once, use the first number also for the second and following references. References to more than one source in the same phrase may be entered like this: (2-4), i.e., references 2 through 4 in the reference list, and (2-4, 8), i.e. the references 2 through 4, plus reference no 8 in the list of references.

Sample for in-text citation:

In a clinical research in healthy individuals, Ellis (25) has studied the sciatic nerve excursion using ultrasound technique.

Wright and Ellis (10) has investigated the excursion of nerves around the elbow joint.

In another and similar cadaveric study by Wright et al (13), the radial nerve median excursion values were 4.1, 8.8, and 0.2, 0.1 mm with motions of shoulder, elbow, wrist and fingers respectively.

Suicide is a major public health problem and globally the second leading cause of death among young adults (1). Studies focusing on how mental health risk factors impact on youth suicidal behaviors suggest that psychopathological symptoms are associated with suicidal behavior (3,4). Adverse effects of H2S on human health vary from local irritation to immediate death depending on the form, concentration, duration and route of exposure (9, 13-15).

Reference Style

The Vancouver system, also known as Vancouver reference style or the author–number system, is a citation style that uses numbers within the text that refer to numbered entries in the reference list. Vancouver style is used by MEDLINE and PubMed. The names "Vancouver system" or "Vancouver style" have existed since 1978. The latest version of the latter is Citing Medicine, per the References > Style and Format section of the ICMJE Recommendations. In 1978, a committee of editors from various medical journals, the International Committee of Medical Journal Editors (ICMJE), met in Vancouver, BC, Canada to agree to a unified set of requirements for the articles of such journals. This meeting led to the establishment of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URMs). Part of the URMs is the reference style, for which the ICMJE selected the long-established author–number principle.

Since the early to mid-2000s, the United States National Library of Medicine (which runs MEDLINE and PubMed) has hosted the ICMJE's "Sample References" pages. Around 2007, the NLM created Citing Medicine, its style guide for citation style, as a new home for the style's details. The ICMJE Recommendations now point to Citing Medicine as the home for the formatting details of Vancouver style.

Interdisciplinary Medical Journal, since the first day of its publication uses the PubMed/NLM reference style. Thus, references list should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles web page and detailed in the NLM's Citing Medicine, 2nd edition.

According to the Vancouver rules, you can only refer to the literature you have read yourself. If you find anything interesting in a text where it is referred to another text, you must read and refer to the original.

References List

The references list should be ordered numerically in the order in which the references appear in the text.

The journal's name may be abbreviated, according to the abbreviation rules for journal titles. Records retrieved from a search for the full journal title in the National Library of Medicine's search page include the abbreviated title.

Authors' names should be given as surname followed by initials. There should be a space between surname and initials. A maximum of two initials are allowed for each author, they should be entered without spaces or punctuation. Different authors should be separated by a space and a comma. A period (.) should follow the last author's name. If six or more authors, list the first six authors followed by et al.

Only capital letter of the first word of the title, proper nouns, proper adjectives, acronyms, and initialisms should be capitalized.

The most reliable method for calculating the impact factor of our journal and number of citations of articles published in our journal or calculating the number of times your own article is cited in a healthy way, is to add DOIs to the references section. In order to give the DOIs to the articles published in Interdisciplinary Medical Journal, the CrossRef membership application has been completed and all the research articles, case reports, and reviews are being assigned DOIs. For this reason, DOIs need to be added to the References section if available for those references. We hope that the Simple Text Query Form will be helpful in referencing articles published in our journal.

With the help of the Simple Text Query Form web page, which has a link in the full-text template, DOI records need to be added to the sources.

https://apps.crossref.org/SimpleTextQuery

Note: Please, **do not insert Pubmed ID (PMID) or Pubmed Central ID (PMCID) records** to the reference list since they are useless in determining the citation counts.

We place great importance to the addition of DOIs to the references list.

Sample for Journal Article without DOI

Dokgöz H, Kar H, Bilgin NG, Toros F. Forensic Approach to Teenage Mothers Concept: 3 Case Reports. Turkiye Klinikleri J Foren Med 2008;5(2):80-4

Kaufman DM, Mann KV, Miujtjens AM, Van der Vleuten CP. A comparison of standard setting procedures for an OSCE in undergraduate medical education. Academic Medicine 2000;75:267–71.

Sample for Journal Article with DOI

Koçak U, Alpaslan AH, Yağan M, Özer E. Suicide by Homemade Hydrogen Sulfide in Turkey a Case Report. Bull Leg Med. 2016;21(3):189-192. https://doi.org/10.17986/blm.2016323754

Article not in English

Kar H, Dokgöz H, Gamsız Bilgin N, Albayrak B, Kaya Tİ. Lazer Epilasyona Bağlı Cilt Lezyonlarının Malpraktis Açısından Değerlendirilmesi. Bull Leg Med. 2016;21(3):153-158. https://doi.org/10.17986/blm.2016323748

Books and Other Monographs

Personal author(s)

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Editor(s), compiler(s) as author

Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

Author(s) and editor(s)

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113

Emmerson BT. Gout and renal disease. In: Massry SG, Glassock RJ (Editors). Textbook of Nephrology 1. Baskı, Baltimore: Williams and Wilkins; 1989. p. 756–760.

Conference proceedings

Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

Article published on the Internet ahead of the print version:

Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15;100(10):3828-31. Epub 2002 Jul 5.

Part of a homepage/Web site [Edited 28 Dec 2016]

American Medical Association [Internet]. Chicago: The Association; c1995-2016 [cited 2016 Dec 27]. Office of International Medicine; [about 2 screens]. Available from: https://www.ama-assn.org/about/office-international-medicine

Thesis

Skrtic L. Hydrogen sulfide, oil and gas, and people's health [Master's of Science Thesis]. Berkeley, CA: University of California; 2006.

Weisbaum LD. Human sexuality of children and adolescents: a comprehensive training guide for social work professionals [master's thesis]. Long Beach (CA): California State University; 2005. 200 p.

For the reference types not listed here, please visit Samples of Formatted References for Authors of Journal Articles available at Medline Web site (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

It would be appropriate to place the tables at the end of the main text. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text. Give each column a short or an abbreviated heading. In the tables, case counts (n) and percentages (%) should be specified in separate columns, not in the same cell.

Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes and use symbols to explain information if needed. Symbols may be as alphabet letters or such symbols as *, p t> T §). Please, identify statistical measures of variations, such as standard deviation and standard error of the mean.

Illustrations (Figures)

The lexical meaning of figure constitutes a number symbol (numeral, digit), a written or printed character, a diagram or pictorial illustration of textual matter, arithmetical calculation or digits representing an amount when plural. While definition of picture includes a design or representation made by various means (as painting, drawing, or photography), illustration means a picture or diagram that helps make something clear or attractive. Although these terms bear distinctive meanings, they are too often used interchangeably. Thus, we meant them in the same way without distinction.

Digital images

The 300 DPI Story

In the ancient times when digital cameras have not been invented, the photos taken by analogue cameras were used to be printed on photo papers. In order to transfer these photos to the digital environment, they had to be scanned by optical devices called scanners. On the same dates, desktop publishing and printing technology was far beyond the digital photography, and many years had passed since the invention of laser printing technology. Here, several technical terms should be explained to make the concept clearer. DPI is used to describe the resolution number of dots per inch in a digital print and the printing resolution of a hard copy print dot gain, which is the increase in the size of the halftone dots during printing. A dot matrix printer, for example, applies ink via tiny rods striking an ink ribbon, and has a relatively low resolution, typically in the range of 60 to 90 DPI (420 to 280 µm). An inkjet printer sprays ink through tiny nozzles and is typically capable of 300–720 DPI. A laser printer applies toner through a controlled electrostatic charge and may be in the range of 600 to 2,400 DPI. Along with the cheaper memory chips, 1200 dpi printers have been widely available in the consumer market since 2008. Monitors do not have dots but do have pixels. The closely related concept for monitors and images is pixels per inch or PPI. Old CRT type video displays were almost universally rated in dot pitch, which refers to the spacing between the sub-pixel red, green and blue dots which made up the pixels themselves. The DP measurement of a printer often needs to be considerably higher than the pixels per inch (PPI) measurement of a video display in order to produce similar-quality output. This dithered printing process could require a region of four to six dots (measured across each side) in order to faithfully reproduce the color in a single pixel. An image that is 100 pixels wide may need to be 400 to 600 dots in width in the printed output; if a 100×100-pixel image is to be printed in a one-inch square; the printer must be capable of 400 to 600 dots per inch to reproduce the image. The dpi of early model laser printers was 300 to 360, thus scanning images at 300 DPI was a common practice at that time.

In printing, DPI (dots per inch) refers to the output resolution of a printer or imagesetter, and PPI (pixels per inch) refers to the input resolution of a photograph or image. DPI refers to the physical dot density of an image when it is reproduced as a real physical entity, for example printed onto paper. A digitally stored image has no inherent physical dimensions, measured in inches or centimeters. Some digital file formats record a DPI value, or more commonly a PPI (pixels per inch) value, which is to be used when printing the image. This number lets the printer or software know the intended size of the image, or in the case of scanned images, the size of the original scanned object. For example, a bitmap image may measure 1,000 × 1,000 pixels, a resolution of 1 megapixel. If it is labeled as 250 PPI, that is an instruction to the printer to print it at a size of 4 × 4 inches. Changing the PPI to 100 in an image editing program would tell the printer to print it at a size of 10×10 inches. However, changing the PPI value would not change the size of the image in pixels which would still be 1,000 × 1,000. An image may also be resampled to change the number of pixels and therefore the size or resolution of the image, but this is quite different from simply setting a new PPI for the file.

Therefore, an image that is 2048 pixels in width and 1536 pixels in height has a total of 2048×1536 = 3,145,728 pixels or 3.1 megapixels. One could refer to it as 2048 by 1536 or a 3.1-megapixel image. Or you can think of it as a very low-quality image (72 ppi) if printed at about 28.5 inches wide, or a very good quality (300 ppi) image if printed at about 7 inches wide.

Since the 1980s, the Microsoft Windows operating system has set the default display "DPI" to 96 PPI, while Apple/Macintosh computers have used a default of 72 PPI. The choice of 72 PPI by Macintosh for their displays arose from the convenient fact that the official 72 points per inch mirrored the 72 pixels per inch that appeared on their display screens. (Points are a physical

unit of measure in typography, dating from the days of printing presses, where 1 point by the modern definition is 1/72 of the international inch (25.4 mm), which therefore makes 1 point approximately 0.0139 in or 352.8 µm). Thus, the 72 pixels per inch seen on the display had exactly the same physical dimensions as the 72 points per inch later seen on a printout, with 1 pt in printed text equal to 1 px on the display screen. As it is, the Macintosh 128K featured a screen measuring 512 pixels in width by 342 pixels in height, and this corresponded to the width of standard office paper (512 px ÷ 72 px/in ≈ 7.1 in, with a 0.7 in margin down each side when assuming 8.5 in × 11 in North American paper size (in Europe, it's 21 cm x 30 cm - called "A4")).

In computing, an image scanner—often abbreviated to just scanner, is a device that optically scans images, printed text, handwriting or an object and converts it to a digital image. Although the history of digital cameras dates back to the 1970s, they have become widely used in the 2000s. While the resolution of the first digital camera invented by Kodak was as low as 100 by 100 pixels (0.01 megapixels), the first commercially available digital camera, Fujix DS-1P had a resolution of 0.4 megapixels. On the other hand, modern scanners are considered the successors of early telephotography and fax input devices. The pantelegraph was an early form of facsimile machine transmitting over normal telegraph lines developed by Giovanni Caselli, used commercially in the 1860s, that was the first such device to enter practical service. The history of the first image scanner developed for use with a computer goes back to 1957. Color scanners typically read RGB (red-green-blue color) data from the array. This data is then processed with some proprietary algorithm to correct for different exposure conditions and sent to the computer via the device's input/output interface. Color depth varies depending on the scanning array characteristics but is usually at least 24 bits. High quality models have 36-48 bits of color depth. Another qualifying parameter for a scanner is its optical resolution, measured in pixels per inch (ppi), sometimes more accurately referred to as samples per inch (spi).

Images in web pages, video, and slide shows can be as low as 72 PPI for a static image or 150 PPI if we are going to focus in on the image. For printing, the DPI needs to be larger, with images scanned in at least 300 DPI. The DPI standard for and images to be printed within journals and books is 300 DPI and for museum exhibits, it's 600 DPI.

The most important factors determining image quality of digital images can be considered as pixel dimensions and color depth. Increasing the dpi value of an image by resampling in Photo Editors (e.g., Adobe Photoshop) has no improving effect on its quality, but it lets us to determine target printing size.

For vector images, there is no equivalent of resampling an image when it is resized, and there is no PPI in the file because it is resolution independent (prints equally well at all sizes). However, there is still a target printing size. Some image formats, such as Photoshop format, can contain both bitmap and vector data in the same file. Adjusting the PPI in a Photoshop file will change the intended printing size of the bitmap portion of the data and also change the intended printing size of the vector data to match. This way the vector and bitmap data maintain a consistent size relationship when the target printing size is changed. Text stored as outline fonts in bitmap image formats is handled in the same way. Other formats, such as PDF, are primarily vector formats which can contain images, potentially at a mixture of resolutions. In these formats the target PPI of the bitmaps is adjusted to match when the target print size of the file is changed. This is the converse of how it works in a primarily bitmap format like Photoshop but has exactly the same result of maintaining the relationship between the vector and bitmap portions of the data.

Long story short, it is not technically possible to talk about DPI value for images that were taken by digital cameras or any type of digital images that were transferred to the computer's storage media. The DPI value stored within exif information of images is just a virtual value just to guide the photo editing software and the graphic artist to determine the target printing size of that image.

Requirements for Digital Media

Figures and Figure Legends

Dear author, since the Journal has decision of publishing online, there is no need to upload the photos, pictures, drawings or shapes in the article as a separate file. However, to avoid blurring of images in the pdf of the article, you should add the photos or other images (X-ray, BT, MR etc.) in your Microsoft Word program as follows.

Insert menu - Pictures - Related image file in your computer

You must add the related image file on your computer and add the picture width to 16 cm. Since the need to upload each image (photo, X-ray, BT, MR or other images) is eliminated, please do not upload it to the system during submission. Place only at the end of full text and blind text.

Due to the reasons explained above, images should be taken by a digital camera of 5 megapixels or more in JPEG, RAW, or TIFF format, and should be inserted in their original form as JPEG, PNG or TIFF files.

Paper-printed images or documents should be scanned at 300 DPI resolution and should be inserted as TIFF, PNG or JPEG files.

Each vector graphic software has its own built-in settings and may have been preset at 72 dpi. So, the document should be created enough big to obtain the image in the desired dimensions. The vector graphics should be exported to a rasterized image format and inserted such as JPEG, PNG or TIFF files.

For X-ray films, CT scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, you should insert high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, we may require deposition of the original photographs of blots on the journal website.

Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication.

Figures should be made as self-explanatory as possible. Titles and detailed explanations belong in the legends— not on the illustrations themselves.

Figures should be numbered consecutively according to the order in which they have been cited in the text.

In the manuscript, legends for illustrations should be in Arabic numerals corresponding to the illustrations. Roman numerals should be avoided. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, you should identify and explain each one clearly in the legend.

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Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Authors must consult the International System of Units (SI).

Authors should add alternative or non-SI units, when SI units are not available for that particular measurement. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Types of paper

Interdisciplinary Medical Journal publishes the following types of articles.

1. Original Articles: Original prospective or retrospective studies **clinical research** in areas relevant to medicine.

The manuscript should contain English abstract, a maximum of 250 words, and the structured abstract should contain the following sections: objective, method, results, and conclusion. Three to six words or determinative groups of words should be written as keywords below the abstract.

The text of articles reporting original research might contain up to 5000 words (excluding abstract, references list and tables) and should be divided into Introduction, Method, Results, and Discussion sections. References list should also be included so that their number does not exceed 50. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles need subheadings within these sections to further organize their content.

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Some authors claim, the influence of the pharmaceutical industry on medical research has been a major cause for concern. In contrast to this viewpoint, some authors emphasize the importance of pharmaceutical industry-physician interactions for the development of novel treatments and argued that moral outrage over industry malfeasance had unjustifiably led many to overemphasize the problems created by financial conflicts of interest.

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Acknowledgement

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Authorship contribution: please indicate which part of the article each author contributed .

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The submitted file must be in Microsoft Word Document format.

The page size must be 210 mm × 297 mm (A4 size). All margins must be

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Do not capitalize diseases or syndromes unless they include a name or proper noun. Note that the words "syndrome" and "disease" are never capitalized; for example, Down syndrome, Hodgkin disease.

The authors should turn off automatic hyphenation. Do not use hyphens with common prefixes unless the word looks confusing when closed up or unless the prefix precedes a proper noun, some other capitalized word, or an abbreviation. Common prefixes that should be "closed up" include ante, anti, hi, co, contra, counter, de, extra, infra, inter, intra, micro, mid, neo, non, over, post, pre, pro, pseudo, re, semi, sub, super, supra, trans, tri, ultra, un, and under.

Use italics sparingly for emphasis in the text.

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Spell out abbreviations at first mention in the manuscript, with the abbreviation following in parentheses (except for units of measure, which are always abbreviated following numerals).

Manuscripts including tables, references list and figure legends, must be typewritten with a Unicode font (e.g., Times New Roman, Arial, etc.) that is available both for Windows and Mac Os operating systems. Please avoid using a mixture of fonts or non-Unicode fonts that do not support accented characters. The recommended font size is 12 points, but it may be adjusted for entries in a table. Authors should use true superscripts and subscripts and not "raised/lowered" characters. For symbols, please use the standard "Symbol" fonts on Windows or Macintosh.

Use the TAB key once for paragraph indents, not consecutive spaces. The pages should be numbered consecutively, beginning with the first page of the blinded article file. The pages should include title and abstract in English, the main text, tables, figures or diagrams-if exists- and reference list.

The title of the article should be centered at the top of the main text page, with the abstract below, and followed by Keywords. The capital letter of the first word of title should start with upper case letter. Please avoid capitalizing all letters of the title and conjunctions. The title, abstract, and keywords should be present in English and must be organized respectively. In order to start the Introduction section in a new page, a page break could be inserted at the end of Keywords.

While figure legends should be placed below the figures themselves, table captions should be placed above each table. Characters in figures, photographs, and tables should be uncapitalized in principal.

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INTERDISCIPLINARY MEDICAL JOURNAL
Interdiscip Med J 2023;14(50)

Reviewer Guide

Dear Reviewer,

Thank you for agreeing to conduct a peer review which will help us decide whether a manuscript is to be published in this journal.

Peer-review is a critical part of the functioning of the scientific community, of quality control, and the self-corrective nature of science. Participating in peer review of scientific publications can be viewed as a responsibility, a burden, and an opportunity all at the same time. Nonetheless, peer review remains a critical component of our profession that helps to ensure the quality, originality, and reliability of scientific findings and claims. Peer review is requested of a colleague with specific interest and expertise in the topic relevant to the manuscript submitted to The Journal. Yet despite the importance of this process in upholding rigorous scientific standards and the integrity of the journal, few if any reviewers receive any formal training or instruction in how to provide a quality manuscript review. This document serves to orient and guide individuals asked to provide peer review for This journal in the process and responsibilities of review and reviewer. In doing so, the hope is to increase scientific quality of the manuscripts and contribution to the medical scientific community.

Process of peer review in The Journal

The journal utilizes a standard online site https://dergipark.org.tr), supported by TUBİTAK, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration of publication to The Journal, the Journal Manager and editorial staff review the submission to assure all required components as outlined in the Guide for Authors are included. The manuscript is then assigned to one of the Co-Editors (either the Editor in Chief or an Associate) Editor who directs and oversees the peer-review process. The Co-Editor then reviews the submission for relevance, content and quality. Those submissions deemed appropriate for consideration of publication are then assigned to at least two peer reviewers. Selection of these reviewers is a key step in the peer review process, as this represents a critical component in ensuring quality of manuscript review and in the overall quality of the Journal. Specifically, the selection of a reviewer with expertise in the topic of the manuscript to be reviewed and without any conflict of interest improves both the timeliness and quality of the review. As such, the designation of an area of interest or expertise by the reviewer (entered at the time of registration into the system (and updated in the change details section of the website, in the subsection areas of expertise) is critical for this component of the process. Reviews are chosen to a great extent from members of the advisory board.

Once the reviewers are selected by the editor, an email is sent requesting the review; 30 days is provided to choose to review (or not review) the manuscript. A lack of response to this request leads to the reviewer being uninvited. Statistics on individual reviewers are maintained and reviewed by the journal editors, including the number of reviews requested (and those accepted, uninvited, and refused). These data help in the process of evaluating the overall quality of a reviewer and are used in the selection of future editorial board members.Before Accepting

Please consider the following:

Does the article you are being asked to review match your expertise?

If you receive a manuscript that covers a topic that does not sufficiently match your area of expertise, please notify the editor as soon as possible. Please feel free to recommend alternate reviewer.

Do you have time to review the paper?

Finished reviews of an article should be completed within four weeks. If you do not think you can complete the review within this time frame, please let the editor know and if possible, suggest an alternate reviewer. If you have agreed to review a paper but will no longer be able to finish the work before the deadline, please contact the editor as soon as possible.

Are there any potential conflicts of interests?

While conflicts of interest will not disqualify you from reviewing the manuscript, it is important to disclose all conflicts of interest to the editors before reviewing. If you have any questions about potential conflicts of interests, please do not hesitate to contact the receiving editorial office.

Finally: Educate yourself on the peer review process through the international guides on how to conduct a good review

Some resources;

https://violentmetaphors.com/2013/12/13/how-to-become-good-at-peer-review-a-guide-for-young-scientists/

https://www.theguardian.com/higher-education-network/blog/2013/sep/27/peer-review-10-tips-research-paper

https://www.degruyter.com/document/doi/10.7556/jaoa.2013.070/html

https://scholar.google.com.tr/scholar?hl=tr&q=good+peer+review&btnG=&lr=

(https://www.google.com.tr/search?num=50&btnG=Ara&q=how+to+write+a+good+peer+review).

Respond to the invitation as soon as you can – delay in your decision slows down the review process, whether you agree to review or not.

General criteria for a peer review

There are a number of general criteria that make for a quality review of a scientific manuscript, and a number of responsibilities that come with being a peer reviewer that further enhances the review process.

The peer reviewer is responsible for critically reading and evaluating a manuscript in their specialty field, and then providing respectful, constructive,

and honest feedback to authors about their submission. It is appropriate for the Peer Reviewer to discuss the strengths and weaknesses of the article, ways to improve the strength and quality of the work, and evaluate the relevance and originality of the manuscript.

Timely – Given the time sensitive nature of many scientific manuscripts, the rapid return of a solicited peer review minimizes the timeline between submission and decision (which helps the authors with resubmission if the manuscript is rejected and helps the journal with a shorter time from submission to publication if accepted). Thus, the reviewer plays a very important role in ensuring expeditious dissemination of data. Peer reviews that cannot be completed on time should not be accepted by the reviewer; every effort should be made to complete those accepted within the time allotted for review.

Fair – A reviewer has a responsibility to both The Journal and the author to provide a review that is thoughtful and complete. While the immediate goal of peer review is providing a decision regarding the suitability for publication in the journal, an additional goal is to provide the author comments that will ultimately improve the science and manuscript and providing it the best chance for publication in a peer-reviewed journal. For manuscripts eventually accepted for publication, quality peer review will ensure that the highest quality science is ultimately published (and will weed out unsound papers). Peer reviews requested in areas outside of the area of expertise of a reviewer should not be accepted; in that case, the review process is facilitated by the reviewer recommending those who could provide a quality review.

Collegial – It is rare for any manuscript to be reviewed without comments or criticisms. However, the responsibility of the reviewers is to provide these critiques constructively and objectively, and in a fashion, that is collegial and respectful. Consider each manuscript as one that was written by a valued colleague when drafting a peer review. Importantly, review the manuscript as you would like your own manuscript reviewed.

Clear – The goal of peer review is to provide an advisory recommendation to the editors as to the suitability of a manuscript for publication in The Journal. As such, the responsibility of the reviewer is to provide a clear signal to the editor regarding the appropriateness and priority for publication of a manuscript. The reviewer is expected to provide comments and criticisms to the editor that clearly justifies their recommendation for disposition of the manuscript. It is also critical that the comments to the editor are consistent with those made to the author (such that the comments of the reviewer justify the recommendation regarding the disposition of the manuscript).

Comprehensive – A quality review will include a number of considerations, and may be specific to the manuscript being reviewed. In order for a manuscript to be considered for publication, it must be original and significant, providing a contribution to research and importance to field. In general, there should be no flaws in the specific procedures used in performance of the study, or in the logic used for the interpretation of the data. It is important that the results of the study support its conclusions, and that there are no errors in reference to prior work (or no exclusions of pertinent references). Where appropriate, confirmation of regulatory review (such as institutional review board approval) must be present. A reviewer is expected to comment on the strengths and weaknesses or limitations of the study. The validity of the statistics used (often including a justification of a sample size) to analyze data is necessary, and the data presented in the figures and tables should be reflective of the results presented and adequate to justify the study conclusions. In general, the manuscript length and quality of the writing are important to ensure its quality.

Considerations for a quality peer review of a manuscript

Structure

Is the article clearly laid out? Are all the key elements present: abstract, introduction, methodology, results, conclusions?

Consider each element in turn:

Title: Does it clearly describe the article? This will be used for medical database searches, so it shouldn't try to be "cute".

Abstract: Does it reflect the content of the article? Are the data consistent with the results reported in the manuscript?

Introduction: Does it describe what the author hoped to achieve accurately, and clearly state the problem being investigated? Normally, the introduction is two or three paragraphs long. It should summarize relevant research to provide context, and explain what findings of others, if any, are being challenged or extended. It should describe the experiment, hypothesis; general experimental design or method.

Methodology: Does the author accurately explain how the data were collected? Is the design suitable for answering the question posed? Is there sufficient information present for you to replicate the research? Does the article identify the procedures followed? Are these ordered in a meaningful way? If the methods are new, are they explained in detail? Was the sampling appropriate? Have the equipment and materials been adequately described? Does the article make it clear what type of data was recorded; has the author been precise in describing measurements?

Results: This is where the author should explain in words, tables and figures what was discovered in the research. It should be clearly laid out and in a logical sequence. You will need to consider if the appropriate analysis been conducted. Are the statistics correct? If you are not comfortable with statistics, advise the editor when you submit your report and recommend review by a statistical editor. Any interpretation should not be included in this section.

Conclusion/Discussion: Are the claims in this section supported by the results, do they seem reasonable? Have the authors indicated how the results relate to expectations and to earlier research? Does the article support or contradict previous theories? Does the conclusion explain how the research has moved the body of scientific knowledge forward?

Language: If an article is poorly written due to grammatical errors, while it may make it more difficult to understand the science, you do not need to correct the language. You may wish to bring it to the attention of the editor, however, and we can refer the authors to an language editing service if you feel the paper may be worth publishing.

Finally, on balance, when considering the whole article, do the figures and tables inform the reader, are they an important part of the story? Do the figures describe the data accurately? Are they consistent (are the bars in the charts the same width, are the scales on the axis logical)? Are the legends appropriate?

Previous Research

If the article builds upon previous research, does it reference that work appropriately? Are there any important works that have been omitted? Are the references accurate and up to date?

Reviewer's Suggestions

Once accepted, the reviewer has 4 weeks to complete the review (details of the components of a review are described in more detail below), which is submitted through The Journal site. Failure to complete the review during this time period leads to a reminder email.

It is the responsibility of the reviewer to provide a recommendation to the editor for the disposition of the manuscript. Importantly, the recommendation of the reviewer is advisory to the editor, as it is ultimately the decision of the editor as to the final disposition of the manuscript.

When the editor has a full complement of reviews completed, the editor reviews the comments and recommendations, and a decision regarding the suitability for publication of the manuscript is made.

The recommendations can be categorized into 6 groups.

Accept Submission (without modification)

Minor Revision (Revisions Required): Accept with minor modification (but manuscript requires modifications to improve its quality)

Major Revision (Resubmit for Review): Major modifications required, manuscript is unique, but requires extensive revision and reevaluation prior to potential acceptance

Resubmit Elsewhere: manuscript is unique, but out of the journal scope.

Decline Submission: manuscript is of low quality or low interest to the readership)

The reviewer has two types of comments that can be provided – one to the authors, and one to the editors. It is strongly encouraged that the reviewer utilizes the comments to the editor to provide confidential comments regarding the manuscript under consideration. These comments help assure that the editor understands the true recommendation of the reviewer and provides key assistance to the Editor in determining a manuscript's ultimate disposition. In addition, completing the manuscript rating form is helpful in supporting a reviewer's recommendation for the disposition of a manuscript, and assists the Editor in justifying the final decision.

Review of the reviewer

The editor evaluates the quality of a review upon its receipt. Utilizing the criteria defining a quality review (timely, fair, collegial, clear, and comprehensive), a reviewer is evaluated and scored (from 0-5) on their review. This statistic, in combination with a separate statistic regarding the timeliness of the review, is helpful in assigning subsequent reviews to a reviewer. Reviewers with low scoring or late reviews are not considered highly for subsequent reviews.

Why be a reviewer?

Reviewing requires the investment of time and a certain skillset. Before you decide if you want to become a reviewer, we recommend that you read more about the peer review process and conducting a review.

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* Before all studies are sent to the reviewer, while they are in the pre-control stage, they are subjected to "Similarity Check" with iThenticate Crosscheck software and if they are above the tolerable level, the author is requested to make the necessary corrections.

* We ask the authors to use a dot as a decimal separator throughout the article, including the Turkish and English abstracts, so this is not an error.

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The editorial and publication processes of the journal are shaped in accordance with the guidelines of The International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).

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Individuals listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org).

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1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work;

2. Drafting the work or revising it critically for valuable intellectual content;

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for

other specific parts of the work. Besides, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged on the title page of the manuscript.

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To summarize, all authors submitting their works to the journal for publication as original articles attest that the submitted works represent their authors' contributions and have not been copied or plagiarized in whole or in part from other works. The authors acknowledge that they have disclosed all and any actual or potential conflicts of interest with their work or partial benefits associated with it.

Ethical Responsibilities of The Reviewer

Given the sensitive nature of peer review, there are ethical responsibilities of the review and review process that are critical to ensure their validity. It is important for reviewers to identify potential conflicts of interest with the authors and the topic of the manuscript. The Journal requires that reviewers disclose potential and relevant conflicts of interest related to employment, consultancies, stock ownership, receipt of honoraria, patents, a professional relationship with, or direct competition in the field of the authors. The reviewer has a responsibility to review the conflict-of-interest forms submitted by the authors, which specifically document any relevant financial relationships.

Given the role of reviewer as an expert in the topic area of the manuscript, a reviewer is requested to report any known situations of duplicate submissions (a manuscript that may be under concurrent review at another journal), fraudulent data, or plagiarism in a manuscript. If identified, these comments should be conveyed to the editor (in the confidential comments to the editor section) so they can be addressed as appropriate. Since peer review of a manuscript allows a reviewer to view data that is not yet in the public domain, strict confidentiality is critical to ensure scientific integrity; destruction of documents and files related to peer review is also mandatory once the review is complete.

The Committee on Publication Ethics (COPE) is a group comprised of editors of academic journals and others interested in publication ethics. Members of COPE were provided with the Ethical Guidelines for Peer Review, describing the basic principles to which reviewers should adhere. These guidelines provide a broad ethical context in which the peer review process should be performed.

COPE Ethical Guidelines for Peer Reviewers

Peer review in all its form plays an important role in ensuring the integrity of the scholarly record. The process depends to a large extent on trust and requires that everyone involved behaves responsibly and ethically. Peer reviewers play a central and critical part in the peer-review process, but too often come to the role without any guidance and may be unaware of their ethical obligations. The COPE Ethical Guidelines for Peer Reviewers set out the basic principles and standards to which all peer reviewers should adhere during the peer-review process. It is hoped they will provide helpful guidance to researchers, be a reference for journals and editors in guiding their reviewers, and act as an educational resource for institutions in training their students and researchers.

Basic principles to which peer reviewers should adhere

Peer reviewers should:

• only agree to review manuscripts for which they have the subject expertise required to carry out a proper assessment and which they can assess in a timely manner

• respect the confidentiality of peer review and not reveal any details of a manuscript or its review, during or after the peer-review process, beyond those that are released by the journal

• not use information obtained during the peer-review process for their own or any other person's or organization's advantage, or to disadvantage or discredit others

• declare all potential conflicting interests, seeking advice from the journal if they are unsure whether something constitutes a relevant interest

• not allow their reviews to be influenced by the origins of a manuscript, by the nationality, religious or political beliefs, gender or other characteristics of the authors, or by commercial considerations

• be objective and constructive in their reviews, refraining from being hostile or inflammatory and from making libelous or derogatory personal comments

• acknowledge that peer review is largely a reciprocal endeavor and undertake to carry out their fair share of reviewing and in a timely manner

• provide journals with personal and professional information that is accurate and a true representation of their expertise

• recognize that impersonation of another individual during the review process is considered serious misconduct

INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2023;14(50)

CONTENTS

Volume: 14, Issue 50, Year: 2023

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1297115
Interdisciplinary Medical Journal 2023;14(50):151-157.

Diagnostic evaluation of viral versus bacterial tonsillopharyngitis using an artificial intelligence mobile application and symptom questionnaire

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Abstract

Objective: In this study, it was aimed to distinguish bacterial/viral tonsillopharyngitis (TP) by scoring the symptom and throat images of pediatric patients with artificial intelligence-based mobile application.

Method: Fifty-one patients who applied to Sakarya University Training and Research Hospital, Department of Pediatrics and Diseases with acute tonsillopharyngitis were included. Samples were taken from patients and mouth/throat pictures were taken so that the tonsils and pharynx were clearly visible. In the microbiology laboratory, identification with culture/MALDI-TOF MS (Biomerieux, France) from the first samples, and nucleic acid isolation from the other for molecular tests were performed. Symptoms such as fatigue, sore throat, muscle pain, cough, sneezing, and runny nose were questioned from each patient on a scale of 1 to 5. By uploading the symptom results and throat pictures to the artificial intelligence application, it was aimed to distinguish bacterial/viral tonsillopharyngitis with the developed scoring system.

Results: Of the 51 samples included in the study, 21 were culture positive and 30 were negative. The artificial intelligence application was defined as 20 out of 21 culture-positive samples, 3 out of 30 culture-negative samples as bacterial tonsillopharyngitis (Sensitivity: 95.2%, specificity: 90%).

Conclusion: This study is one of the first to bring together the artificial intelligence application and microbiology. AI/scoring system may have a role to play in the diagnosis of bacterial vs viral TP, and in doing so may enable more appropriate antibiotic usage targeted to only bacterial TP infections. It is important to distinguish between bacterial and viral tonsillopharyngitis in the COVID-19 pandemic.

Keywords: Artificial Intelligence, Tonsillopharyngitis, Virus, Rational Antibiotic Use

INTRODUCTION

In most of the tonsillopharyngitis cases, it is very difficult to establish the etiological diagnosis by clinical. Although pharyngeal and tonsillar exudates, sensitive lymphadenopathies, skin rashes and conjunctivitis are important in the differential diagnosis, they are not specific findings. Nevertheless, some clinical scoring systems have been developed to predict streptococcal tonsillopharyngitis, especially in line with the clinical studies conducted by McIsaac and Centor (1,2). Each of four clinical features — absence of cough, purulent pharyngeal exudate, anterior cervical lymphadenopathy, and temperature of >38°C — is scored with 1 or 0, depending on whether it is present; 5 scores range from 0 (when none of

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the features are present) to 4 (when all are present) in Centor criteria (3). McIsaac independently derived a prediction system based on a cohort of patients from primary care. In essence, it modifies the Centor system to include an extra variable age. For those aged between 3 years and 14 years, 1 is added to the score, whereas, for those aged ≥45 years, 1 is subtracted from the score; hence, a patient presenting with a sore throat may have a McIsaac score of anything between −1 and 5 (4,5). (Table 1) These clinical scoring systems are especially helpful in preventing unnecessary antibiotic use in primary care.

The clinical use of artificial intelligence systems for detecting and monitoring healthcare-associated infections (HAIs) has become widespread in recent years (6,7). Monitoring with artificial intelligence systems is considered superior because it is faster than conventional surveillance, less people are needed, and it is independent of evaluator errors in traditional monitoring (8,9). Consistent with the idea of "There is no disease, there is a patient" in infections, the results may be uncertain or borderline changes due to the host's immune status, pathogenic characteristics and the interactivity between the two (10).

Due to the difficulties experienced in the rapid and definite diagnosis of TP etiology, an artificial intelligence system including a symptom / photo questionnaire was developed to assist clinical diagnosis. In our study, it is aimed to investigate the clinical diagnostic accuracy of a medical artificial intelligence system that can be used in the rapid and non-invasive diagnosis of throat infections. In this way, it is thought that it can reduce the use of costly tests used in the diagnosis of TP, give an idea about viral/bacterial TP, and provide ease of use since it can reduce the tonsillopharyngeal swab process, which is especially uncomfortable in children. In the artificial intelligence system developed for this purpose, the complaints of the patients in the childhood age group and the photographs of the throat areas were compared with the traditional throat culture.

METHOD

Study Design

Fifty-one patients who applied to Sakarya University Hospital, Department of Pediatrics with the complaint of acute tonsillopharyngitis between 1-30 December 2019 were included in our study. On 11/11/2019, approval was obtained from the xxx Clinical Research Ethics Committee with the decision number 16214662/050.01.04/179. The inclusion of the patients in the study was on a voluntary basis, and the participants were asked to fill out a voluntary consent form. The inclusion criteria for the study are as follows:

Being in the 0-18 age range,

Volunteering to participate in the study,

Presenting with symptoms of tonsillopharyngitis,

Detection of bacterial TP agent in the patient as GAS and

Not taking any antibiotic treatment.

Samples were taken from the patients with 2 different swabs, and mouth/throat pictures were taken to see the tonsils and pharynx. Throat pictures (51 patients) were taken with the mobile camera of healthcare professionals and recorded with the symptom data of the patients and uploaded to the FluAI application. All symptom information questioned in the questionnaire was obtained from the parents of the children.

In the microbiology laboratory, after the detection of growth on culture,identification was performed with Vitek MS (Biomerieux, France) from the first samples, and total nucleic acid isolation (EZ1-Qiagen, Germany) was performed from the other for molecular tests. Growth of Group A beta hemolytic streptococci in culture was accepted as the diagnostic criterion for bacterial TP. Molecular methods were used for the diagnosis of viral agents.

In addition, symptoms such as fatigue, sore throat, myalgia, cough, sneezing, runny nose were questioned on a scale of 1 to 5 from each patient. Symptom results and throat pictures were uploaded to the artificial intelligence application and targeted. Questionnaire and swab sampling were done by the same person throughout the study to minimize interobserver differences. It was aimed to differentiate bacterial/viral tonsillopharyngitis with the developed scoring system. Scoring results by application were compared with the results of the culture and molecular respiratory panel (Qiastat, Qiagen, Germany). True positive samples were considered as replicating bacterial agents in culture and were defined as bacterial tonsillopharyngitis by the artificial intelligence application scoring system. We compared the accuracy and safety of the FluAI upper respiratory decision support system with gold standard diagnostic methods. Accuracy was evaluated for the suitability of the proposed conditions.

Analysis process

With the first algorithm, the photo taken by the mobile application, it is evaluated whether the throat photo is taken correctly or not. If it is a suitable image for analysis, in the next step, the photo is sent to the analysis engine of FluAI and the images of the infection markers in the photo are analyzed as a result of a computational system. As a result of the analysis of the photo, a symptom check is made to the person, including his complaints about upper respiratory tract infections. At the end of this query, symptom and photo analysis are brought together and decision support is provided to the person.

Model

We used ResNet-50 is a 50-layer deep learning model that has been trained to classify images into 1000 categories. Hence, the ResNet-50 pre-trained model has been used to accelerate the training of deep models for other problems through transfer learning. Fine Tuned Resnet-50 the parameters of the ResNet-50 model are used as initialization of a fine-tuned model for the dataset under consideration. All of the convolutional layers were frozen except for the last ten as the throat images are very different from the ImageNet data. We modified the last three layers of ResNet-50 to adapt it to the target domain.

Figure 1 shows the fine-tuning process. Since the Resnet50 model is trained with the ImageNet dataset, we need to organize its architecture according to our data. We can also speed up training by freezing the first layers of the pretrained Resnet50 model.

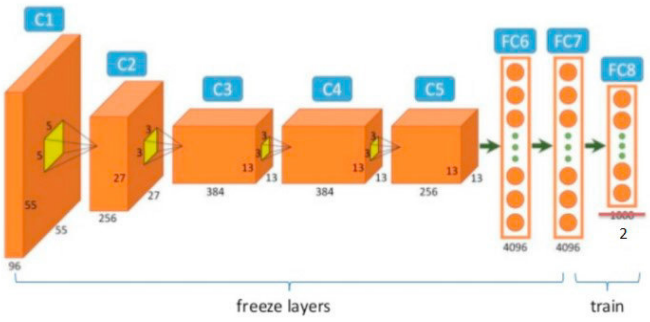

Figure 1. Resnet-50 layers.

ResNet-50 is a convolutional neural network. Convolutional neural networks learn which filters to apply to pictures in the training process. For example, a simple filter can help us distinguish edges or corners. Learned filters become more complex and specialized in our data as layers deepen. Our model distinguishes between 2 classes, so we trained with bacterial and viral TP pictures. In the estimation phase, we estimated the class of the test visuals with our pre-trained model.

Preprocessing of 2D Resnet-50

Pre-processing: The photos we use in the training process can be of many different sizes. The input layer of convolutional neural networks is fixed size, so we have to resize all images in the training and prediction process. During the training process, the size was 224x224. In addition, normalizing the pixel values will positively affect the training process.

Data Augmentation

Data augmentation is the increase of data by exposure to various distortion effects to increase performance, especially in small data sets. In this way, the model is provided to learn about different conditions. With this method, we have more data, and our model is immune to changes in light, angle, and distance.

To avoid the overfitting problem since the number of training throat pictures was limited, various data augmentation strategies were applied including random affine transformation. The affine transformation was composed of rotation (0◦±10◦), horizontal and vertical translations (0%±10%), scaling (0%±20%), shearing in the width dimension (0%±10%), and brightness range (0%±10%).

Heatmap generation

Especially in the field of health, the interpretability of artificial intelligence is very important. To reduce this problem, the method of heat mapping is used in convolutional neural networks. A heat map shows us where the deep learning algorithm focuses the most in the picture when distinguishing between bacterial or viral classes.

To visualize the heatmap, we used a technique called Grad-CAM. The idea behind it is to find the importance of a certain class in our model, we simply take its gradient concerning the final convolutional layer and then weigh it against the output of this layer. We choose the activation_49 layer to create the heatmaps.

RESULTS

Culture results

Of the 51 samples, 21 were culture positive and 30 were negative. The artificial intelligence application contains 20 of the 21 culture-positive samples; it defined 3 of 30 culture-negative samples as bacterial tonsillopharyngitis (Sensitivity: 95.2%, Specificity: %90). (Table 1) When patients whose complaint period exceeds 3 days are excluded from the statistics, the sensitivity of the application increases to 100%.

Table 1: Centor and McIsaac score criteria

Centor score	
Symptom	**Score**
Body temperature (in the history) >38 °C	1
No cough	1
Cervical lymph node swellings	1
Tonsillar swelling or exudation	1
Total point	**Probability of GABHS proof in the swab (%)**
0	~2.5
1	~6-7
2	~15
3	~30-35
4	~50-60

Table 1: Centor and McIsaac score criteria

McIsaac score	
Symptom	**Score**
Body temperature (in the history) >38 °C	1
No cough	1
Cervical lymph node swellings	1
Tonsillar swelling or exudation	1
Age (years) 3-14 15-44 ≥45	 1 0 -1
Total point	**Probability of GABHS proof in the swab (%)**
-1 or 0	1
1	10
2	~17
3	~35
4 or 5	~50

Respiratory panel results

In the details of the study, there is also a distinctive examination as to whether viral tonsillopharyngitis infections are flu or common cold, and when the application and respiratory panel molecular test results are compared, the sensitivity of the application for influenza and cold was found to be 55.6% and 90.5%, and the specificity was 95.2% and 93.3%, respectively.

Application model performance

The experiments were carried out using NVIDIA T4 GPU where the baseline model required 5 minutes (for model training and testing), the ResNet-50 model required 100 seconds (for model testing), and the fine-tuned method required 32 minutes (for training and testing).

Scoring and accuracy

A total of 51 patients were included. For all patients, our model achieved a sensitivity of 0.952, the specificity of 0.9, and accuracy of 0.921. The patients in the first 3 days of their complaints, achieved a sensitivity of 0.1, specificity of 0.916, and accuracy of 0.947 (Figure 2).

Figure 2 is a confusion matrix. "0" values present "Viral pharyngitis", "1" values present "Bacterial Tonsillopharyngitis". Colors change with numerical values.

The empirical ROC curve corresponding to the culture method of the artificial intelligence application developed for the diagnosis of tonsillopharyngitis was drawn in Figure 3 with a non-parametric method using SPSS Version 25.0 software (AUC=0.927, 95% confidence interval: 0.84-1.00, p< 0.001). This ROC curve and the corresponding AUC value indicate that AI, as a preliminary diagnostic method, has the predictive ability to distinguish bacterial tonsillopharyngitis from viral.

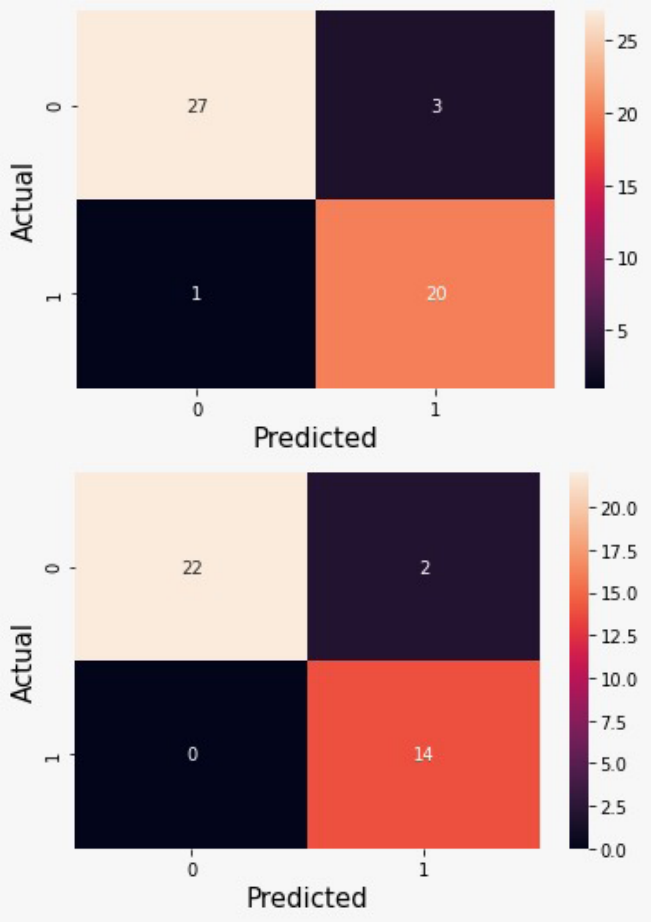

Figure 2. a) All patients. b) First 3 days of complaints.

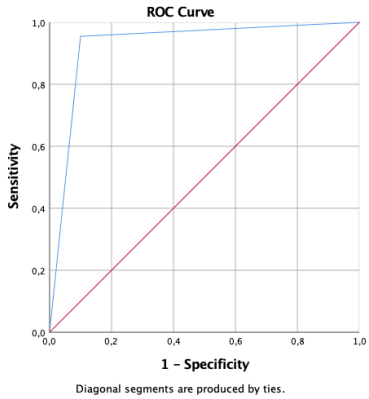

Figure 3: ROC curve analysis for AI and culture method.

The following throat images of patients show original photo and heatmap version, which points the artificial intelligence focuses on during the analysis, thus presenting the decision according to which regions in a more transparent way.

Patients have severe fatigue, severe cough, moderate throat pain, mild headache, and moderate muscle pain. Diagnose was bacterial tonsillopharyngitis. FluAI engine analyzed as "bacterial tonsillopharyngitis" and it shown focused suspected bacterial infection area (Figure 4, 5, 6).

Table 2. Culture and FluAI comparison

	Culture								
	Negative				Positive				Total (n)
	FluAI Negative		FluAI Positive		FluAI Negative		FluAI Positive		
	n	%	n	%	n	%	n	%	51
	27	90	3	10	20	95.23	1	4.77	
Total (n)	30				21				

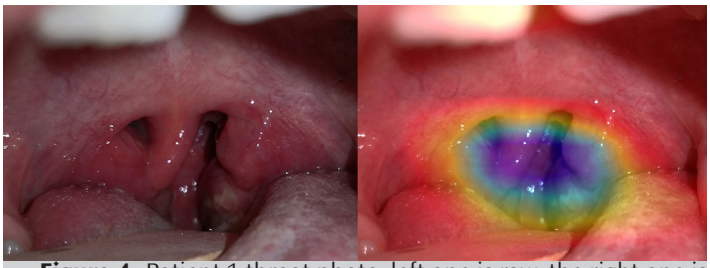

Figure 4. Patient 1 throat photo, left one is raw, the right one is heatmap edition, after the AI analysis

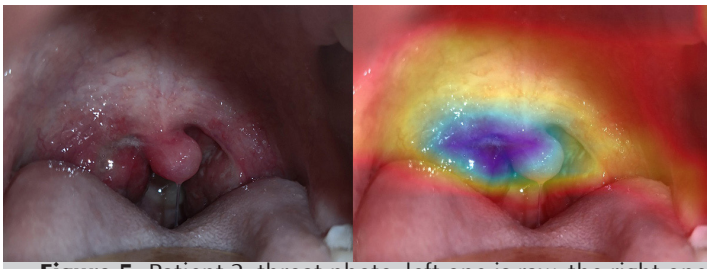

Figure 5. Patient 2, throat photo, left one is raw, the right one is heatmap edition, after the AI analysis

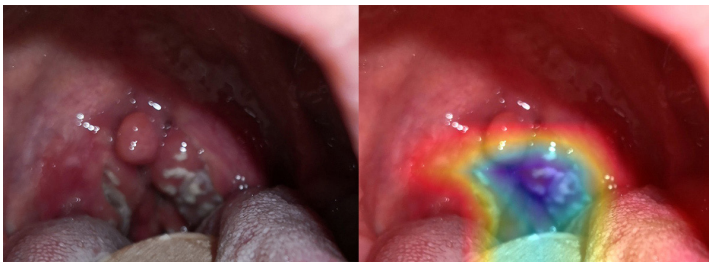

Figure 6. Patient 3, throat photo, left one is raw, the right one is heatmap edition, after the AI analysis

DISCUSSION

The range of applications of AI and AI-mediated technologies in healthcare is broadly and rapidly increasing. As patients gain more and more ownership of their care, we expect more AI solutions that support the transition from hospital-based service to home care.

There are many studies in the literature as examples of the use of artificial intelligence in clinical diagnosis. A group has recently shown the possibility to develop a low-cost point of care for lymphoma diagnosis based on basic imaging and deep learning (14). New research has shown the added value of machine learning for image processing where classical tools could not identify early signs of diseases (15). This is particularly true for cancer in which diagnosis and treatment are often assisted by AI approaches (16). Also, recent approaches using mathematical modeling are improving surveillance studies. A similar system was developed by Sun et al. (2015) to detect infected patients by classification using vital signs. In this way, respiration rate, heart rate, and facial temperature were used to successfully classify individuals at higher risk for influenza using neural network and fuzzy clustering method (17). Support vector machine by developed Saybani et al (2016) is a much robust classifier and was applied to a tuberculosis cohort. With an accuracy of 100%, sensitivity of 100%, specificity of 100%, Youden's Index of 1, area under the curve (AUC) of 1, and root mean squared error of 0, the new artificial immune recognition system method was able to successfully classify tuberculosis patients (18). Babalık and Güler (2007) have developed a medical expert system that can be used in the diagnosis of tonsillopharyngitis infections (19). It is possible to expand these examples. In our study, the comparison of the artificial intelligence system developed with the photos of the complaints and throat areas of the patients in the pediatric age group was made, and the sensitivity and specificity of this system were measured according to the culture method.

With our study, we think that this artificial intelligence system, which developed for patients with upper respiratory tract infection, which is one of the biggest responsible for unnecessary antibiotic use and related antibiotic resistance development, has a great potential in raising the awareness of patients about their diseases and conditions from the right source and helping to reduce antibiotic resistance.

Leelasantitham and Kiattisin developed a program for the diagnosis of tonsillitis with an artificial intelligence system and the overall accuracy was found to be about 90% when compared with the doctor's diagnoses (20). Our study was carried out using NVIDIA T4 GPU technology. A total of 51 patients were included in the study. Of the 51 samples, 21 were culture positive and 30 were negative.

The artificial intelligence application contains 20 of the 21 culture-positive samples; it defined 3 of 30 culture-negative samples as bacterial tonsillopharyngitis (Sensitivity: 95.2%, Specificity: %90). When patients whose complaint period exceeds 3 days are excluded from the statistics, the sensitivity of the application increases to 100%. In the details of the study, there is also a distinctive examination as to whether viral tonsillopharyngitis infections are flu or common cold, and when the application and molecular test results are compared, the sensitivity of the application for influenza and cold was found to be 55.6% and 90.5%, and the specificity was 95.2% and 93.3%, respectively.

The limitations of our study are the small sample size, performing the study in a limited time period and the single-center nature of our study. In addition, due to the limitation of the number of patients in laboratory parameters, a statistically limit value could not be shown.

CONCLUSION

Most bacterial pharyngitis is caused by Group A Streptococci (GAS). Therefore, discrimination between bacterial-viral causes, and rapid diagnosis of GAS are important in terms of guiding treatment in acute tonsillopharyngitis cases (21). The usability of an artificial intelligence application developed in this study to distinguish bacterial / viral agents of tonsillopharyngitis clinically and visually was tested. There are many different artificial intelligence techniques that have the capacity to solve various diseases. More controlled studies are required to measure the practical success of these techniques. Studies so far show that medical artificial intelligence is vital in helping doctors to increase the efficiency of healthcare services. As a result of our study, it was concluded that the FluAI system can be used safely in the diagnosis of tonsillopharyngitis and that it will bring benefits such as early diagnosis and rational use of antibiotics. The comparison of the prediction value of AI versus culture of the swab could be very helpful in the COVID scenario when physicians/pediatricians have less possibility to directly visit patients, potentially limiting the overuse of antibiotic for non-streptococcal infections and thus limiting antibiotic resistance. The potential of artificial intelligence methods in clinical medicine is understood from thousands of publications in a wide variety of fields. The power of these methods in the research and treatment of diseases arouses excitement.

As a result of our study, it was found that FluAI symptom questionnaire and image application have high sensitivity and specificity in differentiation of viral / bacterial TP.

Individuals can understand whether the etiology of tonsillopharyngitis is bacterial or viral in the COVID-19 pandemic, thanks to its highly accurate application, without entering environments with a high risk of infection. In today's world where the pandemic is intense, the ability of individuals to make this distinction without burdening the health system will also contribute to the economy.

Our application can be economically beneficial in that it can reduce the use of high-cost tests required to make this distinction.

It can reduce inappropriate and excessive antibiotic prescription in terms of giving an idea about viral and bacterial infections. It can reduce antibiotic resistance in bacteria, which is an indirectly important problem.

FluAI provides ease of use as it may reduce the tonsillopharyngeal swab process which is uncomfortable especially in children.

However, the widespread use of this technology may cause patients to resort to wrong treatments without consulting the physician.

Conducting such studies with a larger sample for longer periods for future studies will contribute to diagnostic guidelines developed for different diseases.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Sakarya University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 11/11/2019 and number 16214662/050.01.04/179, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: MA, YY Design: YY, MA, HT, EPKK Supervising: YY, MA, HT, EPKK, OB, ÖÖ, BE, MK Financing and equipment: YY, MA, HT, OB, ÖÖ, BE, MK Data collection and entry: YY, MA, ÖÖ, BE, MK Analysis and interpretation: YY, MA, HT, EPKK, OB, ÖÖ, BE, MK, Literature search: YY, MA, HT, OB, BE, MK, Writing: YY, MA, HT, EPKK, OB, ÖÖ, BE, MK, Critical review: YY, MA, BE, MK

REFERENCES

1. National Comprehensive Cancer Network (NCCN 2.2015). NCCN Clinical practice guidelines in oncology. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed December 13, 2022.
2. Wirth A, Yuen K, Barton M, Roos D, Gogna K, Pratt G, et al. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. Cancer 2005;104:1221. https://doi.org/10.1002/cncr.21303
3. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. Med Decis Making 1981;1:239-46. https://doi.org/10.1177/0272989X8100100304
4. McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ 1998;158:75-83.
5. Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 2002;35:113-25. https://doi.org/10.1086/340949
6. McCarthy J. What is artificial intelligence? Computer Sci- ence Department, Stanford University. Available at: http://www-formal.stanford.edu/jmc/whatisai.pdf. Accessed October 10, 2020.
7. Nabiyev VV. Yapay zeka/artificial intelligence. Ankara, Seckin Yayinlari; 2003: 35-40.
8. Begley RJ, Riege M, Rosenblum J, Tseng D. Adding intelligence to medical devices. Medical Device & Diagnostic Industry Magazine 2000;3:150.
9. Industrial application of fuzzy logic control. Available at: http://www.fuzzytech.com/. Accessed October 10, 2020.
10. Atici E. The Concept of Patient-Physician Relationship. Uludag Universitesi Tip Fak Derg 2007;33:45-50.
11. Celebi ARC, Bektaş B, Ankaralı H, Yeşıl Y, Yüksel C, Karasu B, Özgür Ö, Tunç U. Diyabetik Retinopatide Farklı Makine Öğrenmesi Tekniklerinin Kullanımı ile Tanı Koymadaki Doğruluk Ölçütlerinin Karşılaştırılması. Tepecik Eğitim ve Araştırma Hastanesi Dergisi, Kongre Özel Sayısı 2020;30:64-66.
12. Rosebrock A. Detecting COVID-19 in X-ray Images with Keras, TensorFlow, and Deep Learning. PyImageSearch, 16 March, 2020.
13. Maghdid H, Ghafoor K, Sadiq A, Curran K, Rabie K. A Novel AI-enabled Framework to Diagnose Coronavirus COVID-19 using Smartphone Embedded Sensors: Design Study. ArXiv, https://arxiv.org/abs/2003.07434. Accessed October 15, 2022.
14. Im H, Pathania D, McFarland PJ, Sohani AR, Degani I, Allen M, et al. Design and clinical validation of a point-of-care device for the diagnosis of lymphoma via contrast-enhanced microholography and machine learning. Nat Biomed Eng 2018;2:666-674. https://doi.org/10.1038/s41551-018-0265-3
15. Chen JH, Asch SM. Machine learning and prediction in medicine-beyond the peak of inflated expectations. N Engl J Med 2017;376:2507-2509. https://doi.org/10.1056/NEJMp1702071
16. Boon IS, Yong TPTA, Boon CS. Assessing the role of artificial intelligence (AI) in clinical oncology: utility of machine learning in radiotherapy target volume delineation. Medicines (Basel) 2018;5:E131. https://doi.org/10.3390/medicines5040131
17. Sun G, Matsui T, Hakozaki Y, Abe S. An infectious disease/fever screening radar system which stratifies higher-risk patients within ten seconds using a neural network and the fuzzy grouping method. J Infect 2015;70:230-236. https://doi.org/10.1016/j.jinf.2014.12.007
18. Saybani MR, Shamshirband S, Golzari S, Wah TY, Saeed A, Mat Kiah ML, et al. RAIRS2 a new expert system for diagnosing tuberculosis with real-world tournament selection mechanism inside artificial immune recognition system. Med Biol Eng Comput 2016;54:385. https://doi.org/10.1007/s11517-015-1323-6
19. Babalik A, Guler I. Boğaz enfeksiyonlarının teşhis ve tedavisinde uzman sistem kullanımı. Selçuk Teknik Dergisi 2007;6:109-119.
20. Leelasantitham A, Kiattisin S. A diagnosis of tonsillitis using image processing and neural network. International Journal of Applied Biomedical Engineering 2009;2:36-42.
21. Altindis M, Elmas B, Kilic U, Aslan FG, Kucukkkara G, Koroglu M. Loop-Mediated Isothermal Amplifi cation PCR (LAMP-PCR) For Rapid Molecular Diagnosis of Group A Streptococci. J Biotechinol & Strategic Health Res 2017;1:11-16.

ORIGINAL RESEARCH

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The relationship of preterm birth with fetal fibronectin level in cervicovaginal fluid and cervical lenght in ultrasonography

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Abstract

Objective: In this study, the compatibility between fetal fibronectin determination and the use of cervical length measured by transvaginal ultrasonography of patients who were at risk of preterm birth in the examination performed at 24-34 weeks of gestation, and patients with an increased risk of preterm birth according to the result were defined.

Method: 40 patients who applied to Mustafa Kemal University Training and Research Hospital Gynecology and Obstetrics outpatient clinic between May 2021 and May 2022 were included in the study. Fibronectin results were evaluated using the liquid ELISA method taken from the vaginal secretion by a swap. Cervical lengths were evaluated as 25 mm and below, between 25-30 mm and 30 mm and above in statistical data.

Results: For fFN-positive patients, the preterm delivery rate of patients with a cervical length of 25 mm and less was determined as 100%, while the rate of preterm birth was determined as 77.8% for patients with a cervical length between 25 mm and 30 mm. In addition, the preterm labor rate of fFN-positive patients with a cervical length of 30 mm and above was determined as 78.57%.

Conclusion: All patients with a cervical length of 25 mm or less have a positive fFN test, and a strong correlation can be established between these two values. Accordingly, fFN positivity was found to have a higher sensitivity in determining the probability of preterm delivery compared to the cervical length ratio.

Keywords: Preterm Labor, Fetal Fibronectin, Cervical Length

INTRODUCTION

All the acts of birth which happen before 37. week of pregnancy is called preterm birth and it is one of the most important reasons of neonatal morbidity and mortality. Although the border (line) between preterm birth and abortion differs in many sources, births that occur after the 20th gestational week are called preterm births (1). Recently, the use of many new techniques has come to the fore to determine the risk of preterm labor. Some of these techniques are cervical length measurement with ultrasonography and determination of fetal fibronectin in cervicovaginal secretions (2).

In normal conditions the fetal fibronectin is not found in cervicovaginal fluid of pregnants between 24 and 34 weeks of pregnancy. It exists of high concentration in cervicovaginal fluid before 20. week of pregnancy. The presence of fetal fibronectin in the cervicovaginal fluids of pregnant women at 24 to 34 weeks with intact amniotic membranes has been shown in many studies (3).

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It was shown a relationship between early birth and cervical length in patients with a threat of preterm birth in many studies. In a study in UK, cervical length measurement helped distinguish between true and false labor in pregnant women with intact membranes at risk of preterm birth. In this study, the incidence of preterm birth within seven days was 8% in the entire study population; While it was 0.6% in cases with a cervical length of 25 mm and above, it was found to be 37% in cases with a cervical length less than 25 mm (4).

In our study, it was aimed to evaluate the compatibility between fetal fibronectin determination and the use of cervical length measured with the help of transvaginal ultrasonography in pregnant women with preterm birth risk, and to evaluate the increased risk of preterm birth according to the result.

METHOD

This study was performed between the dates of May 2021-May 2022. Ethics committee approval was obtained for the study from the Clinical Research Ethics Committee of Hatay Mustafa Kemal University with the decision number 29/06/2021-106. Informed consent form, which was accepted by the ethics committee, was obtained from the volunteers included in the study at the beginning of the study.

In the study, the criterion sampling size, which is one of the simple random sampling methods, was utilized and the data were obtained from the patients who presented to the outpatient clinic between May 2021 and May 2022. Forty pregnant women who has early birth risk (the existence of contraction 3 or more in 20 minutes, cervical dilatation with less than 3 cm and cervical effacement with a rate of 80%) diagnosed in their 24 – 34. week of pregnancy were included to this study prospectively. The concordance between fetal fibronectin determination in the fluid to be taken from the vaginal secretion with the help of a swab and the use of cervical length measured with the help of transvaginal ultrasonography, and according to the result of this, patients with increased risk of preterm birth were defined. Pregnant women with diabetes and hypertension, pregnant women with diagnosed fetal anomaly, pregnant women with a history of preterm birth ,pregnant women with mullerian anomaly, pregnant women younger than 18 years old, patients who had undergone cervical excisional procedure and cervical conization were excluded in the study. The study included patients who presented to the outpatient clinic and had a pregnancy defined preterm birth.

Demographic features of all cases were recorded after taken identities and addresses. In order to determine the preterm birth risk, the patients were prepared in the lithotomy position, a sterile speculum examination was performed without the use of any chemicals before the digital examination, and a sterile swab from the posterior vaginal fornix was used for fetal fibronectin test. For the purpose of ensuring standardization, all measurements were done by the same physician. Sampling was done for genital secretion smear and culture. The existence of fetal fibronectin in vaginal secretions was evaluated with ELISA method.

Postpartum required information was recorded and available data were entered into IBM SPSS Statistics 28.0.1.0 software. Frequency, percentage, mean, standard deviation, median, minimum and maximum values were used in descriptive statistics. In the analysis of the data, mean/standard deviation evaluation was made and Mean±SD tests were used. Sensitivity, specificity, negative and positive predictive value of the results of the data used were calculated. P values <0.05 were considered significant. fFN positivity or negativity and cervical length 25 mm and below, between 25-30 mm and above 30 mm; The relationship in terms of demographic characteristics, clinical features and newborn characteristics was examined.

RESULTS

Age, body mass index (BMI, kg/m2), gravida, parity, number of abortions, previous weeks of preterm birth (PBW), hemoglobin (Hb) levels, fFN positive and negative patients are listed in Table 1 of 40 pregnant patients included in the study. Mean of the patients were evaluated, and the mean was also evaluated according to the cervical lengths.

There were multiple pregnancies in 11 of 40 pregnant who were included to study. When the results are also considered; all 11 pregnants had preterm birth was observed. However, when the fFN test results of these cases were examined, the test results of 8 pregnant women were positive and 3 pregnant women were found to be negative. When the cervical lengths were evaluated, the cervical length of 7 patients with fFN positive was determined as 30 mm and above, while 1 patient was determined as 25-30 mm. The cervical lengths of 3 negative pregnant women differed from each other, and 1 patient was 25-30 mm, while 2 pregnant women were 30 mm and above.

As seen in table 2, when compared the clinical features of patients showed that Bishop score was less in patients with positive test result (For fFN 1.23 ± 0.8 vs 2. 2 ± 1.8; for cervical length bishop score 25 mm and below 0.9 ± 0.05/ for the range of 25- 30 mm 0.9 ± 0.10 ve 30 mm and for above 1.02 ± 0.05). As seen in Table 2, the week of birth (DH) was significantly lower (31.3 ± 2.16 weeks for fFN positive vs 36.8 ± 2.8 weeks for negative); for cervical length 25 mm and less at birth week 33.5 ± 2.7 weeks; 32.5 ± 3.00 weeks for 25 mm-30 mm and 32.4 ± 2.5 weeks for 30 mm and above) cervical lengths were evaluated. The tocolysis time (TS) is shorter in fFN positive patients (7.1 ± 14.3 hours in positive patients, 10.1 ± 9.8 hours in negative patients).

Table 1. Comparison of features before birth in terms of fFN and cervical length

	Mean± SS* fFN			Mean± SS* Cervical Length (mm)			
	+	-	P value	n≤ 25	25< n<30	n ≥ 30	P value
Age (Year)	25.5 ± 4. 5	24.3 ± 3. 3	0.058	34.5 ± 5. 2	29.5 ± 3. 2	32.8 ± 5. 1	0.067
BMI, kg/m2	22.0 ± 5.5	26.7 ± 4. 2	0.063	28.2 ± 4. 5	27.2 ±2. 5	26.9 ± 4. 4	0.068
Gravida (n)	3.2 ± 1. 2	2.2 ± 1. 4	0.053	3.4 ± 1. 1	2.1 ± 1. 1	3.2 ± 1. 6	0.052
Parity (n)	0.59 ± 0. 8	0.89 ± 0. 1	0.06	1.02 ± 0. 9	2.02 ± 0. 7	0.88 ± 1. 3	0.064
Abortus (n)	2.7 ± 0. 5	1.8 ± 0. 7	0.019	1.3 ± 0. 6	0.7 ± 0. 4	0.98 ± 0. 4	0.041
PBW (week)	21.1± 4. 2	32.6 ± 1. 1	0.031	32.6 ± 5. 8	32.6 ± 3. 8	34.5 ± 3.0	0.059
Hb (gr/dl)	13.2 ± 2.1	15.3 ± 1. 0	0.057	13.2 ± 1. 7	11.2 ± 1. 72	12.3 ± 1. 4	0.054

PBW: preterm birth week

Table 2. The relationship of clinical features in terms of fFN and cervical length

	Mean± SS* fFN		Mean± SS* Cervical length (mm)		
	+	-	n≤ 25	25< n <30	n ≥ 30
Bishop	1.23 ± 0.8	2.2 ± 1. 8	0.9 ± 0.05	0.9 ± 0.10	1.02 ± 0.05
Dilatation(cm)	1.8 ± 1. 2	1.4 ± 1. 0	2.1 ± 1. 2	2.0 ± 0.8	1.4 ± 1. 0
Effacement (%)	32.2± 20. 5	29.0 ± 20. 3	37.6 ± 18. 7	28. 6 ± 15. 2	26.6 ±20. 4
Tocolysis Time (hour)	7.1 ± 14. 3	10.1 ± 9. 8	6.9 ± 16. 1	7.2 ± 15,0	7.8 ± 7. 8
Birth Week	31.3 ± 2. 16	35.5 ± 3.7	33.5 ± 2.7	32.5 ± 3.00	32.4 ± 2. 5

The fFN and cervical length ratios were calculated to predict delivery before 7, 14, 21 days and before 34, 37 weeks. While fFN gave better results in terms of specificity, cervical length gave lower results in terms of sensitivity than fFN. The best results were obtained when both results were evaluated together. Details are given in Tables 3 and 4.

Table 3. Predictive value of fFN for birth before 7, 14, 21 days and before 34, 37 weeks

	≤ 7 days	≤ 14 days	≤ 21 days	≤ 34 weeks	≤ 37 weeks
Sensitivity (%)	% 76.08	% 84.2	% 75.01	% 88.3	% 81.7
Specificity (%)	% 90.00	%79.01	% 71.09	%82.8	%78.02

Sensitivity: The ability of the test to identify patients among real patients.
Specificity: The ability of the test to determine the healthy ones among the real healthy ones

Tablo 4. Predictive value of cervical length for birth before 7, 14, 21 days and before 34, 37 weeks

	≤ 7 days	≤ 14 days	≤ 21 days	≤ 34 weeks	≤ 37 weeks
Sensitivity (%)	% 66.05	% 64.03	% 65.01	% 78.8	% 71.7
Specificity (%)	% 70.00	%69.05	% 77.03	%72.3	%68.09

Sensitivity: The ability of the test to identify patients among real patients.
Specificity: The ability of the test to determine the healthy ones among the real healthy ones

The power of predicting age, BMI, multiple pregnancy, preterm birth history, Bishop score, cervical dilatation, deletion, applied tocolysis fFN positivity, and cervical length to deliver within these weeks of deliveries under ≤ 7 days, ≤ 14 days, ≤ 21 days, ≤ 34 weeks, ≤ 37 weeks examined.

In line with these data the pregnancy week of patients go to hospital and birth week were examined. Patients whose cervical lengths were measured according to their complaints were tested for pregnant women who met the fFN test criteria. In line with this test, the diagnosis of preterm birth was made by considering the gestational weeks of the patients on the day of admission to the hospital. According to the test results of 32 patients with fFN positive out of 40 patients included in the study, it was predicted in how many days preterm delivery would occur.

In general, when the findings were evaluated, it was determined while 8 patients to be fFN test negative, 32 patients were fFN test positive. The evaluation of cervical length of fFN positive 32 patients; fFN test positive 3 patients' cervical length were 25 mm and below and in those patients, preterm birth occurred at 34th week of pregnancy. According to our findings patients with 25 mm – 30 mm cervical length were fFN test positive and they all gave birth before 34th week of pregnancy.

It was determined 9 patients with a cervical length 25 mm – 30 mm. Seven of these 9 patients were found to be fFN test

positive. In this group (fFN test positive 7 patients) 3 of them gave preterm birth before 34th week of their pregnancy. Other 4 patients gave birth before 37th week of pregnancy. According to these results patients who have 25 mm – 30 mm cervical length and fFN test positive, gave preterm birth all.

Tablo 5. The relationship of cervical lenght and fetal fibronectin

	Cervix Lenght		
	n≤ 25	25< n <30	n ≥ 30
FFN +	3	7	22
FFN-	0	2	6

Among 28 patients with a cervix length of 30 mm and above, 22 patients with positive fFN test were found. Eleven of these patients had preterm birth before 34th week. The other 5 patients with fFN test positive gave birth before 37th week of pregnancy.

When fFN results were evaluated in line with these data, it was determined that the predictive power of preterm birth was highly effective. Moreover, the specificity of fFN test results were higher than cervical length specificity.

DISCUSSION

In the study, it would be a more meaningful diagnostic method to evaluate fFN positivity/negativity and cervical length status together to diagnose preterm birth in patients.

Iams et al. (5) have examined fFN samples taken from 192 patients with ELISA method in their study. In the process from sample taken till birth was significantly higher in fFN (-) patients when compared with fFN (+) patients. When the results of this study were compared with the literature data in terms of time to birth and weeks of gestation at birth, it was determined that births occurred in a shorter time and earlier weeks. Including the pregnants who have up to 4 cm cervical opening is the reason of this result. Whereas the pregnants who have 2 cm and less cervical opening were included most of the studies. However, in cases with positive fibronectin results, births could be predicted in about 10 days, and patient management was reviewed within this framework.

Chuileannain et al. (6) retrospectively evaluated 70 women with regular uterine contractions, a singleton pregnancy before 34th weeks, and who underwent fFN (qualitative test kit) testing. In this study 20 pregnants were fFN positive and 50 were negative had been found. Ten births (14.3%) occurred before 34th week of pregnancy. It was determined in patients with positive test result tocolytic treatment and usage of corticosteroid was higher when compared with patients with negative test result.

In their study, Chuileannain et al. (6) presented the process from sampling till birth and this time was found to be 29.3 days in women with fFN test positive and 62.5 days in women with fFN test negative. The gestational week of birth was 34.9 weeks in women with fFN (+) and 38.2 weeks in women with fFN (-) were found.

In the study performed by Tekesin et al. (7), the week of gestation at birth and the time to birth were found to be significantly lower in women with positive fFN test.

In the study performed by Chuileannain et al. (6), it was determined that the rate of needing neonatal intensive care unit or receiving special care service was 6 times higher in newborn babies of pregnant women who were positive for fFN test compared to newborns of pregnant women with negative fFN test.

In a multicentered study which performed by Peaceman et al. (8), 725 singleton and 38 multiple pregnancies (totally 763 pregnants) were evaluated. In this study it was determined birth within 7 days, preterm birth, increased risk of neonatal morbidity and mortality.

Sakai et al. (9) have evaluated 185 pregnants with symptom of preterm labor by fFN test and preterm labor index (uterine contractions, bleeding, cervical dilatation). The patients with preterm labor index 4 and more were evaluated as positive, 3 and less were evaluated as negative. Preterm labor index is a simple method which can guess the preterm labor results with preterm birth or not. It improved the results of the combined use of the two tests in terms of predicting birth within a week. As a result, it was commented that, predicting the preterm birth, usage of two determinants instead of one would be increase of right diagnosis.

Rozenberg et al. (10) have evaluated symptomatic 76 pregnants with fFN test and cervical length in their study. Abnormal cervical length was determined as 26 mm. It was determined as preterm birth risk is 5.6% if fFN test (-) with normal cervical length; preterm birth risk is 30% if fFN test (+) with normal cervical length; preterm birth risk is 44% if fFN test (-) with short cervical length; preterm birth risk is 52% if fFN test (+) with short cervical length. With regard of these results of the study the patient is in safe if fFN test (-) with normal cervical length. However preterm birth risk would be increased if one of these parameters is abnormal. Preterm birth risk is maximum if these parameters are both abnormal. As can be seen, combining the two tests provides stronger predictive power than either alone.

In our study 11 multiple pregnancy was observed among total 40 pregnants. It has been observed that the incidence of multiple pregnancy has increased due to assisted reproductive techniques. Preterm birth is observed in 27% of pregnancies with assisted reproductive techniques (11). It was

determined that multiple pregnancies were 8,7% percentages of all preterm births. Thirty-50% of all multiple pregnancies end before 37 weeks (12). This is thought to be due to the stretching of the uterus. The prediction of preterm labor was considered in 11 patients with multiple pregnancies in our study.

In the study, when the clinical findings were compared, it was significantly higher in patients who have Bishop score, fFN test positive in both groups. When cervical dilatation and effacement were evaluated, a significant increase was found in cases with positive fFN test. No significant difference was found in those with fFN-positive tocolysis duration. Within the scope of the study, the relationship between fFN positivity/ negativity and cervical lengths of 40 pregnant women was examined, and fFN tests of pregnant women with a cervical length of 25 mm and below were determined as positive in line with this study, and delivery occurred before the 34th week in pregnant women. As a result of these findings, fFN results of patients with cervical lengths of 25 mm or less are directly proportional, there is a risk of premature birth in pregnant women and pregnant women should be observed in this process. But when the fFN test positivity and negativity were tested, there was no significant relationship was observed in pregnants who have 30 mm and above cervical length. It was observed that 78.57% of pregnant women with cervical lengths of 30 mm and above had preterm delivery.

As a result of these findings, when the relationship between fFN and cervical length is examined; For fFN positive patients, the preterm delivery rate of patients with a cervical length of 25 mm and less was determined as 100%, while the rate of preterm delivery in patients with a cervical length between 25 mm and 30 mm was determined as 77.8%. In addition, the preterm labor rate of fFN-positive patients with a cervical length of 30 mm and above was determined as 78.57%. Considering these results, while the cervical length was found to be significantly higher for fFN positive cases below 25 mm, its power in predicting preterm labor in cases between 25 mm and 30 mm and above 30 mm was found to be close to each other. When fFN results and cervical lengths are taken into account, all patients with a cervical length of 25 mm or less have a positive fFN test, and a strong correlation can be established between these two values. But the rate of patients who have fFN test positivity with normal cervical length was found to be high. In line with this result, it was determined that fFN positivity has a higher sensitivity in determining the probability of preterm birth compared to the cervical length ratio. More than 50% of twin pregnancies give birth at <37 weeks, and although ultrasonographic short cervix and fFN scanning are useful in detecting preterm birth, there is no effective method to predict preterm labor and prevent birth, since the delivery process is multifactorial in multiple pregnancies.

The small number of samples and the inclusion of multiple pregnancies in the study are limitations of the study.

Considering fetal fibronectin results and cervical lengths, all patients with cervical lengths of 25 mm and less were found to have positive fFN test, and a strong correlation was established between these two values. However, the rate of patients who have fFN test positivity with normal cervical length was found to be high. Fetal fibronectin positivity was found to have a higher sensitivity in determining the probability of preterm birth compared to the cervical length ratio.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: AA, Design: AA Supervising: AA, Financing and equipment: AA, Data collection and entry: AA,OSK , Analysis and interpretation: AA,OSK Literature search: OSK, Writing: OSK, Critical review: OSK

REFERENCES

1. Spong C.Y. Defining "term" pregnancy: Recommendations from the defining "term" pregnancy workgroup. Obstetrical and Gynecological Survey 2013;68(9):611-2. https://doi.org/10.1097/01.ogx.0000435519.66840.48
2. Simhan HN, Caritis SN. Prevention of preterm delivery. N Engl J Med 2007;357(5):477-87 https://doi.org/10.1056/NEJMra050435
3. Slattery MM, Morrison JJ. Preterm delivery. Lancet 2015;360(9344):1489-97. https://doi.org/10.1016/S0140-6736(02)11476-0
4. Iams JD, Berghella V. Care for Women with Prior Preterm Birth. In: Preterm Birth: Prevention and Management. Am J

Obstet Gynecol 2010;203(2):89-100. https://doi.org/10.1016/j.ajog.2010.02.004

5. Iams JD, Goldenberg RL, Mercer BM, et al. The Preterm Prediction Study: Recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1998;178(5):1035-40. https://doi.org/10.1016/S0002-9378(98)70544-7
6. Chuileannain FN, Bell R, Brennecke S. Cervicovaginal fetal fibronectin testing in threatened preterm labor - Translating research findings into clinical practice. Aust NZ Obstet Gynaecol 1998;38(4):399-402. https://doi.org/10.1111/j.1479-828X.1998.tb03096.x
7. Tekesin I, Marek S, Hellmeyer L, Reitz D, Schmidt S. Assessment of Rapid Fetal Fibronectin in Predicting Preterm Delivery. Obstet Gynecol 2005;105(2):280-4. https://doi.org/10.1097/01.AOG.0000150557.00298.47
8. Peaceman AM, Andrews WW, Thorp JM, Cliver SP, Lukes A, Iams JD, et al. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: a multicenter trial. Am J Obstet Gynecol 1997;177:13-8. https://doi.org/10.1016/S0002-9378(97)70431-9
9. Sakai M, Sasaki Y, Yamagishi N, Tanebe K, Yoneda S, Saito S. The preterm labor index and fetal fibronectin for prediction of preterm delivery with intact membranes. American College of Obstetricians and Gynecologists 2003;101:123-8. https://doi.org/10.1016/S0029-7844(02)02463-8
10. Rozenberg P, Goffinet F, Malagrida L, Giudicelli Y, Perdu M, Houssin I, et al. Evaluating the risk of preterm delivery: A comparison of fetal fibronectin and transvaginal ultrasonographic measurement of cervical length. Am J Obstet Gynecol 1997;176(1):196-9. https://doi.org/10.1016/S0002-9378(97)80035-X
11. Rottenstreich A, Levin G, Kleinstern G. History-indicated cervical cerclage in management of twin pregnancy. Ultrasound Obstet Gynecol 2019;54:517-23. https://doi.org/10.1002/uog.20192
12. Sen C. Preterm labor and preterm birth. J Perinat Med 2017;27;45(8):911-13. https://doi.org/10.1515/jpm-2017-0298

ORIGINAL RESEARCH

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The effect of obesity on oxidative stress parameters in pregnant women

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Abstract

Objective: In recent years, there has been a growing public concern about obesity, since it is known to reduce fertility in women and increase the duration of conception. Maternal obesity is also related to adverse pregnancy outcomes affected by placental malfunction. Therefore, in this study, we aimed to compare levels of oxidative stress between obese women and women of normal weight in the second trimester.

Method: We assessed lipid peroxidation by measuring the thiobarbituric acid reactive species (TBARS), as well as the antioxidant defense system by measuring the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) enzymes in 50 obese women (body mass index, BMI:36.60±4.95) and 51 women of normal weight (BMI:24.51±3.47).

Results: Increased lipid peroxidation and SOD enzyme activity were determined in obese pregnant women when compared to women of normal weight. Also, we found a significantly positive correlation (r:0.286, p:0.0435) between BMI and TBARS level as well as a significantly negative correlation (r: -0.421, p:0.002) between TBARS level and SOD enzyme activity. No significant difference was observed between the two groups in CAT and GPx enzymes activities.

Conclusion: Although increased SOD enzyme activity indicates that the antioxidant defense system is activated to deal with increased production of reactive oxygen species, maternal obesity is induced by oxidative stress via increased lipid peroxidation. Hence, maternal-obesity-induced oxidative stress in the second trimester should be followed up by clinicians since it may cause oxidative damage in the placenta during pregnancy.

Keywords: Antioxidant Defense System, Lipid Peroxidation, Maternal Obesity, Oxidative Stress

INTRODUCTION

Obesity is a serious health concern and is accepted as the fourth most common risk factor for noncommunicable diseases worldwide, after hypertension, dietary risks, and tobacco. According to the World Health Organization Obesity Report (1), nearly 60% of the adult population is either overweight or obese. Unfortunately, the numbers have also shown that the levels of both overweight and obesity in women of childbearing age are also at alarming levels. For instance, almost 70% of women of childbearing age are overweight and 40% are obese in Turkey. Also, a similar tendency has been reported in women of childbearing age in EU countries, including Hungary, Ireland, Portugal, Spain and UK (1). Our knowledge from previous studies is that maternal obesity not only affects mother health but also negatively affects health of the newborn. For instance, it enhances the risk of miscarriage, preeclampsia, gestational diabetes, excessive weight gain, and postpartum hemorrhage

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(2,3). Also, it is responsible for an increased risk of neural tube defects, fetal cardiac malformation, and congenital malformation (4-6).

Obesity is related to disturbances in metabolic balance, including lipid metabolism, inflammatory and hormonal processes. However, the etiology of obesity is a highly complex process including genetic, physiologic, psychological, and environmental factors (7). The latest studies have focused on the role of oxidative stress as a key mechanism that may increase the adverse conditions mentioned (8,9). Oxidative stress can be defined as an imbalance between oxidants like reactive oxygen species (ROS) and antioxidants. Reactive oxygen species include superoxide anion, hydroxyl radical, hydrogen peroxide etc. Oxygen-containing metabolites can be generated during normal cellular metabolism, but they are highly reactive and can oxidize macromolecules like lipids, proteins, and DNA (10,11). During pregnancy, mothers face several anatomical, physiological, and metabolic changes in their organisms. For fetal growth and maternal placental tissues, supplemental energy is required. For instance, it has been calculated that a mother needs 80.000 kcal of additional energy for 9 months (12). Therefore, it's known that the susceptibility to oxidative stress increases during pregnancy since the mother's body supports ROS production, especially in the second trimester, due to an increasing basic metabolism and oxygen consumption, as well as the use of fatty acids as a primary energy source for placental tissues (13). However, the placental antioxidant defense system has the ability to reduce the harmful effects of ROS for a healthy pregnancy (12). Bioindicators have become critical due to early diagnosis of several diseases in recent years. Thiobarbituric acid reactive substances (TBARS) are known as lipid peroxidation byproducts, and they are commonly used as one of the indicators of oxidative stress (14). Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) provide primer protection against ROS, and they are also mostly used as biomarkers to determine the body`s antioxidant status. Superoxide dismutase (SOD) catalyzes superoxide anion dismutation to hydrogen peroxide. Catalase (CAT) and glutathione peroxidase (GPx) catalyze the reduction of hydrogen peroxide to water (15). A few studies have revealed that total antioxidant levels are reduced in obese people, and as a result, oxidative stress is induced (16). It is also reported that excessive ROS production has adverse effects, including miscarriages, premature births, and malformations during pregnancy (13). On the other hand, some studies have shown that total antioxidant status is increased in the second trimester of pregnancy (12).

In light of these facts, it's important to use oxidative stress parameters as a routine laboratory test to reduce or take precautions against unexpected situations such as preeclampsia and miscarriage. The effect of obesity on oxidative stress is not fully elucidated during pregnancy; thus, in this study, we investigated the relationship between lipid peroxidation, antioxidant enzymes and body mass index to understand the role of overweight on oxidative stress during pregnancy.

METHOD

After the approval Local Ethics Committee (2018-82), women of normal weight (n:51) as a control group and obese women (n:50) who were in the second trimester of pregnancy were included in this study (Table 1). To find out whether obesity on its own is an independent risk factor for oxidative stress, subjects with a history of smoking, regular drug use, previous miscarriage and other diseases such as diabetes and hypertension were excluded. The body mass index (BMI) for each subject was calculated as weight divided by height squared and was used to assess obesity. Women whose BMI was higher than 30 kg/m^2 BMI were evaluated as obese. Venus blood samples (3 mL) from women were collected into EDTA tubes. Erythrocytes were washed with NaCl after centrifugation. Then, hemolysates, which are added with tris/HCl (20 mM, pH 8.0) were stored at -80 ^{0}C until analysis.

Table 1. Characteristics of the study population

	Control	Obese
Number	51	50
Age (years)	27.059±4.483	29.680±3.381
Gestation weeks	23.275±1.898	22.840±1.730
BMI	24.510±3.477	36.60±4.955*

BMI: Body mass index (kg/m^2). Asterisks indicate a significant difference between the control and obese groups ($p \leq 0.05$).

Biochemical Analysis

Lipid peroxidation (TBARS) analysis was determined by the method of Wills and Wilkinson (17), which measures thiobarbituric acid reagents and thiobarbituric acid (TBA) in aerobic conditions at 100 ^{0}C to give a pink-colored complex at 535 nm. Superoxide dismutase enzyme activity was analyzed indirectly by the method of McCord and Fridovich (18), which contained the inhibition of cytochrome c reduction at 550 nm. Firstly, 1.87 mU/mL xanthine oxidase was added to the medium containing 50 mM phosphate buffer, 0.1 mM EDTA, 10 mM cytochrome c, 0.05 mM hypoxanthine and the supernatant. Catalase enzyme activity was measured by the method of Aebi (19), which observes the reduction of absorbance due to hydrogen peroxide (H_2O_2) consumption at 240 nm for 1 min. The reaction was started after adding 20 µL of supernatant into the medium, including 75 mM phosphate buffer /pH 7.4) and 25 mM H_2O_2. Glutathione peroxidase enzyme activity was analyzed according to nicotinamide adenine dinucleotide phosphate (NADPH) reduction at 340

nm (ε = 6.22 µmol/cm2) for 1 min (20).

Statistical Analysis

The Kolmogorov-Smirnov test was conducted to determine the data normality, and Levene`s test was performed to control variance homogeneity among groups. Unpaired T test was performed to determine differences between groups (p≤0.05 considered significant). Pearson correlation analysis was conducted to calculate the correlation between biochemical analysis and BMI. All statistical analyses were performed using GraphPad Prism 9.0 software. All data were represented as the mean value ± standard deviation (SD). For estimating the sample power (1-β err prob) of the analyses, we first calculated the effect size (Cohen's d) for the respective T-test. Then, a power analysis was performed with Cohen's d and the sample size of each group using G*Power 3.1.7.

RESULTS

TBARS level was found to be significantly higher in the obese group than the control group (p≤0.001; 1-β err prob=0.912), (Figure 1). Also, SOD activity was found to be higher in the obese group when compared to the control (p≤0.0001; 1-β err prob=1.00), (Figure 2). However, no significant difference was detected for CAT and GPx activities between the control and obese groups (p≤0.05; 1-β err prob=0.798 for CAT; 0.697 for GPx). A Pearson correlation analysis in the obese group revealed a positive correlation between BMI and TBARS level (r: 0.286; p:0.0435) as well as a strong negative correlation between TBARS level and SOD activity (r: -0.421; p: 0.002), (Table 2).

Table 2. Correlation analysis between BMI and biochemical parameters in obese group

	BMI	TBARS	SOD	CAT	GPx
TBARS	r:0.2867 p:0.0435*	1	r: -0.4215 p: 0.0023*	r: 0.05249 p:0.717	r: 0.06187 p:0.821
SOD	r:0.0875 p:0.545	r: -0.4215 p: 0.0023*	1	r: 0.01665 p:0.9086	r: 0.02201 p: 0.8013
CAT	r: 0.01025 p: 0.9437	r: 0.05249 p:0.717	r: 0.01665 p:0.9086	1	r: 0.04309 p:0.638
GPx	r:0.01221 p:0.8752	r: 0.06187 p:0.821	r: 0.02201 p: 0.8013	r: 0.04309 p:0.638	1

BMI: Body mass index (kg/m²), TBARS: Thiobarbituric acid reactive substances (nmol/mg protein) SOD: Superoxide dismutase (U/mg protein) CAT: Catalase (µmol H_2O_2/mg protein/minute), GPx: Glutathione peroxidase (µmol/mg protein/minute) (p≤0.05). Asterisks indicate a significant difference between BMI and biochemical parameters (p≤0.05).

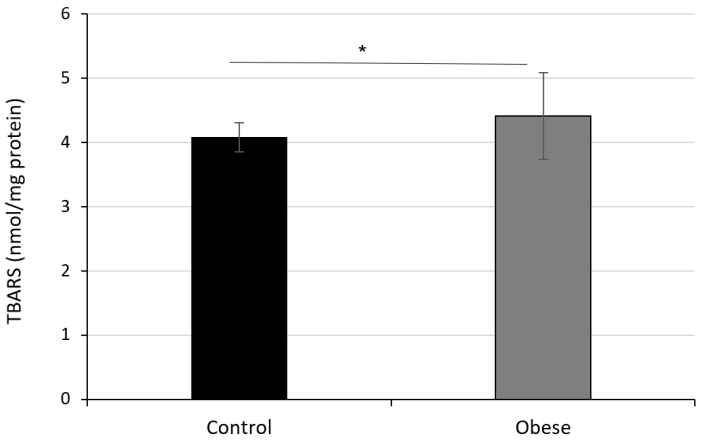

Figure 1: TBARS levels (nmol/mg protein) in the control and obese groups. Asterisks indicate a significant difference between the control and obese groups (p≤0.05).

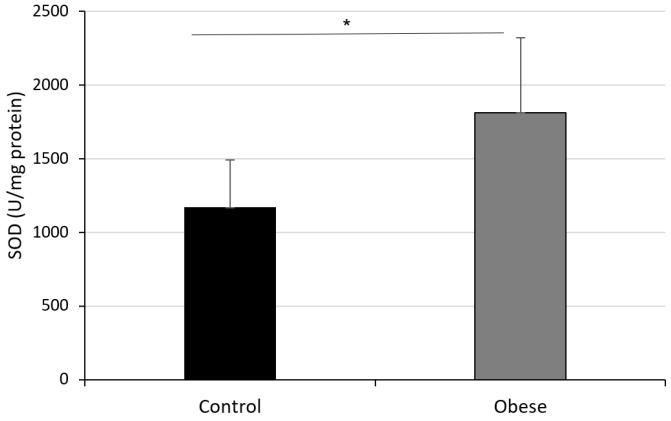

Figure 2: SOD activity (U/mg protein) in the control and obese groups. Asterisks indicate a significant difference between the control and obese groups (p≤0.05)

DISCUSSION

As we mentioned in the Introduction, the susceptibility to oxidative stress increases during pregnancy due to increased metabolic activity of the placenta and decreased antioxidant capacity, which are related to placental dysfunction. Dividing placental cells causes an increase in the production of ROS such as superoxide anion, which is a byproduct of aerobic respiration by the mitochondrial electron transport chain (21). Therefore, it is accepted by researchers that normal pregnancy is also a state close to the limit at which oxidative stress may alter to pathology (22). On the other hand, our knowledge from previous studies is that oxidative stress markers such as lipid peroxidation are increased in obese, non-pregnant women (23,24). However, the relationship between maternal obesity and placental oxidative stress is not fully clear. Adipose tissue in obesity has been recognized as a key underlying factor in several metabolic diseases (25). Previous studies have declared that the antioxidant defense

system is activated via upregulation of antioxidant enzymes to prevent oxidative damage in tissues in the early stages of obesity, but as fat accumulation increases, the antioxidant defense system is suppressed, and oxidative stress occurs (9). In normal conditions, there is a common belief that placental oxidative stress happens after 10 weeks of gestation due to high intervillous oxygen tension and contact between the fetal circulation and uterine spiral arteries (26). Thus, we have selected the second trimester of pregnancy to compare oxidative stress parameters in obese and pregnant women of normal weight. We found that TBARS levels, a byproduct of lipid peroxidation, are increased in obese pregnant women when compared to women of normal weight. Similar results were also reported in previous studies (27,28). For instance, Alanis et al. (22) have shown that maternal oxidative stress was found to be 31% higher in the obese group compared to the control group. In this study, we also determined a significantly positive correlation between BMI and TBARS levels in obese women, which is also in accordance with previous findings (28). The data of this experiment support the hypothesis that obesity promotes the induction of lipid peroxidation and suggest that increased lipid peroxidation can induce the production of ROS and oxidative stress.

On the other hand, in this study, antioxidant SOD enzyme activity in obese group was found to be significantly higher than in the control group. Similar findings were reported in the animal studies. For instance, SOD enzyme activity was increased in rats with diet-induced obesity (29). Also, we determined a significantly negative correlation between TBARS and SOD levels in obese women. However, no significant difference was observed for CAT and GPx activities in both groups. Amirkhizi et al. (30) have shown an inverse relationship between BMI and SOD activity in obese pregnant women. They mentioned that maternal obesity did not induce CAT enzyme activity. According to our results, despite the elevated SOD activity, increased TBARS levels in obese pregnant women suggest that elevated SOD enzyme activity alone is not adequate to protect placental lipids against oxidation.

Limitations of the Study

The study includes various limitations, such as a lack of results from other trimesters in comparison with the second trimester, as well as a lack of understanding of how maternal obesity affects oxidative stress parameters in newborns. Despite all these limitations, we believe that this study will help clinicians to take precautions to protect the health of obese pregnant women and their newborns.

CONCLUSION

In conclusion, results showed that maternal obesity is related to oxidative stress. This may be due to 1) the failure of the upregulation of antioxidant defense system, which may be affected by the duration of obesity, or 2) an increased availability of polyunsaturated lipids in the placenta, which triggers oxidative damage via lipid peroxidation. Therefore, maternal obesity-induced oxidative stress in the second trimester should be followed up by clinicians since it may cause oxidative damage in the placenta during pregnancy and affect newborns.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Cukurova University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 2018 and number 82, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: DK, SMY, Design: DK, SA, GAD, Supervising: DK, BG, SMY, Financing and equipment: DK, SA, GAD, SMY, Data collection and entry: DK, GAD, SMY, SA, Analysis and interpretation: DK, BG, SMY, GAD, Literature search: SA, GAD, Writing: DK, SMY, BG, Critical review: BG, SMY

REFERENCES

1. WHO European Regional Obesity Report 2022.
2. Wang G, Bartell TR, Wang X. Preconception and Prenatal Factors and Metabolic Risk. In: Halfon N, Forrest CB, Lerner RM, Faustman EM, editors. Handbook of Life Course Health Development. Cham (CH)2018. p. 47-59. https://doi.org/10.1007/978-3-319-47143-3_3
3. Farpour-Lambert NJ, Ells LJ, Martinez de Tejada B, Scott C. Obesity and Weight Gain in Pregnancy and Postpartum: An Evidence Review of Lifestyle Interventions to Inform Maternal and Child Health Policies. Front Endocrinol (Lausanne). 2018; 9:546. https://doi.org/10.3389/fendo.2018.00546
4. Martinez-Frias ML, Frias JP, Bermejo E, Rodriguez-Pinilla E, Prieto L, Frias JL. Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes. Diabet Med. 2005;22(6):775-81. https://doi.org/10.1111/j.1464-5491.2005.01492.x

5. Garcia-Patterson A, Erdozain L, Ginovart G, Adelantado JM, Cubero JM, Gallo G, et al. In human gestational diabetes mellitus congenital malformations are related to pre-pregnancy body mass index and to severity of diabetes. Diabetologia. 2004;47(3):509-14. https://doi.org/10.1007/s00125-004-1337-3

6. Rasmussen SA, Chu SY, Kim SY, Schmid CH, Lau J. Maternal obesity, and risk of neural tube defects: a metanalysis. Am J Obstet Gynecol. 2008;198(6):611-9. https://doi.org/10.1016/j.ajog.2008.04.021

7. Paolini B, Maltese PE, Del Ciondolo I, Tavian D, Missaglia S, Ciuoli C, et al. Prevalence of mutations in LEP, LEPR, and MC4R genes in individuals with severe obesity. Genet Mol Res. 2016;15(3). https://doi.org/10.4238/gmr.15038718

8. Alcala M, Sanchez-Vera I, Sevillano J, Herrero L, Serra D, Ramos MP, et al. Vitamin E reduces adipose tissue fibrosis, inflammation, and oxidative stress and improves metabolic profile in obesity. Obesity (Silver Spring). 2015;23(8):1598-606. https://doi.org/10.1002/oby.21135

9. Alcala M, Gutierrez-Vega S, Castro E, Guzman-Gutierrez E, Ramos-Alvarez MP, Viana M. Antioxidants and Oxidative Stress: Focus in Obese Pregnancies. Front Physiol. 2018; 9:1569. https://doi.org/10.3389/fphys.2018.01569

10. Lushchak VI. Free radicals, reactive oxygen species, oxidative stress and its classification. Che Biol Interact. 2014; 224:164-75. https://doi.org/10.1016/j.cbi.2014.10.016

11. Ray PD, Huang BW, Tsuji Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell Signal. 2012;24(5):981-90. https://doi.org/10.1016/j.cellsig.2012.01.008

12. Juan-Reyes SS, Gómez-Oliván LM, Islas-Flores H, Dublán-García O. Oxidative stress in pregnancy complicted by preeclampsia. Arch Biochem Biophys 2020; 681, 108255. https://doi.org/10.1016/j.abb.2020.108255

13. Tobola-Wrobel K, Pietryga M, Dydowicz P, Napierala M, Brazert J, Florek E. Association of oxidative stress on pregnancy. Oxid Med Cell. 2020; 6398520. https://doi.org/10.1155/2020/6398520

14. Devrim E, Tarhan I, Erguder IB, Durak I. Oxidant/antioxidant status of placenta, blood, and cord blood samples from pregnant women supplemented with iron. J Soc Gynecol Investig. 2006;13(7):502-5. https://doi.org/10.1016/j.jsgi.2006.07.004

15. Koc F, Atli G, Menziletoglu SY, Kose S. Antioxidant imbalance in the erythrocytes of Myotonic dystrophy Type 1 patients. Arch Biochem Biophys. 2020; 680:108230. https://doi.org/10.1016/j.abb.2019.108230

16. Vincent HK, Innes KE, Vincent KR. Oxidative stress, and potential interventions to reduce oxidative stress in overweight and obesity. Diabetes Obes Metab. 2007;9(6):813-39. https://doi.org/10.1111/j.1463-1326.2007.00692.x

17. Wills ED, Wilkinson AE. Release of enzymes from lysosomes by irradiation and the relation of lipid peroxide formation to enzyme release. Biochemical Journal. 1966;99(3):657-66. https://doi.org/10.1042/bj0990657

18. McCord JM, Fridovich I. Superoxide Dismutase. Journal of Biological Chemistry. 1969;244(22):6049-55. https://doi.org/10.1016/S0021-9258(18)63504-5

19. Aebi H. Catalase in Bergmeyer Hans Ulrich, Methods of Enzymatic Analysis: Academic Press Incorporated, New York; 1974. 273-278. https://doi.org/10.1016/B978-0-12-091302-2.50032-3

20. Carlberg I, Mannervik B. Purification and characterization of the flavoenzyme glutathione reductase from rat liver. J Biol Chem. 1975;250(14):5475-80. https://doi.org/10.1016/S0021-9258(19)41206-4

21. Wu F, Tian FJ, Lin Y. Oxidative Stress in Placenta: Health and Diseases. Biomed Res Int. 2015; 2015:293271. https://doi.org/10.1155/2015/293271

22. Alanis MC, Steadman EM. Maternal Obesity and Placental Oxidative Stress in the First Trimester. Journal of Obesity & Weight Loss Therapy. 2012;2(7). https://doi.org/10.4172/2165-7904.1000143

23. Keaney JF, Jr., Larson MG, Vasan RS, Wilson PW, Lipinska I, Corey D, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. Arterioscler Thromb Vasc Biol. 2003;23(3):434-9. https://doi.org/10.1161/01.ATV.0000058402.34138.11

24. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. Journal of Clinical Investigation. 2004;114(12):1752-61. https://doi.org/10.1172/JCI21625

25. Matsuda M, Shimomura I. Increased oxidative stress in obesity: implications for metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and cancer. Obes Res Clin Pract. 2013;7(5): e330-41. https://doi.org/10.1016/j.orcp.2013.05.004

26. Jauniaux E, Gulbis B, Burton GJ. Physiological implications of the materno-fetal oxygen gradient in human early pregnancy. Reprod Biomed Online. 2003;7(2):250-3. https://doi.org/10.1016/S1472-6483(10)61760-9

27. Malti N, Merzouk H, Merzouk SA, Loukidi B, Karaouzene N, Malti A, et al. Oxidative stress and maternal obesity: feto-placental unit interaction. Placenta. 2014;35(6):411-6. https://doi.org/10.1016/j.placenta.2014.03.010

28. Rakić G U-BA, Fabri Galambos I, Dobrijević D, Uram-Dubovski J, Drašković B. Relationship between maternal pregestational body mass index and neonatal oxidative stress. Progr Nutr. 2022;23(4): e2021319. https://doi.org/10.23751/pn.v23i4.12288

29. Dobrian AD, Davies MJ, Prewitt RL, Lauterio TJ. Development of hypertension in a rat model of diet-induced obesity. Hypertension. 2000;35(4):1009-15. https://doi.org/10.1161/01.HYP.35.4.1009

30. Amirkhizi F, Siassi, F., Minaie, S., Djalali, M., Rahimi, A., Chamari, M. Is obesity associated with increased plasma lipid peroxidation and oxidative stress in women? ARYA Atherosclerosis Journal. 2007;2(4):189-92.

ORIGINAL RESEARCH

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Prevalence of impaired glucose tolerance and its association with adverse perinatal outcomes in non-gestational diabetes pregnancies

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Abstract

Objective: Gestational diabetes mellitus (GDM) is characterized by glucose intolerance with onset during pregnancy and is one of the most common metabolic disorders complicating pregnancy. The aim of this study was to evaluate the risk of maternal and neonatal outcomes in non-gestational diabetes pregnancies with abnormal glucose challenge test (GCT) and abnormal glucose tolerance test (GTT) results.

Method: In this retrospective cohort study of 2982 singleton pregnancies, all patients underwent a non-fasting 50 g GCT at 24 to 28 weeks of gestation. A GCT cutoff of ≥ 140 mg/dl was selected. Women with an elevated GCT underwent prompt diagnostic testing with a 3-hour GTT. Subjects were divided into four groups according to GCT and GTT results.

Results: There was an impaired glucose tolerance in 19.2 % of patients and 14.7 % of them had mild glucose intolerance and 4.5 % of them had moderate glucose intolerance. As expected, there was statistically significant difference in fetal macrosomia, neonatal hypoglicemia, PE, primary CS, and preterm birth between secreening negative and GDM patients ($p < 0.0001$). We also observed statistically significant difference in neonatal hypoglicemia ($p = 0.0001$) and PE ($p = 0.0277$) between screning negative and mild glucose intolerance group. Moreover, there was a significant difference in fetal macrosomia ($p=0.0480$) between mild glucose intolerance and moderate glucose intolerance groups.

Conclusion: Compared with screening negative group, mild and moderate glucose intolerance are associated with increased adverse maternal and neonatal outcomes even in the absence of GDM.

Keywords: Gestational diabetes mellitus, Fetal macrosomia, Neonatal hypoglicemia, Cesarean section, Glucose intolerance

INTRODUCTION

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance with onset during pregnancy and common metabolic disorders complicating pregnancy that affect mother and fetus (1). Its prevalence varies among different races and different ethnic groups dependent on their underlying risk of diabetes and approximately 4-17% of all pregnant women are affected by diabetes mellitus (DM) in pregnancy (2, 3).

There are several adverse outcomes for pregnant women and their fetuses associated with GDM. Complications include higher risk for preeclampsia (PE), preterm delivery, operative and cesarean delivery, shoulder dystocia, birth trauma, stillbirth, hydramnios, fetal macrosomia and large for gestational age (LGA) infant, neonatal intensive

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care unit (NICU) admission, perinatal mortality, neonatal respiratory problems, hyperbilirubinemia and hypocalcemia (4–12).

Adequate and efficient screening may prevent these maternal and fetal adverse outcomes. The purpose of GDM screening is to detect asymptomatic individuals. There is no universally accepted approach to screening for GDM nor even agreement on appropriate glucose thresholds at which gestational diabetes is diagnosed (13–16). There are many different strategies for the screening of GDM in pregnancy (17). The American College of Obstetricians and Gynecologists (ACOG) recommends a two-stage approach using cutoff of the Carpenter-Coustan criteria (1). The first step is the glucose challenge test (GCT) and the second step to screen positive patients is the 100-gram, three-hour oral glucose tolerance test (GTT), a diagnostic test for GDM. If two or more of the four values increase in the GTT, the patient is diagnosed with GDM.

Minor degrees of glucose intolerance in pregnancy, defined as mild or moderate glucose-intolerant state, intermediate between normal and GDM. The criteria used to classify glucose tolerance in pregnancy show some differences (18). In studies, these women's metabolic state are referred to impaired glucose tolerance (IGT), insulin resistance, carbonhydrate intolerance, gestational impaired glucose tolerance (G-IGT) and borderline gestational glucose intolerance (BGGI) (18–25).

It is obvious that patients with GDM are at increased risk for adverse obstetric and perinatal outcomes and treatment with close monitoring are required. However, adverse perinatal outcomes of insulin resistant group of patients who have abnormal 1-hour GCT with negative 3-hour GTT and have abnormal 1-hour GCT with one abnormal value on GTT as well as their management during and after pregnancy is controversial (1, 19–22, 26, 27).

This study aimed to investigate the rate of mild and moderate glucose intolerance in non-GDM pregnancies and their relationship with adverse maternal and neonatal outcomes..

METHOD

Study population

A total of 2982 single pregnant women of Turkish ethnic origin, aged between 18-48 years, between January 2013 and December 2016 were included in this retrospective cohort study. All subjects were divided into four groups according to GCT and GTT results; Group I (Screen negative subject, n=2304): GCT value ≤ 140 mg/dl. Group II (mild glucose intolerance, n = 438): GCT value ≥ 140 mg/dl, with normal GTT. Group III (moderate glucose intolerance, n=133): GCT value ≥ 140 mg/dl with one abnormal value on GTT, and Group IV (gestational diabetes mellitus, n=107): GCT ≥ 140mg/dl with two or more abnormal value on GTT, or GCT ≥ 200 mg/dl.

Patients who were diagnosed with multiple pregnancies, pre-gestational diabetes and GDM diagnosed before two step screening at 24-28 weeks of gestations were excluded from the study. Also, women who have negative OGTT results, but receiving diet and/or insulin therapy during follow up due to incident macrosomia and elevated fasting glucose and thus being classified as GDM were excluded. In addition, pregnant women who gave birth before the 20th gestational week and gave birth to babies weighing less than 500 grams were excluded from the study.

All procedures performed were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was taken from the institutional Ethical Committee of the Balikesir University, School of Medicine (Date:19.10.2016/ registration number: 2016/94).

Glucose testing

All participants underwent a non-fasting 50 g GCT at 24 to 28w of gestation. Those with a GCT value of 200 mg/dl or higher are diagnosed as GDM. A GCT cutoff of ≥ 140 mg/dl was selected. Those with elevated GCT underwent prompt diagnostic testing with a fasting 100 g GTT. Blood samples were drawn 1, 2, and 3 hours after glucose intake. All tests were performed in outpatient clinics, during routine antenatal care. GDM was diagnosed in patients in whom two of the four values in the oral glucose tolerance test were found to be abnormal according to the Carpenter and Coustan criteria (28) (0h, 95 mg/dl; 1h, 180 mg/dl; 2h, 155 mg/dl; and 3h, 140 mg/dl). Pregnant women who did not have GDM on diagnostic testing returned to routine pregnancy follow-up.

Data collection

All data of patients were obtained from medical records. These data include demographic information, pregnancy complications, obstetric history, delivery process and outcomes, as well as neonatal outcomes.

Study outcomes

Maternal and neonatal outcomes were compared among the groups. Maternal outcomes were primary cesarean section (CS) and PE. Neonatal outcomes were fetal macrosomia, stillbirth, neonatal death, and neonatal hypoglicemia.

Gestational weeks were calculated according to the last menstrual period of all patients. If there was a 7-day or more difference between the gestational week calculated according to the fore-aft length distance measured in the first trimester ultrasound and the gestational week calculated according to the last menstrual date, the gestational week calculated by ultrasound was accepted (29). The preeclampsia was diagnosed with the current guideline of ACOG (American College of Obstetricians and Gynecologists). According to this guideline (21), hypertension (140/90 mmHg or higher blood pressure at least twice with an interval of at least 6 hours after 20 weeks of gestation), proteinuria (300 mg in 24-hour urine or ≥1+ with dipstick) were considered as preeclampsia (30). Macrosomia was regarded as birthweight above 4000 g (29). Neonatal Hypoglycemia was defined as neonatal glucose ≤ 1.6 mmol/l during the first 24 h after birth (31). According to international standards, death occurring at or after the 24th week of pregnancy is defined as stillbirth (32).

Statistical analysis

MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used for statistical analysis. A p-value of < 0.05 was considered statistically significant. The distribution of evaluated variables in four groups was studied by describing the mean ± standard deviation (SD) or median (minimum-maximum), where applicable. One-way analysis of variance (ANOVA) or Kruskal–Wallis test were used to analyse more than two independent groups. Levene's test was used to analyse variances. When the p value from one-way ANOVA or Kruskal–Wallis test statistics was statistically significant, the Scheffé test or Post-Hoc (Conover) analysis was used to determine which group differed from the others. Odds ratio (OR) and the 95% confidence intervals (CI) were calculated with univariate analysis. The Chi-square test was used to compare categorical data.

RESULTS

A total of 3336 pregnant women were evaluated between the study periods. 581 pregnancies were excluded, 93 (2.8 %) had overt diabetes, 164 (4.9 %) had twin pregnancies and 97 (2.9 %) had GDM diagnosed before 24 weeks of gestation (Figure 1). 2982 pregnant women who underwent GDM screening at 24 to 28 weeks of gestation were included in this study. We found that the total prevalance of GDM was 6.5 % (2.9 % diagnosed before the 24 weeks of gestation and 3.6 % diagnosed with two step screening between 24-28 weeks of gestation). On the other hand, there was an impaired glucose tolerance in 19.2 % of patients and 14.7 % of them had mild glucose intolerance and 4.5 % of them had moderate glucose intolerance. We also found that the rate of the fetal macrosomia, neonatal hypoglicemia, preeclampsia and preterm birth were 5.6 %, 4.2 %, 3.6% and 5.6 %, respectively. Additionally, the rate of the stillbirth was 0.5 % in our studied population. The demographic features of participants was summarized in Table 1.

Table 1 Demographic features of participants

Characteristics	Total patients	
Age (year), mean±SD	26.8 ± 5.6	
Parity, median (min-max)	1 (0-6)	
BMI (kg/m2), mean±SD	24.45 ± 3.63	
Gestational weeks at delivery	39w + 2d	
Newborn Sex		
Female	1488	49.9
Male	1494	50.1
Birth weight (gram) mean±SD	3248.2 ± 525.2	
Mild Glucose intolerance	438	14.7
Moderate Glucose intolerance	133	4.5
Gestational diabetes mellitus	204	6.5
Fetal macrosomia rate, n (%)	167	5.6
Neonatal hypoglicemia rate, n (%)	124	4.2
Preeclampsia rate, n (%)	108	3.6
Delivery type, n (%)		
Vaginal Delivery	1713	57.3
Cesarean Section	872	29.2
Assissted Vaginal Delivery	20	0.7
Primary Cesarean Section	387	12.8
Preterm Birth, n (%)	166	5.6
Stillbirth, n (%)	14	0.5

According to the present results, maternal age was significantly lower in screen negative group. However there were no differences between patients with mild glucose intolerance, moderate glucose intolerance and GDM. Maternal pre-pregnancy BMI were significantly higher in patients with GDM than those patients with screen negative and mild glucose intolerance. There were no differences in parity between the groups (Table 2).

We showed that there was a statistically significant difference between the groups in terms of fetal macrosomia, neonatal hypoglycemia, PE, primary cesarean section and preterm delivery rates ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$, $p < 0.0001$ and $p = 0.0001$, respectively) (Table 2).

Table 2 Demographic and clinical characteristics of groups

Characteristics	Group 1 (n = 2304) Screen Negative		Group 2 (n = 438) Mild Glucose Intolerance		Group 3 (n = 133) Moderate Glucose Intolerance		Group 4 (n = 107)GDM		P value
	n	%	n	%	n	%	n	%	
Age (year), mean±SD	26.2 ± 5.5[a,b,c]		28.7 ± 5.4		28.2 ± 5.9		29.6 ± 6.1		< 0.0001[$]
<25	1118	48.5	125	28.5	43	32.3	33	30.8	
25-30	575	24.9	127	28.9	35	26.3	20	18.9	
30-35	418	18.1	117	26.7	35	26.3	31	28.9	
≥35	193	8.4	69	15.8	20	15.1	23	21.4	
Parity, median (min-max)	1 (0-6)		1 (0-4)		1 (0-5)		1 (0-6)		0.0528[#]
0	849	36.8	148	33.8	41	30.8	33	30.8	
1	1221	52.9	233	53.2	72	54.1	60	56.1	
2	174	7.6	31	7.1	12	9.0	9	8.4	
≥3	60	2.6	26	5.9	8	6.0	5	4.7	
BMI (kg/m2), mean±SD	24.4±3.6[c]		24.5±3.5[e]		25.1±4.1		25.7±3.3		< 0.0001[#]
<18.5	6	0.5	6	2.4	3	4.3	1	2.1	
18.5-25	735	57.6	118	47.4	29	42.0	20	41.7	
>25	536	41.9	125	50.2	37	53.6	27	56.2	
Gestational weeks at delivery									
<37	117	5.1 [c]	22	5.0 [e]	11	8.3	16	14.9	0.0001[#]
37-41	2072	89.9	395	90.2	114	85.7	91	85.1	
>41	115	5.0	21	4.8	8	6.0	0	0.0	
Newborn Sex									
Female	1166	50.6	212	48.4	61	45.9	54	50.5	0.3998[#]
Male	1138	49.4	226	51.6	72	54.1	53	49.5	
Birth weight (gram) mean±SD	3245.1±512.9[c]		3226.7±511.8[e]		3234.7±669.5		3400.8±558.0		0.0004 [#]
<2500	158	6.9	27	6.2	11	8.3	6	5.6	
2500-4000	2035	88.3	384	87.6	109	81.9	86	80.4	
>4000	111	4.8	27	6.2	13	9.8	15	14.0	
Fetal macrosomia, n (%)									
Yes	111	4.8 [b,c]	27	6.2 [d,e]	15	11.3	15	14.0	<
No	2193	93.2	411	(93.8	120	90.3	92	86.0	0.0001[#]
Neonatal hypoglicemia, n(%)									
Yes	63	2.7 [a,b,c]	28	6.4 [e]	14	10.5	19	17.8	<
No	2241	97.3	410	93.6	119	89.5	88	82.2	0.0001[#]
Preeclampsia, n (%)									
Yes	66	2.8 [a,c]	22	5.1 [e]	7	5.3	13	12.1	<
No	2238	97.2	416	94.9	126	94.7	94	87.9	0.0001[#]
Delivery type n (%)									
Vaginal Delivery	1358	58.9	218	49.8	71	53.4	56	52.3	<
Cesarean Section	673	29.2	155	35.4	33	24.8	11	10.3	0.0001[#]
Assissted Vaginal Delivery	12	0.5	2	0.5	2	1.5	4	3.7	
Primary Cesarean Section	261	11.3 [b,c]	63	14.4 [e]	27	20.3 [f]	36	33.6	
Preterm Birth, n (%)									
Yes	117	5.1 [c]	22	5.0 [e]	11	8.2	16	14.9	0.0001[#]
No	2187	94.9	416	95.0	122	91.8	91	85.1	
Stillbirth, n (%)									
Yes	10	0.4	3	0.7	0	0	1	0.9	0.6621[#]
No	2294	99.6	435	99.3	133	100	106	99.1	

ANOVA *Kruskal Wallis test, # Chi-Squared test
Data are presented mean ± SD or median (minimum-maximum)
a. Screen negative group versus mild glucose intolerance group ($p < 0.05$)
b. Screen negative group versus moderate glucose intolerance group ($p < 0.05$)
c. Screen negative group versus GDM group ($p < 0.05$)
d. Mild glucose intolerance group versus moderate glucose intolerance group ($p < 0.05$)
e. Mild glucose intolerance group versus GDM group ($p < 0.05$)
f. Moderate glucose intolerance group versus GDM group ($p < 0.05$)

Our subgroup analysis showed that the rate of fetal macrosomia was significantly lower in screening negative group than in patients with moderate glucose intolerance and GDM (adjusted Odds Ratio (aOR) (95% confidence interval (CI)): 2.14 (1.17-3.91) p = 0.0037 and aOR (95% CI): 3.22 (1.81-5.74) p < 0.0001, respectively). Also, compared with mild glucose intolerance patients, fetal macrosomia rate was significantly higher in patients with GDM (p =0.0064). Neonatal hypoglicemia rate was significantly lower in screen negative group than patients with mild glucose intolerance, moderate glucose intolerance and GDM (aOR (95% CI): 2.43 (1.54-3.84), p = 0.0001, aOR (95% CI): 4.18 (1,72-5,13), p < 0.0001, and aOR (95% CI): 7.68 (4.41-13.38), p < 0.0001, respectively). Moreover, neonatal hypoglicemia rate was significantly lower in patients with mild glucose intolerance than those and with GDM (p = 0.0002, respectively). PE rate was significantly lower in screening negative group than mild glucose intolerance and GDM group (aOR (95% CI): 1.79 (1.09- 2.94), p = 0.0277 and aOR (95% CI): 4.68 (2.49-8.80) p < 0.0001, respectively). Additionaly, PE rate was significantly lower in patients with mild glucose intolerance than those with GDM (p = 0.0133). Primary CS rate was significantly lower in screening negative group than patients with moderate glucose intolerance and GDM (aOR (95% CI): 1.98 (1.25- 3.14), p = 0.0029 and aOR (95% CI): 3.34 (2.16-5.19), p < 0.0001, respectively). Moreover, primary CS rates were significanly different in mild and moderate glucose intolerance groups than GDM (p < 0.0001 and p = 0.0287, respectively) (Table 3). Additionally, preterm birth rates were significantly lower in screening negative and mild glucose intolerance groups than GDM (p < 0.0001 and p = 0.0003, respectively). However, there was no difference in the rate of stillbirth between the groups (p = 0.6621) (Table 3).

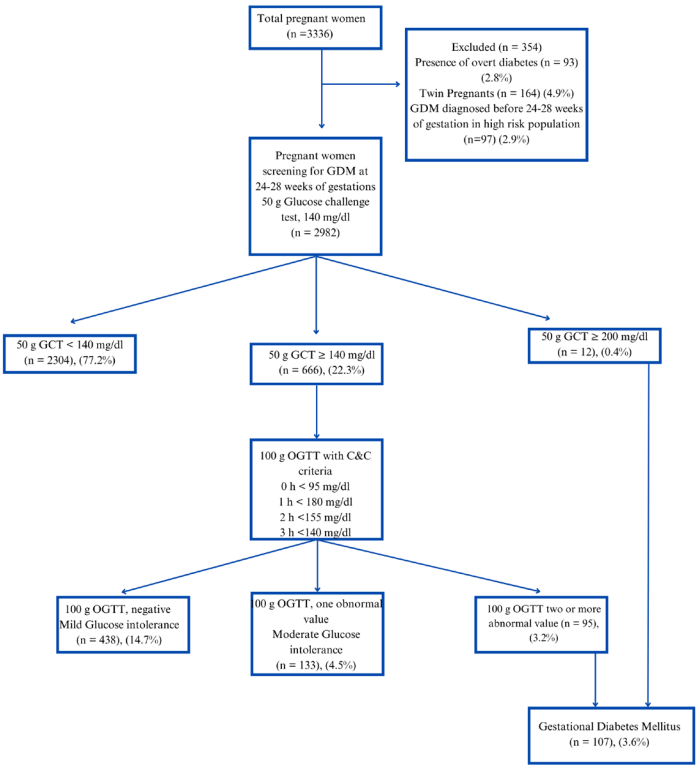

Figure 1. Flow chart showing recruitment of the study women and prevalence of glucose intolerance

Table 3 Comparable analysis of maternal and fetal outcomes of women in screening negative, mild glucose intolerance, moderate glucose intolerance and GDM groups.

Total cohort n=2.982	Group 1 (n = 2304) Screen Negative Group	Group 2 (n = 438) Mild Glucose Intolerance Group	Group 3 (n = 133) Moderate Glucose Intolerance Group	Group 4 (n = 107) GDM
	n aOR (95% CI)	n aOR (95% CI)	n aOR (95% CI)	n aOR (95% CI)
Fetal macrosomia	111/2193 Ref	27/411 1.30 (0.84- 2.00)	13/120 2.14 (1.17-3.91)	15/92 3.22 (1.81- 5.74)
Neonatal hypoglicemia	63/2241 Ref	28/410 2.43 (1.54-3.84)	14/119 4.18 (2.28-7.68)	19/88 7.68 (4.41-13.38)
Preeclampsia	66/2238 Ref	22/416 1.79 (1.09- 2.94)	7/126 1.88 (0.85- 4.19)	13/94 4.69 (2.50-8.80)
Primary Cesarean section	261/1358 Ref	63/218 1.50 (1.10-2.05)	27/71 1.98 (1.25- 3.14)	36/56 3.34 (2.16-5.19)
Preterm Birth	117/2187 Ref	22/416 0.99 (0.62-1.58)	11/122 1.69 (0.88-3.21)	16/91 3.29 (1.87-5.77)

Logistic regression included the outcomes; crude and adjusted (aOR); 95% confidence intervals (CI).
aOR, adjusted odds ratio, CI, confidence interval; GDM, gestational diabetes mellitus.

DISCUSSION

In this retrospective cohort study, we evaluated GDM screening results of pregnant women with mild glucose intolerance, moderate glucose intolerance and GDM. According to our present results, the prevalance of GDM and impaired glucose tolerance were 6.5% and 19.2%, respectively. Pregnant women with impaired glucose tolerance and GDM; demonstrated significantly higher adverse maternal and perinatal outcomes, including increased rate of fetal macrosomia, neonatal hypoglicemia, PE, primary CS and preterm birth.

The prevalence of GDM greatly alterable depending on population characteristics and the diagnostic criteria used. Previous studies demonstrated that the prevalence of GDM varies from 6% to 18% (2, 3) and is rising worldwide in line with increasing trends of maternal obesity, physical inactivity, and maternal age (4, 33). Comperable with these results, the total prevalance of GDM was 6.5% in our study population. Present result may be due to the fact that our participants are relatively young and underweight.

In literature, a number of studies have demonstrated that GDM is associated with increased rates of short and long-term advers maternal and fetal outcomes including fetal macrosomia, shoulder dystocia, birth injury, gestational hypertension, PE, CS, polyhydramnios, preterm birth, neonatal hypoglycemia, neonatal intensive care unit admission and respiratory distress (4–6, 8, 9). Comparable with these results, we found that compared to screening negative group, patients with GDM had increased rate of primary CS, fetal macrosomia, neonatal hypoglicemia, PE and preterm birth. In the present study, to reduce probability of errors, we screened high risk pregnancies with maternal age ≥ 25 years, family history of diabetes, previous macrosomic babies or stillbirth in the first trimester with fasting plasma glucose, random plasma glucose, HbA1c, and 75-g 2-hour OGTT and those patients with diabetes (n = 97, 2.9%) were excluded from the study.

Previous studies have revealed that mild to moderate glucose intolerance is associated with increased rates of adverse pregnancy outcomes such as shoulder distosia, fetal macrosomia, PE, neonatal hypoglicemia, admission of neonatal intensive care unit, preterm birth and cesarean delivery in non-diabetic population (5, 15, 18, 21). Temming et al. compared screening negative patients with screening positive patients who had one abnormal GTT value without GDM had increased risk of pregnancy-induced hypertension (PIH), PE, cesarean delivery, and macrosomia (18). Similarly, Metzger et al. showed a strong correlation between mild or severe hyperglycemia without GDM and increased rates of large for gestational age (LGA), primary CS, shoulder dystocia, PE and elevated cord blood c-peptide levels in Caucasian and Asian women (34). In another study conducted by Dodd et al., it is reported that Australian women with an elevated 1h 50-g GCT and mild glucose intolerance but no GDM on a 2h 75-g GTT had raised risks of shoulder dystocia, PE and neonatal hypoglycemia (21). Landon et al. compared women with a normal 1-hour 50-gram screening test with women with varying degrees of insulin resistance. There were increasing rates of cord blood c-peptide, hypoglycemia, hyperbilirubinemia, LGA, birth trauma and shoulder dystocia across increasing groups with insulin resistance (35). Comperable with these results, we found a linear relationship between presence of mild or moderate glucose intolerance and the rate of pregnancy complications such as primary CS, fetal macrosomia, neonatal hypoglycaemia, PE and preterm birth in non-GDM Turkish pregnants.

However, results of some studies investigating the relationship between GDM and perinatal death were varied. A cohort study conducted by Billionet et al. showed that compared with non-diabetic population, the perinatal mortality was significantly higher in patients with GDM (6). Contrary to these results, some recent large-population based cohort studies demonstrated that perinatal mortality in offsprings from GDM mothers was significantly lower than or similar to the non-diabetic population (9, 36). We found no significant difference between the groups in terms of results for stillbirth. This may be associated with small sample size of participants or exclusion of high risk pregnancies diagnosed as diabetes before 24 weeks of gestations.

In literature, different groups and societies recommend different approaches and criteria for screening and diagnosis of GDM (1, 33, 37–40). Most common known screening strategies are one step 75g 2h test using The International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (33) and two step 50g 1h followed for abnormals by 100gr 3h test using C&C criteria (37, 40). In clinical practice, two step aproaches are commonly used in our country for screening and diagnosis of GDM. In order to control blood glucose levels, pregnant women with GDM are recommended a healty diet, oral anti-diabetics or insulin use during pregnancy according to the guideline. However, for other women who is screening negative, screening positive and 100g negative, or screening positive and one abnormal value in GTT, the routine prenatal care is suggested as recommended by the guideline (37, 40). As seen in the results of previous studies and the present study, pregnancy outcomes of patients with negative screening and patients with mild glucose intolerance or moderate glucose intolerance are different and new strategies or approaches are needed to optimize prenatal care in these patient groups.

Limitations of the study

The present study has some limitations. The main limitations were retrospective study design and relatively

small number of patients included in the studied population. Additionally, collection of all data and accounting for all potential confounding variables are not possible and there was some missing data of BMI even though they were included in the analysis.

CONCLUSION

In conclusion, according to the present results, it is obvious that there are two separate groups between screening negative patients and GDM in terms of GDM screening and presence of pregnancy complications. The present study suggests further studies to prevent or minimize pregnancy complications in these groups.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Balikesir University Research Ethics Committee for this study with date 19.10.2016 and number 2016/94, and Helsinki Declaration rules were followed to conduct this study.

Author Contribution

Concept: AU, MH, CBBH, CSU, Design: AU, CSU, Supervising: AU, MH. CSU, Financing and equipment: AU, MH, CBBH, CSU, Data collection and entry: AU, CBBH, CSU, Analysis and interpretation: AU, MH, CBBH, CSU, Literature search: AU, MH, CBBH, CSU, Writing: AU, MH, CBBH, CSU, Critical review: AU, MH, CBBH, CSU.

REFERENCES

1. Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018;131(2):e49-e64. https://doi.org/10.1097/AOG.0000000000002501
2. Zhou T, Du S, Sun D et al. Prevalence and trends in gestational diabetes mellitus among women in the United States, 2006–2017: a population-based study. Frontiers in Endocrinology. 2022;13. https://www.frontiersin.org/articles/10.3389/fendo.2022.868094
3. Nigatu B, Workneh T, Mekuria T, et al. Prevalence of Gestational Diabetes Mellitus among pregnant women attending antenatal care clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. Clinical diabetes and endocrinology. 2022;8(1):1-6. https://doi.org/10.1186/s40842-022-00139-w
4. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational diabetes mellitus: mechanisms, treatment, and complications. Trends in Endocrinology & Metabolism. 2018;29(11):743-754.
5. Malaza N, Masete M, Adam S, Dias S, Nyawo T, Pheiffer C. A Systematic Review to Compare Adverse Pregnancy Outcomes in Women with Pregestational Diabetes and Gestational Diabetes. International Journal of Environmental Research and Public Health. 2022;19(17):10846. https://doi.org/10.3390/ijerph191710846.
6. Billionnet C, Mitanchez D, Weill A, et al. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. Diabetologia. 2017;60:636-644.
7. Ugwudike B, Kwok MH. Update on gestational diabetes and adverse pregnancy outcomes. Current Opinion in Obstetrics and Gynecology. 2023.https://doi.org/10.1097/GCO.0000000000000901.
8. Wendland EM, Torloni MR, Falavigna M, et al. Gestational diabetes and pregnancy outcomes-a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. BMC pregnancy and childbirth. 2012;12:1-13.
9. Fadl HE, Östlund IKM, Magnuson AFK, Hanson US. Maternal and neonatal outcomes and time trends of gestational diabetes mellitus in Sweden from 1991 to 2003. Diabetic Medicine. 2010;27(4):436-441.
10. Prevention C for DC and. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: US department of health and human services, centers for disease control and prevention. 2011;201(1):2568-2569.
11. Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes and insulin resistance: role in short-and long-term implications for mother and fetus. The Journal of nutrition. 2003;133(5):1674S-1683S.
12. Parlakgumus HA, Durukan T. The relationship between cardiac adaptation to uteroplacental Doppler flow and perinatal outcome in pregnant women with diabetes. Clinical & Experimental Obstetrics & Gynecology. 2010;37(1):39.
13. Buckley BS, Harreiter J, Damm P, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabetic medicine. 2012;29(7):844-854.
14. Savvato K, Wafa A, Anwar A, Hanan A, Sofia C. Self-management and self-efficacy of women with gestational diabetes mellitus: a systematic review. Global Health Action.2022;15:1, https://doi.org/10.1080/16549716.2022.2087298.
15. Metzger BE, Gabbe SG, Persson B, et al. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy: Response to Weinert. Diabetes Care. 2010;33(7):e98. https://doi.org/10.2337/dc10-0719
16. Aung YY, Sowter M, Kenealy T, Herman J, Ekeroma A. Gestational

diabetes mellitus screening, management and outcomes in the Cook Islands. Published online 2015.

17. Huhn EA, Rossi SW, Hoesli I, Göbl CS. Controversies in screening and diagnostic criteria for gestational diabetes in early and late pregnancy. Frontiers in endocrinology. 2018;9:696.

18. Bonomo M, Corica D, Mion E. et al. Evaluating the therapeutic approach in pregnancies complicated by borderline glucose intolerance: a randomized clinical trial. Diabetic Medicine, 2005;22(11), 1536-1541. https://doi.org/10.1111/j.1464-5491.2005.01690.x

19. Punnose J, Malhotra RK, Sukhija K, Choudhary N, Sharma A, Vij P, Bahl P. Gestational diabetes mellitus in early pregnancy amongst Asian Indian women: Evidence for poor pregnancy outcomes despite treatment. Diabetic Medicine.2023;40(1): e14993. https://doi.org/10.1111/dme.14993.

20. Seo N, Lee YM, Kim YJ, Sung JH, Hur KY, Choi SJ, Roh CR, Oh SY. Obesity Is Associated With Higher Risk of Adverse Maternal and Neonatal Outcomes Than Supervised Gestational Diabetes. J Korean Med Sci. 2023 Aug;38(33):e268. https://doi.org/10.3346/jkms.2023.38.e268.

21. Dodd JM, Crowther CA, Antoniou G, Baghurst P, Robinson JS. Screening for gestational diabetes: the effect of varying blood glucose definitions in the prediction of adverse maternal and infant health outcomes. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2007;47(4):307-312.

22. Stamilio DM, Olsen T, Ratcliffe S, Sehdev HM, Macones GA. False-positive 1-hour glucose challenge test and adverse perinatal outcomes. Obstetrics & Gynecology. 2004;103(1):148-156.

23. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122-1131. doi:10.1097/01.AOG.0000437382.03963.88

24. Bonomo M, Corica D, Mion E, et al. Evaluating the therapeutic approach in pregnancies complicated by borderline glucose intolerance: a randomized clinical trial. Diabetic Medicine. 2005;22(11):1536-1541.

25. Sermer M, Naylor CD, Gare DJ, et al. Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes: the Toronto Tri-Hospital Gestational Diabetes Project. American journal of obstetrics and gynecology. 1995;173(1):146-156.

26. Savona-Ventura AS. Risk factors for gestational impaired glucose tolerance in the Maltese population: a cross-sectional study. Journal of Obstetrics and Gynaecology. 2001;21(6):591-594.

27. Tallarigo L, Giampietro O, Penno G, Miccoli R, Gregori G, Navalesi R. Relation of glucose tolerance to complications of pregnancy in nondiabetic women. New England Journal of Medicine. 1986;315(16):989-992.

28. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. American journal of obstetrics and gynecology. 1982;144(7):768-773.

29. Arbib N, Gabbay-Benziv R, Aviram A, et al. Third trimester abnormal oral glucose tolerance test and adverse perinatal outcome. The Journal of Maternal-Fetal & Neonatal Medicine. 2017;30(8):917-921. doi:10.1080/14767058.2016.1190825

30. ACOG Committee on Obstetric Practice. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet. 2002;77(1):67-75.

31. Fuka F, Osuagwu UL, Agho K, Gyaneshwar R, et al. Factors associated with macrosomia, hypoglycaemia and low Apgar score among Fijian women with gestational diabetes mellitus. BMC Pregnancy and Childbirth, 2020;20(1), 1-14. https://doi.org/10.1186/s12884-020-2821-6

32. Ji J, Sundquist J, Sundquist K. Stillbirth and neonatal death among female cancer survivors: A national cohort study. International Journal of Cancer. 2016;139(5):1046-1052. doi:10.1002/ijc.30156

33. Lavery J, Friedman A, Keyes K, Wright J, Ananth C. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. BJOG: An International Journal of Obstetrics & Gynaecology. 2017;124(5):804-813. doi:10.1111/1471-0528.14236

34. Metzger BE, Contreras M, Sacks DA, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991–2002. https://doi.org/10.1056/NEJMoa0707943

35. García-Moreno RM, Benítez-Valderrama P, Barquiel B, González Pérez-de-Villar N, Hillman N, Lora Pablos D, Herranz L. Efficacy of continuous glucose monitoring on maternal and neonatal outcomes in gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials. Diabetic Medicine. 2022;39(1). https://doi.org/10.1111/dme.14703.

36. Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in Incidence of Diabetes in Pregnancy and Serious Perinatal Outcomes: A Large, Population-Based Study in Ontario, Canada, 1996–2010. Diabetes Care. 2014;37(6):1590-1596. doi:10.2337/dc13-2717

37. IDF Diabetes Atlas. Accessed March 26, 2020. https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/19-atlas-6th-edition.html

38. Ramezani Tehrani F, Farzadfar F, Hosseinpanah F, Rahmati M, Firouzi F et al. Does fasting plasma glucose values 5.1-5.6 mmol/l in the first trimester of gestation a matter?. Frontiers in Endocrinology. 2023;14. https://doi.org/10.3389/fendo.2023.1155007.

39. Diabetes Canada | Clinical Practice Guidelines - 2018 Full Guidelines. http://guidelines.diabetes.ca/cpg. Accessed 26 Mar 2022

40. 2018 Surveillance of Diabetes in Pregnancy: Management from Preconception to the Postnatal Period (NICE Guideline NG3). National Institute for Health and Care Excellence (UK); 2018. Accessed March 26, 2020. http://www.ncbi.nlm.nih.gov/books/NBK550982/

ORIGINAL RESEARCH

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The relationship between age and mortality and morbidity of patients diagnosed with breast cancer: a retrospective clinical study

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Abstract

Objective: Breast cancer, the most common malignancy among women, is a universally challenging health problem. It is a known fact that the incidence of breast cancer increases with age. In addition, mortality and morbidity increase with age. For now, it does not seem possible to reduce the incidence of breast cancer but it is possible to limit deaths caused by it. Patients are encouraged to get early diagnosis and age-appropriate screening tests. Because regular screening and early diagnosis are very important in improving breast cancer outcomes. Factors such as age, hormonal status and genetics are associated with the incidence of breast cancer. In this study, we aimed to contribute to the literature by examining age-related mortality and morbidity of breast cancer.

Method: This study was carried out at a University Hospital. The sample consisted of 214 women between 01.09.2018/01.09.2022 diagnosed with breast cancer, aged 30 to 80 years.

Results: The mean age of women was 51.9 ± 7.6 years, with 52.8% being <50 years. Breast-conserving surgery was performed on 56.5% of the total participants (n=121). In our series, deaths due to breast cancer are less than 1% under the age of 50 and over 3% in those over the age of 50.

Conclusion: Education campaigns should focus on increasing breast cancer awareness among young women, highlighting the importance of early detection and regular screenings. Each patient should receive a tailored treatment plan that considers their age, tumor characteristics, fertility preservation preferences, and long-term health goals.

Keywords: Breast Cancer, Survival, Incidence, Surgery

INTRODUCTION

Breast cancer is the most common type of cancer among women worldwide. The incidence of breast cancer increases with age and is highest among women aged 50 years and older. The mortality and morbidity rates for breast cancer also increase with age, with the highest rates observed among women over 70 years old (1).

According to the Centers for Disease Control (CDC), breast cancer is the second leading cause of cancer death among women overall in the United States, and the leading cause of cancer death among Hispanic women (2). The age-adjusted death rate for female breast cancer in the United States during 2019 was 19.5 per 100,000 women (2).

As for morbidity, breast cancer survivors may face long-term side effects such as lymphedema, fatigue, and cognitive changes, as well as an increased risk of developing other health problems such as osteoporosis and heart disease (3). Depression, stress

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caused by the disease, and sexual dysfunction are important problems caused by the disease and the treatment process. These problems are more common at young ages.

Early detection through regular screening tests such as mammograms and clinical breast exams is key to improving outcomes for breast cancer. Women are encouraged to talk to their healthcare providers about their individual risk factors and the appropriate screening tests within their age group (3).

The aim of this study is to examine the relationship between mortality and morbidity of breast cancer and age and to compare our experiences with the literature.

METHOD

This study was carried out at Hatay Mustafa Kemal University Faculty of Medicine Hospital. The sample consisted of 214 women between 01.09.2018/01.09.2022 diagnosed with breast cancer, aged 30 to 80 years. They were divided into two groups with a cut-off age of 50, which is the average age of menopause in the rest of the World (5). Similarly, this age limit is widely used in the literature studying variables related to quality of life. The patients' age, gender, diagnosis, onset time of symptoms, laboratory tests and diagnostic imaging studies, post-operative complications, relapse and mortality will be examined and compared.

The women selected for the study also met the inclusion criteria: 1) having a diagnosis of cancer,2) having had surgery as part of the treatment, 3) receiving chemotherapy (CTX) or radiotherapy (RT). The main exclusion criteria were being pregnant at the time of diagnosis and having undergone breast reconstruction.

Statistical Analysis Data will be transferred to Microsoft Excel for group allocation and SPSS software (IBM Corp 24.0) will be used for statistical analysis. One-way analysis of variance was used to compare continuous variables between groups; $\chi 2$ test and Fisher exact test will be used to analyze categorical variables. Statistical significance of 0.05 (α) was determined for the analysis. Post hoc test (Tukey test or Bonferroni test) will be performed statistically to compare significant differences between groups.

RESULTS

The mean age of women was 51.9 ± 7.6 years, with 52.8% being <50 years. Breast-conserving surgery was performed on 56.5% of the total participants (n=121) (Figure 1).

Demographic data regarding age groups of the patients were presented on Figure 2. Compared with all other age groups, patients <40 years (n = 42) and 40 to 49 years (n = 71) were more likely to be diagnosed with breast cancer with ductal histology, grade 3, and lymphovascular invasion positive. These younger patients (<40 and 40–49 years) were less likely to have positive estrogen receptor (ER) and progesterone receptor (PR) expression and were more likely to have HER2-positive or triple-negative disease. Patients under 40 years of age and between 40 and 49 years of age were more likely to have more advanced TNM stage at diagnosis; node positivity and T3 tumor rates were higher.

In contrast, patients aged ≥50 years (n = 93) generally had more clinical-pathological features than nearby middle-aged cohorts, all with a higher likelihood of lobular histology, lower grade, and a lower negative rate of lymphovascular invasion. They were more likely to have ER and PR receptors and less likely to have HER2-positive or triple-negative disease. They were overall more likely to have node-negative disease and to have T1 or T2 tumors, although there was a slight increase in the occurrence of de novo metastatic disease observed in patients aged ≥50 years compared with younger age groups.

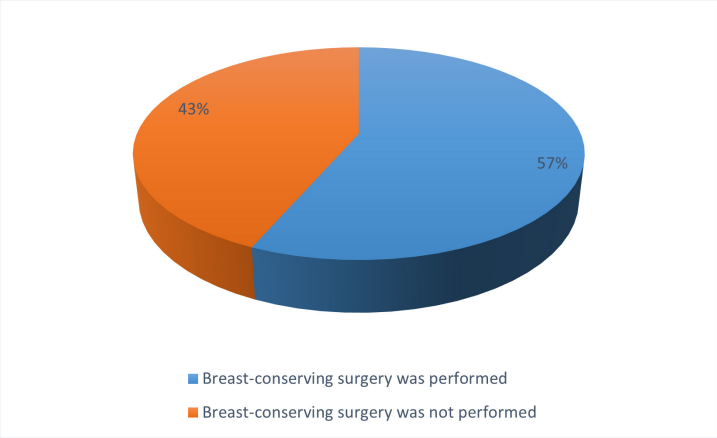

Figure 1. Ratio of the surgical methods in terms of conserving breast.

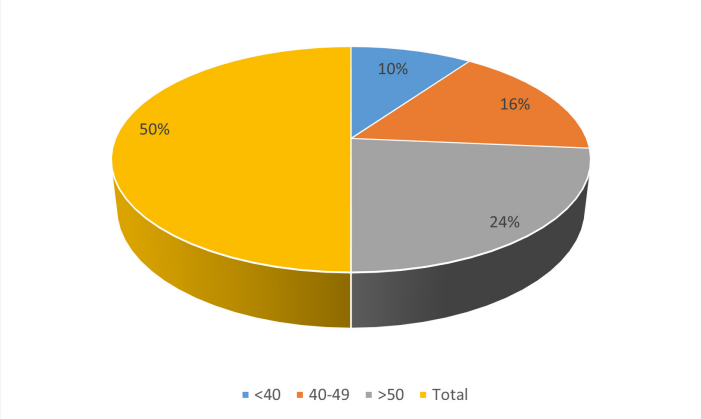

Figure 2. Age groups of the cases

Significant differences were shown in the systemic effects of treatment (hair loss, etc.) (p = 0.002). Patients over the age of 50 are less affected by anxiety; Those under the age of 50 reported less surgery-related symptomatology (p=0.043)

In our series, deaths due to breast cancer are less than 1% under the age of 50 and over 3% in those over the age of 50.

DISCUSSION

Treating breast cancer at a young age can present a specific set of challenges and potential complications.

Younger women may have a lower awareness of breast cancer and its symptoms, leading to delayed diagnosis. This can result in more advanced stages of cancer at the time of detection, making treatment more difficult (4).

Breast cancer in younger women tends to be more aggressive, with faster-growing tumors and a higher likelihood of spreading to nearby lymph nodes. This aggressive nature can make treatment more challenging (6).

Due to the potential desire for fertility preservation or pregnancy in the future, younger women may prefer less aggressive treatment options. This can limit the available treatment strategies and make achieving optimal outcomes more complex (8).

Younger women often have a higher tolerance for chemotherapy and radiation, but they may also experience more severe side effects due to their overall health and a longer expected lifespan. These side effects can impact the quality of life and increase the risk of complications (7).

Addressing these challenges is crucial to minimize mortality rates in young breast cancer patients.

Treating breast cancer in older women can also present unique challenges and potential complications.

Older women often have a higher burden of other health conditions, such as heart disease, diabetes, or arthritis. These conditions can complicate treatment decisions and increase the risk of side effects from cancer therapies (8).

Age-related decline in physical abilities and overall functional status can impact the tolerance and response to treatments. Older women may experience more difficulties in recovering from surgical procedures or managing the side effects of chemotherapy or radiation (7).

Older women are often underrepresented in clinical trials, which can limit the availability of evidence-based treatment options tailored to their needs. This may result in suboptimal treatment decisions and outcomes (8).

Older women may take multiple medications for various health conditions. The interactions between cancer treatments and these medications can lead to complications or adverse effects, including reduced treatment efficacy (4).

Addressing these challenges is critical to minimize complications and mortality rates in older breast cancer patients.

A thorough assessment of an older patient's overall health, functional status, cognitive abilities, and social support can help tailor treatment plans to their specific needs and minimize potential complications (6).

Treatment decisions should be based on the patient's health status, tumor characteristics, and overall goals and preferences. Less aggressive treatment options may be considered if the risks outweigh the benefits (6).

Close monitoring and proactive management of treatment-related side effects, including adjusting medication doses or schedules, can help older patients tolerate and adhere to their treatment plans.

CONCLUSION

Education campaigns should focus on increasing breast cancer awareness among young women, highlighting the importance of early detection and regular screenings.

Each patient should receive a tailored treatment plan that considers their age, tumor characteristics, fertility preservation preferences, and long-term health goals.

Providing comprehensive supportive care services, such as counseling, fertility preservation options, and survivorship programs, can help manage the physical, emotional, and psychological challenges faced by young women with breast cancer.

Continued research is essential to better understand breast cancer in young women and develop effective treatment strategies. Clinical trials specifically targeting this population can provide valuable insights.

It is important for young women diagnosed with breast cancer to work closely with their healthcare team to develop a comprehensive treatment plan that addresses their specific needs and concerns. Regular follow-up and adherence to recommended surveillance guidelines can also contribute to improving outcomes and reducing mortality rates.

Involving geriatric specialists, oncologists, surgeons, pharmacists, and other healthcare professionals in the patient's care can provide a comprehensive and coordinated approach to treatment and support.

Increasing awareness among older women about the importance of breast cancer screening, early detection, and maintaining overall health can contribute to timely diagnosis and better treatment outcomes.

Continued research is needed to better understand the unique biology of breast cancer in older women and develop effective treatment strategies targeted to this population.

Older women diagnosed with breast cancer should have open and informed discussions with their healthcare team to develop treatment plans that consider their specific needs, preferences, and goals. Regular communication, monitoring, and follow-up with their healthcare providers are essential to optimize outcomes and minimize complications.

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Ethical Declaration

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Authorship Contributions

Concept: MBD, Design: MBD,Supervising: MBD, Financing:-, Tools and equipment: -, Data Collection and entry: MT, Analysis and interpretation: MBD, Literature search: MBD, Writing: MBD, Critical review: MBD

REFERENCES

1. Jackson E B, Gondara L, Speers C et al. Does age affect outcome with breast cancer? The Breast 70 (2023) 25-31. https://doi.org/10.1016/j.breast.2023.06.001
2. Pardo S A, Pérez E M R, Castañeda N C et al. Quality of Life in Breast Cancer Survivors in Relation to Age, Type of Surgery and Length of Time since First Treatment Int. J. Environ. Res. Public Health 2022, 19, 16229. https://doi.org/10.3390/ijerph192316229
3. Zheng, Yadi, et al. "Use of breast cancer risk factors to identify risk-adapted starting age of screening in China." JAMA network open 5.11 (2022): e2241441-e2241441. https://doi.org/10.1001/jamanetworkopen.2022.41441
4. Arinkan S A, Gunacti M Factors influencing age at natural menopause J. Obstet. Gynaecol. Res. Vol. 47, No. 3: 913-920, March 2021 https://doi.org/10.1111/jog.14614
5. Daly M B, Rosenthal E, Cummings S et al. The association between age at breast cancer diagnosis and prevalence of pathogenic variants Breast Cancer Research and Treatment (2023) 199:617-626. https://doi.org/10.1007/s10549-023-06946-8
6. Miller K, Gannon M R, Medina J et al. The Association Between Survival and Receipt of Post-mastectomy Radiotherapy According to Age at Diagnosis Among Women with Early Invasive Breast Cancer: A Population-Based Cohort Study Clinical Oncology 35 (2023) e265ee277. https://doi.org/10.1016/j.clon.2023.01.008
7. Guliyeva G, Huayllani M T, Boczar D et al. Age as a risk factor for breast cancer-related lymphedema: a systematic review Journal of Cancer Survivorship (2023) 17:246-253 https://doi.org/10.1007/s11764-021-00994-z.

ORIGINAL RESEARCH

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Relationship between atrial fibrillation and P wave dispersion in inpatients with COVID-19

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Abstract

Objective: Various cardiac arrhythmias, primarily atrial fibrillation (AF), have been reported to occur in 7% to 22% of patients hospitalized due to coronavirus disease 2019 (COVID-19). It has been shown that P wave dispersion (PWD) predicts the development of AF in different clinical situations and is closely related to the inflammatory process. The aim of this study is to determine the relationship between PWD and the development of new-onset AF in hospitalized patients due to COVID-19.

Method: 51 COVID-19 patients who developed AF and 72 COVID-19 patients who did not develop AF were included in the study as the control group retrospectively. Electrocardiography (ECG) was performed in all patients and PWD was calculated. In addition, demographic data, imaging findings and laboratory test results of all COVID-19 patients were obtained from the institutional digital database and recorded.

Results: Patients who developed AF were older and had a higher frequency of hypertension and heart failure ($p<0.05$ for all). Patients who developed AF during hospitalization had higher neutrophil/lymphocyte ratio (NLR), C-reactive protein (CRP) ($p<0.05$ for all)). The PWD value was significantly longer in the AF group ($p<0.05$). In addition, a significant positive correlation was observed between PWD and cTn-I, CRP and NLR.

Conclusion: Our study showed that PWD predicts new-onset AF during follow-up of COVID-19 patients and is associated with inflammatory markers. Multivariate logistic regression analysis showed that PWD is an independent predictor of AF development. We believe that pretreatment PWD assessment in COVID-19 patients may be useful in estimating the risk of AF.

Keywords: P Wave Dispersion, COVID-19, Atrial Fibrillation

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in a global pandemic (1-3). While the majority of COVID-19 cases manifest with a mild clinical course, some individuals develop a severe disease phenotype (1-3). Those experiencing a severe clinical course are typically of advanced age, presenting with increased comorbidities such as coronary artery disease (CAD), hypertension, diabetes mellitus (DM), and heart failure (HF) (1-3). Particularly in hospitalized patients, various cardiac complications, predominantly arrhythmias, may ensue (4). Diverse studies report an incidence of arrhythmias in hospitalized patients ranging from 7% to 22%, with atrial fibrillation (AF) being the most commonly

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observed (4-6). AF, the most prevalent arrhythmia associated with aging and various cardiovascular comorbidities, is unsurprisingly frequent in COVID-19 patients undergoing inpatient care due to a shared risk profile. The Italian Ministry of Health has reported AF development in 19-22% of hospitalized COVID-19 patients (7,8).

P-wave dispersion (PWD) is defined as the difference between the maximum and minimum P-wave durations assessed on the standard electrocardiogram (ECG) (9). Increased PWD is well-established to be particularly associated with various atrial-origin arrhythmias such as AF (10). PWD serves as a simple and useful electrocardiographic parameter predicting the development of AF in various clinical scenarios (11,12).

In COVID-19 pathology, increased systemic inflammation, heightened adrenergic stimulation, myocardial injury secondary to hypoxia, and microvascular thrombosis resulting from endothelial inflammation occur (13-16). All these processes may lead to changes in atrial tissue through electrical and structural abnormalities in the context of COVID-19 disease, potentially impacting P-wave parameters. Therefore, in this study, the objective was to determine the relationship between PWD values and the development of AF in patients hospitalized due to COVID-19, with the aim of elucidating the potential link between PWD and AF in the context of COVID-19-induced cardiac alterations.

METHOD

Study Population and Patient Selection

This multicenter study was conducted through a retrospective review of the records of patients hospitalized between May 20, 2020, and January 15, 2021. A total of 61 patients who developed AF during the follow-up were included in the study. All patients were treated in accordance with the guidelines outlined in the Turkish Ministry of Health COVID-19 treatment protocols (17). In order to avoid bias, no exclusion criteria were defined, except for valvular AF, individuals with a history of pre-existing AF, pregnancy or breastfeeding, and those with mechanical heart valve prostheses. After excluding 10 patients, a total of 51 patients constituted the group. Subsequently, 72 COVID-19 patients who did not develop AF were randomly selected to form the control group. The diagnosis of new-onset AF was confirmed through daily electrocardiograms, bedside monitors, or Holter devices. Additionally, patients were regularly examined during daily follow-ups, and pulse examinations were conducted systematically. Patients with insufficient information in their hospital records were excluded from the study.

Demographic characteristics, cardiovascular risk factors, comorbidities, medication usage, smoking habits, and laboratory values of the patients included in the study were recorded.

Diagnosis of COVID-19

Patients meeting the criteria for a potential SARS-CoV-2 infection according to the Turkish Ministry of Health COVID-19 Treatment Guidelines and the World Health Organization (WHO) underwent viral screening using molecular methods (17,18). Throat and nasopharyngeal swab samples were collected from all patients in this study to detect SARS-CoV-2 RNA. Real-time reverse transcription polymerase chain reaction (RT-PCR) molecular method was employed for the analysis of SARS-CoV-2 virus RNA. The RT-PCR test was conducted in accordance with WHO guidelines, utilizing the SARS-CoV-2 (2019 nCoV) qPCR Detection Kit (Bioeksen R&D Technologies Co Ltd, Istanbul, Türkiye) recommended by the Turkish Ministry of Health (17,19). Cases with detectable SARS-CoV-2 RNA by the RT-PCR method were considered as confirmed cases of COVID-19. The definition of comorbidities was based on relevant guidelines, and elevated cardiac troponin I values, with at least one value above the 99th percentile upper reference limit, were characterized as myocardial injury.

ECG

All ECGs of the patients included in the study were assessed before the initiation of treatment. 12-lead ECGs (Mortara, Jackson, USA) were recorded in the supine position at rest, with a speed of 25 mm/s and a voltage of 10 mm/mV. To minimize measurement errors, all ECGs were scanned, transferred to a personal computer, and then examined at 400% magnification using Adobe Photoshop software. All measurements were performed manually on the screen using appropriate programs. The baseline ECGs of all patients were reviewed, and all exhibited a sinus rhythm. The first detectable point of atrial depolarization from the isoelectric line was defined as the onset of the P-wave. Subsequently, the

turning point on the isoelectric line was defined as the end of the P-wave. ECG derivations where the beginning or end of the P-wave could not be precisely determined were excluded from the analysis. P-maximum (P-max) was determined as the P-wave duration in any derivation with the longest interval, while P-minimum (P-min) was defined as the P-wave duration in any derivation with the shortest interval. PWD was calculated by subtracting P-min from P-max, as measured in any of the 12 ECG derivations. A cutoff value of at least 36 ms was established to categorize PWD, as previously demonstrated (20). P-wave amplitude was defined as the vertical distance between the peak of the P-wave and the isoelectric line, calculated in millivolts from derivations V1 and D2. The PR interval was defined as the distance between the onset of the P-wave and the onset of the QRS complex. QRS duration was defined as the distance from the end of the PR interval to the end of the S-wave. QT interval was defined as the interval from the beginning of the QRS complex to the end of the T-wave. QT interval measurements were taken from all derivations, and the longest QT interval was recorded. The R–R interval was measured, and heart rate (HR) was calculated, and corrected QT intervals (QTc) were calculated using the Bazett formula: QTc=QTH (R–R interval) (21). All ECG measurements were made in three consecutive beats, and the average of three measurements was taken for analysis. Two independent cardiologists, blinded to other patient information, performed all ECG measurements. These values were calculated three times for each study patient. Intraobserver and interobserver variations for measurements were calculated as 3.5% and 3.2%, respectively.

Transthoracic Echocardiography (TTE)

Echocardiography was performed on all patients using the Philips Affiniti 50C system (Philips Medical Systems, Netherlands) in the left lateral position. Measurements were taken simultaneously with a single-lead electrocardiogram recording, and the average of three cardiac cycles was recorded. Measurements were conducted in accordance with the recommendations of the American Society of Echocardiography (22).

Laboratory Measurements

Following the immediate diagnosis of COVID-19 and during hospitalization, routine blood laboratory tests were conducted. Routine blood test results, including serum cTn-I, were obtained from the institutional digital database, and values below the 99th percentile upper reference limit were considered normal. Hemogram, biochemical parameters, cTn-I, D-dimer, ferritin, and CRP measurements were performed for all patients. Using hemogram measurements, NLR and PLR were calculated.

Statistical Analysis

All measurements were evaluated for normal distribution using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), and categorical variables as percentages. For the comparison of groups, the student-t test or Mann-Whitney U test was used for continuous variables, and the chi-square test for categorical variables. Enter method regression analysis was applied for multivariate analysis of independent variables that could predict the development of AF. Variables with an unadjusted p-value < 0.10 were included in the multivariate model to identify predictors of new-onset AF development. Statistical significance was defined as $p < 0.05$. SPSS version 22.0 (SPSS 22.0 for Windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

RESULTS

A total of 532 patient records admitted due to COVID-19 were retrospectively reviewed. It was determined that AF developed in 61 patients during hospitalization (11.4%). Ten patients were excluded from the study due to exclusion criteria, leaving 51 patients included in the analysis. Additionally, 72 COVID-19 patients without AF were randomly selected to form the control group. All data between the groups with and without AF were compared.

The demographic and clinical characteristics of both groups are presented in Table 1. The mean age was significantly higher in the AF group (74.8±9.3 vs. 65.7±12.1, $p<0.001$). No statistically significant differences were observed between the groups in terms of gender, DM frequency, smoking, body mass index (BMI), hyperlipidemia (HL) frequency, coronary artery disease (CAD), chronic obstructive pulmonary disease, and history of prior stroke or embolism ($p>0.05$). However, in patients with AF, hypertension (68.6% vs. 40.1%, $p<0.001$), heart failure (13.7% vs. 6.9%, $p<0.001$), admission oxygen saturation (87.5% vs. 91.2%, $p<0.001$), intensive care admission rate (21.5% vs. 16.6%,

p<0.001), CHA_2DS_2VASc score (2.48±0.56 and 1.73±0.76, p<0.001), intubated patient count (7.8% vs. 4.2%, p<0.001), and frequency of inotropic agent use (9.8% vs. 5.5%, p<0.001) were higher. There was no statistically significant difference in medication use between the two groups. AF developed within the first 96 hours after hospitalization in 36 patients and within the first week in the remaining 15 patients. Among these 51 patients, 11 were monitored in the intensive care unit.

Table 1: Comparison of the demographic characteristics of the study population.

	AF group (n=51)		Control group (n=72)		p value
Age (year)	74.8 ± 9.3		65.7 ± 12.1		<0.001
Gender (male)	31	61.1%	45	62.5%	0.643
BMI kg/m²	30.2±8.5		29.8±7.3		0.271
Hypertension, count (%)	35	68.6%	29	40.1%	<0.001
Diabetes mellitus, count (%)	13	25.4%	17	23.6%	0.328
Hyperlipidemia, count (%)	18	35.3%	25	34.7%	0.321
Coronary artery disease, count (%)	6	11.7%	8	11.1%	0.501
Heart failure, count (%)	7	13.7%	5	6.9%	<0.001
Cigarette, count (%)	15	29.4%	21	27.7%	0.253
COPD, count (%)	5	9.8%	7	9.7%	0.427
CVA or history of embolism, count (%)	2	3.9%	3	4.1%	0.738
CHA2DS2VASc	2.48±0.56		1.73 ±0.76		0.021
Intensive care hospitalization, count (%)	11	21.5%	12	16.6%	0.003
Need for intubation, count (%)	4	7.8%	3	4.2%	0.012
Use of inotropic, count (%)	5	9.8%	4	5.5%	0.023
Use of anticoagulants, count (%)	51	100%	72	100%	0.786
Admission oxygen saturation (%)	87.5±7.2		91.2±6.4		0.004

Abbreviations: AF; atrial fibrillation, BMI; body mass index, CHA2DS2VASc; congestive heart failure (1), hypertension (1), age>75 (2), Diabetes mellitus (1), Previous cerebrovascular accident or transient ischemic attack (2), history of vascular disease (1), age 65-74 (1), female gender (1), COPD; chronic obstructive pulmonary disease, CVA; cerebrovascular accident

Laboratory findings of the patients are presented in Table 2. In the AF group, WBC (7.9±3.2 vs. 6.3±1.4, p=0.003), neutrophil count (5.7±2.1 vs. 3.9±1.9, p<0.001), NLR (6.4±2.1 vs. 4.7±1.9, p=0.012), PLR (274.1±96.2 vs. 213.3±77.9, p=0.023), ferritin (739.2±201.2 vs. 431.2±141.4, p<0.001), D-dimer (5821±1234 vs. 3021±1064, p=0.031), cTn-I (0.063±0.013 vs. 0.025±0.09, p<0.001), and CRP (47.1±19.3 vs. 29.4±11.9, p<0.001) levels were significantly higher compared to the non-AF group. Lymphocyte count (1.2±0.4 vs. 1.5±0.5, p=0.002) was significantly lower in the AF group. No statistically significant differences were observed between the groups in terms of other laboratory values (p>0.05).

Table 2: Comparison of laboratory characteristics of the study population.

	AF group (n =51)	Control group (n=72)	p value
WBC (10^3 µl)	7.9±3.2	6.3±1.4	0.003
Neutrophil (10^3 µl)	5.7±2.1	3.9±1.9	<0.001
Lymphocyte (10^3 µl)	1.2±0.4	1.5±0.5	0.002
Monocyte (10^3 µl)	0.58±0.23	0.57±0.29	0.435
Platelet (10^3 µl)	233.5±78.8	229.9±74.7	0.245
Ferritin	739.2±201.2	431.2±141.4	<0.001
CRP (mg/l)	47.1±19.3	29.4±11.9	<0.001
Troponin I (ng/mL) (cut off=0.021)	0.063±0.013	0.025±0.09	<0.001
D-Dimer (ng/mL)	5821±1234	3021±1064	0.031
Hemoglobin (g/dl)	12.9±1.3	13.5 ± 1.6	0.510
Glucose (mg/dl)	97.2±8.8	95.9±8.9	0.345
Aspartate aminotransferase (IU/l)	31.1±6.8	29.8±8.1	0.248
Alanine aminotransferase (IU/l)	29.8±8.4	27.3±9.1	0.123
Creatinine (mg/dl)	0.93±0.21	0.87±0.23	0.712
Sodium (mEq/l)	139.1±3.3	137.2±3.1	0.162
Calcium (mg/dl)	9.43±.2.32	9.34±1.98	0.123
Potassium (mmol/l)	4.12±0.74	4.23±0.62	0.279
NLR	6.4±2.1	4.7±1.9	0.012
PLR	274.1±96.2	213.3±77.9	0.023

Abbreviations: AF; atrial fibrillation, CRP; C-reactive protein, NLR; neutrophil/ lymphocyte ratio, PLR; platelet/lymphocyte ratio

The electrocardiographic and echocardiographic values of both groups are presented in Table 3. Maximum P-wave duration (111.2±12.9 vs. 96.8±7.5, p<0.001), minimum P-wave duration (69.2±8.9 vs. 60.1±6.3, p<0.001), and PWD value (47.1±9.2 vs. 36.1±5.1, p<0.001) were significantly higher in patients with AF. PR interval (147.1±17.2 vs. 139.3±14.3, p=0.003), P-wave amplitude in lead V1 (0.131±0.011 vs. 0.122±0.07, p<0.001), P-wave amplitude in lead D2 (0.139±0.013 vs. 0.125±0.008, p<0.001), and left atrial diameter (38.5±3.3 vs. 35.6±3.1, p=0.013) were significantly higher in the AF group. There were no statistically significant differences between the groups in terms of other electrocardiographic and echocardiographic results (P>0.05).

Significant parameters found in univariate regression analysis were included in multivariate logistic regression analysis. In multivariate logistic regression analysis, PWD

(Odds ratio (OR): 3.345, 95% CI: 1.607-7.697, p<0.001), age (OR: 1.099, 95% CI: 1.026-1.715, p=0.002), hypertension (OR: 2.134, 95% CI: 1.242-6.789, p=0.002), and CRP (OR: 1.321, 95% CI: 1.213-1.713, p=0.005) were predictors for the development of AF in hospitalized COVID-19 patients (Table 4). Particularly, among these parameters, PWD was the strongest independent determinant of AF development. It was observed that 45 patients with AF returned to sinus rhythm upon discharge, while 6 did not.

Table 3: Comparison of electrocardiographic and echocardiographic characteristics of the study population.

	AF group (n =51)		Control group (n=72)		p value
Heart rate (beats/minute)	82.2±7.7		80.1±6.9		0.467
LVEF (%)	60.2±2.1		61.7±1.7		0.315
Left atrium diameter (mm)	38.5±3.3		35.6±3.1		0.013
PR interval (ms)	147.1±17.2		139.3±14.3		0.003
PR interval >160 ms, n (%)	23	45.1%	8	11.1%	0.007
PR interval >200 ms, n (%)	3	5.8%	4	5.5%	0.231
P-wave amplitude (mV) V1 derivation	0.131±0.011		0.122±0.007		<0.001
P-wave amplitude (mV) D2 derivation	0.139±0.013		0.125±0.008		<0.001
Maximum P-wave duration (ms)	111.2±12.9		96.8±7.5		<0.001
Minimum P-wave duration (ms)	69.2±8.9		60.1±6.3		<0.001
PWD (ms)	47.1±9.2		36.1±5.1		<0.001
PWD>36 ms, count (%)	26	50.1%	11	15.2%	<0.001
QRS width (ms)	118.9±4.7		119.2±4.5		0.325
QTc interval (ms)	396.1±9.5		392.7±8.9		0.546

Abbreviations: AF; atrial fibrillation, PWD; P-wave dispersion, LVEF; left ventricular ejection fraction.

DISCUSSION

In this study, it was found that the PWD value was longer in the group where AF developed among COVID-19 patients receiving inpatient treatment. Additionally, inflammatory markers such as CRP, NLR, and PLR, as well as the cardiac damage indicator cTn-I, were significantly higher in patients with AF. Increased PWD value was shown to be associated with the development of new-onset AF in COVID-19 patients. This study suggests that PWD value in hospitalized COVID-19 patients may be used to predict AF development.

The novel coronavirus named SARS-CoV-2 was first detected in Türkiye in March 2020 (17). The COVID-19 caused by SARS-CoV-2 has led to a global pandemic as it rapidly spread worldwide (20). Although COVID-19 was initially considered a disease characterized by respiratory symptoms, it was observed that cardiovascular diseases and complications often accompanied COVID-19 infections as the number of patients increased (4,5). Various studies have reported various cardiovascular complications such as myocardial injury, cardiac decompensation, and arrhythmias, ranging from 7% to 17% in these patients, significantly contributing to mortality (2,23). These results indicate that cardiovascular involvement is considerable in COVID-19 patients. Especially, cardiac arrhythmias are the most commonly reported cardiovascular complications in COVID-19 patients, with new-onset AF being the most common form (5,6). There are some mechanisms underlying the development of AF in COVID-19 patients (13-16). This novel virus readily attaches to type 2 alveolar cells in the lungs and the angiotensin-converting enzyme 2 receptor in myocardial tissue in humans, exerting direct cytotoxic effects on these cells (24,25). The presence of interstitial mononuclear cells in the myocardium supports this theory (26). Additionally, increased sympathetic stimulation following

Table 4: Univariate and multivariate regression analysis showing independent predictors of atrial fibrillation

	Univariate OR	95%CI	p value	Multivariate OR	95% CI	p value
PWD	2.142	1.798–7.123	0.001	3.345	1,607-7.697	<0.001
Age	1.198	1.072-3.150	0.005	1.099	1.026-1.715	0.002
Hypertension	1.856	1.370-6.145	0.001	2.134	1.242-6.789	0.002
CRP	1.141	1.056-1.634	0.002	1.321	1.213-1.713	0.005
Admission oxygen saturation	0.645	0.456-0.914	0.003	1.477	0.742-1.987	0.871
cTn-I	1.156	1.142-1.287	0.041	1.123	0.898-1.323	0.245
CHA2DS2-VASc	1.123	1.098-1.323	0.045	0.980	0.938-1.023	0.351
HF	1.348	1.087-1.657	0.034	1.333	0.719-2.472	0.362
Ferritin	1.080	1.038-1.098	0.023	1.447	0.749-2.792	0.271
NLR	1.333	1.119-2.472	0.012	0.966	0.896-1.042	0.370
Left atrium diameter	1.266	1.196-1.942	0.032	1.234	0.856-2.178	0.317
PLR	1.592	1.156-5.214	0.009	0.992	0.962-1.023	0.622

Abbreviations: CHA2DS2VASc; [congestive heart failure (1), hypertension (1), age>75 (2), Diabetes mellitus (1), Previous cerebrovascular accident or previous transient ischemic attack (2), history of vascular disease (1), age 65-74 (1), female gender (1)], CRP; C-reactive protein, cTn-I; cardiac troponin I, HF; heart failure, NLR; neutrophil/lymphocyte ratio, OR; Odds ratio, PWD; P-wave dispersion PLR; platelet/lymphocyte ratio.

infection, hypoxia, cytokine storm secondary to inflammation, increased tendency for coagulation, intravascular volume, and neurohormonal abnormalities can indirectly affect the cardiovascular system (27). All these pathophysiological mechanisms can lead to a proarrhythmic effect. With the effect of these mechanisms, various arrhythmias, particularly AF, can occur during COVID-19 infection (5,6). Pan et al. found in their study that arrhythmia developed in 16.7% of cases hospitalized due to COVID-19 (2). Guo et al. showed that arrhythmias frequently developed in COVID-19 patients they followed during hospitalization (4). Similarly, the Italian Ministry of Health reported that 19-22% of hospitalized COVID-19 patients developed AF in their studies (7,8). In this study, new-onset AF was detected in 11.4% of patients. These results support the idea that arrhythmic events are not rare in COVID-19 patients.

Previous information indicates the presence of an increased inflammatory state and elevated levels of TNF-α, IL-6, and IL-1β in patients with SARS-CoV-2 infection (23). It is now known that inflammation plays a significant role in the development of AF, beyond traditional risk factors (27). Therefore, SARS-CoV-2 infection may induce a severe inflammatory response associated with the formation of AF (14-16). This relationship has been explained by the infiltration of inflammatory cells into the atrium, myocyte necrosis, and fibrosis formation. Previously, it has been reported that inflammatory mediators such as CRP, IL-6, and TNF-α, especially released during the inflammatory process, induce the development of AF (27). Additionally, some studies have shown that an increase in serum CRP levels is associated with an increased risk of AF development and a high rate of AF recurrence after catheter ablation (28,29). Moreover, CRP level and NLR are significant indicators of systemic inflammation in COVID-19 patients (14). A study investigating the early stages of COVID-19 found that CRP levels reflect disease severity and should be used as a key indicator for disease monitoring (30). Yang et al. demonstrated high NLR levels in patients with COVID-19 (14). A meta-analysis reported that increased NLR levels in COVID-19 patients may be associated with poor prognosis (31). In this study, CRP and NLR levels were significantly higher in patients who developed AF. Therefore, it can be said that increased systemic inflammatory activity is more prevalent in these patients. Multivariate regression analysis found that the CRP level in blood taken upon admission to the hospital is an independent predictor of AF development in SARS-CoV-2 patients. The significantly higher levels of inflammatory markers such as CRP, procalcitonin, erythrocyte sedimentation rate, and NLR in COVID-19 patients who developed AF compared to those who did not support this study (32). WBC value and subtypes such as NLR and PLR have been reported as indicators of inflammation in various cardiovascular diseases. NLR, especially in recent years, in addition to traditionally used inflammatory markers, is a systemic inflammatory marker that is inexpensive and easily obtainable and can be used for risk classification in various cardiovascular diseases, and an increase in NLR has been reported as a predictor of AF development (33). PLR, similar to NLR, is another inflammatory marker that has been studied in various cardiovascular patient groups in recent years and has proven prognostic importance (34,35). An increase in PLR has also been reported to be associated with adverse cardiovascular events (34). Gungor et al. reported that an increase in PLR values is an independent predictor of paroxysmal AF (36). In this study, it was determined that SARS-CoV-2-infected patients who developed AF had higher WBC, NLR, and PLR levels at the time of admission compared to those without AF. The higher levels of inflammatory markers such as CRP, NLR, and PLR in patients with AF support the view that the severity of infection may be a trigger for AF.

Regional delays in atrial depolarization can lead to an uneven P-wave duration. This heterogeneity, termed P-wave dispersion (PWD), is defined as the difference between the longest and shortest P-wave durations recorded from surface ECG derivations (37). PWD has been used to assess the risk of developing AF in various clinical conditions, including cardiovascular diseases (11). In many studies, increased PWD measurement has been reported as a sensitive and specific ECG predictor for AF (10). When compared with the control group, higher PWD values were found in the group that developed AF. Our results indicate the importance of PWD measurement due to the increased risk of AF development in COVID-19 patients. Increased inflammatory activity leads to tissue damage in atrial myocardium, and resulting fibrosis causes atrial remodeling. This can alter the membrane potential in atrial myocytes and lead to heterogeneous refractory periods in atrial conduction. These changes may be reflected as prolonged P-wave duration and increased PWD on surface ECG (37). Similarly, in this study, it was determined that P-wave parameters were prolonged in patients who developed AF. In many studies, PWD value has been closely associated with inflammation (37-38). Yenerçağ et al., in their study comparing patients diagnosed with COVID-19 with healthy adults, demonstrated that PWD values were higher in COVID-19 patients than in healthy individuals (38). According to these results, inflammation occurring in COVID-19 patients may lead to an increase in PWD, causing the development of atrial arrhythmias. Additionally, in this study, PWD was found to be the strongest independent predictor indicating the development of AF.

Increased age, heart failure, and hypertension are among the key risk factors for the development of new-onset AF (39, 40). All these risk factors lead to an increase in atrial pressure and atrial remodeling, causing slowing of

atrial conduction and the formation of a substrate for AF (40). In this study, hypertension and HF were more frequent in patients who developed AF, and age and CHA2DS2-VASc score were significantly higher compared to the other group. These results suggest the development of atrial myopathy in the group with AF and an increased arrhythmic sensitivity of atrial tissue. Furthermore, these results support the increased PWD value in the group of patients who developed AF. Our current data support the hypothesis that these factors could play a significant role in the development of AF in COVID-19 patients. Additionally, cTn-I levels were found to be significantly higher in patients who developed AF. This result suggests that the occurring ventricular dysfunction may lead to increased left atrial pressure, contributing to the development of AF (41). In conclusion, it has been reported that the risk of developing AF is high in COVID-19 patients with a high PWD value, and we believe that these patients may require closer monitoring. These results confirm the results of previous studies emphasizing the role of inflammation in the pathogenesis of AF.

Limitations

There were several limitations in this study. Firstly, the sample size was small, and a larger cohort study is needed to confirm our results. Secondly, other inflammatory parameters, detailed echocardiographic measurements, and IL-6 with erythrocyte sedimentation rate couldn't be evaluated due to the fact that it was a retrospective study, the study conditions were limited, there was a possibility of viral infection, and the urgency of COVID-19. Thirdly, partly due to limitations in the available data and partly due to potential delays in the diagnosis of atrial arrhythmias during the COVID-19 pandemic, the exact onset of AF may not be accurately determined. Therefore, it is challenging to distinguish the temporal relationship between factors associated with the development of AF and their occurrence during the hospitalization. It is also worth noting that these data only pertain to hospitalized patients. Unhospitalized COVID-19 patients may have different predictors and outcomes for developing AF. However, since the likelihood of developing AF is higher in the most critical patients regardless of viral etiology, it is likely that the patients with the highest probability of developing AF were admitted to the hospital. Finally, since our follow-up only extended until discharge from the hospital, the impact of atrial arrhythmias on the post-hospitalization clinical course of the patients was not examined in this analysis. Additionally, there was no post-discharge follow-up to evaluate the occurrence of atrial arrhythmias after hospitalization.

CONCLUSION

In this study, it was found that new-onset AF occurred in 11.4% of hospitalized COVID-19 patients. The PWD is an easily accessible, cost-effective, and noninvasive ECG parameter, assessing the risk of AF development. It was determined to be high in COVID-19 patients who developed AF in this study. Furthermore, a significant relationship among PWD, CRP and NLR was identified. The evaluation of these ECG P-wave measurements in newly diagnosed COVID-19 patients may be beneficial in predicting the risk of AF development before treatment. Given the increased risk of AF development in COVID-19 patients with high PWD values, closer monitoring is anticipated. The presence of AF is associated with the increased clinical symptoms of severe COVID-19, high levels of inflammation, and markers of cardiac injury. Large-scale, long-term studies are needed to support our data.

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Peer-Review

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical approval was obtained from Hospital's Research Ethical Committee with date 11.02.21 and number (FSMEAH-KAEK 2021/19 , and Helsinki Declaration rules were followed to conduct this study.

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Author Contributions

Concept: HE, MBO, ÜK, SA, ZD, Design: HE, MBO, ÜK, SA, ZD, Supervising: HE, MBO, ÜK, SA, ZD, Financing and equipment: HE, MBO, ÜK, SA, ZD, Data collection andentry: HE, MBO, ÜK, SA, ZD, Analysis and interpretation: HE, MBO, ÜK, SA, ZD, Literature search: HE, MBO, ÜK, SA, ZD, Writing: HE, MBO, ÜK, SA, ZD, Critical review: HE, MBO, ÜK, SA, ZD

REFERENCES

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323 (11):1061-1069. Erratum in: JAMA. 2021 Mar 16;325 (11):1113. https://doi.org/10.1001/jama.2020.2648

2. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, et al. Association of Public Health Interventions With the Epidemiology of the

COVID-19 Outbreak in Wuhan, China. JAMA. 2020 May 19;323 (19):1915-1923. https://doi.org/10.1001/jama.2020.6130.

3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395 (10223):497-506. Epub 2020 Jan 24. Erratum in: Lancet. 2020 Jan 30;: https://doi.org/10.1016/S0140-6736 (20)30183-5

4. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19) [published correction appears in JAMA Cardiol. 2020 Jul 1;5 (7):848]. JAMA Cardiol. 2020;5 (7):811-818 https://doi.org/10.1001/jamacardio.2020.1017

5. Iacopino S, Placentino F, Colella J, P Francesca, Pardeo A, Filannino P, et al. New-Onset Cardiac Arrhythmias During COVID-19 Hospitalization. Circ Arrhythm Electrophysiol. 2020;13 (11):e009040. https://doi.org/10.1161/CIRCEP.120.009040

6. Peltzer B, Manocha KK, Ying X, Kirzner J, Ip JE, Thomas G, et al. Arrhythmic Complications of Patients Hospitalized With COVID-19: Incidence, Risk Factors, and Outcomes. Circ Arrhythm Electrophysiol. 2020;13 (10):e009121. https://doi.org/10.1161/CIRCEP.120.009121

7. Report sulle caratteristiche dei pazienti deceduti positivi a COVID-19 in Italia Il presente report è basato sui dati aggiornati al 20 Marzo 2020. https://www.epicentro.iss.it/coronavirus/ sars-cov-2-decessi-italia (accessed May 31, 2020).

8. Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy [published correction appears in Eur Heart J. 2020 Dec 21;41 (48):4591]. Eur Heart J. 2020;41 (19):1821-1829. https://doi.org/10.1093/eurheartj/ehaa388

9. Aytemir K, Ozer N, Atalar E, Sade E, Aksöyek S, Ovünç K, et al. P wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol. 2000;23 (7):1109-1112. https://doi.org/10.1111/j.1540-8159.2000.tb00910.x

10. Okutucu S, Aytemir K, Oto A. P-wave dispersion: What we know till now? JRSM Cardiovasc Dis. 2016 Mar 21;5:2048004016639443. https://doi.org/10.1177/2048004016639443.

11. Magnani JW, Mazzini MJ, Sullivan LM, Williamson M, Ellinor PT, Benjamin EJ. P-wave indices, distribution and quality control assessment (from the Framingham Heart Study). Ann Noninvasive Electrocardiol. 2010;15 (1):77-84. https://doi.org/10.1111/j.1542-474X.2009.00343.x

12. Dilaveris PE, Gialafos JE. P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol. 2001;6 (2):159-165. https://doi.org/10.1111/j.1542-474x.2001.tb00101.x

13. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol. 2020;31 (5):1003-1008. https://doi.org/10.1111/jce.14479

14. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504. https://doi.org/10.1016/j.intimp.2020.106504

15. Chan AS, Rout A. Use of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in COVID-19. J Clin Med Res. 2020;12 (7):448-453. https://doi.org/10.14740/jocmr4240

16. Lissoni P, Rovelli F, Monzon A, Privitera1 C, Messina1 G, Porro G, et al. Evidence of abnormally low lymphocyte-to-monocyte ratio in covid-19-induced severe acute respiratory syndrome. J Immuno Allerg 2020;1:1–6. https://doi.org/10.37191/Mapsci-2582-6549-1 (2)-011

17. Ministry of Health. COVID-19 rehberi. Republic of Turkey Ministry of Health; 2020. https://covid19bilgi.saglik.gov.tr/depo/ rehberler/COVID-19 _Rehberi.pdf. [Accessed 17 April 2020]

18. World Health Organization. Clinical management of severe acute respiratoryinfection when novel coronavirus (nCoV) infection is suspected: interim guidance. World Health Organization; 2020. Available from: https://www.who.int/publications-detail/clinicalmanagement-ofsevereacute-respiratory-infection-when-novelcoronavirus- (ncov)-infectionis- suspected. [Accessed 29 March 2020]

19. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance 2020 Jan 23;25(3). http://dx.doi.org/10.2807/1560-7917.es.2020.25.3.2000045

20. Pérez-Riera AR, de Abreu LC, Barbosa-Barros R, Grindler J, Fernandes-Cardoso A, Baranchuk A. P-wave dispersion: an update. Indian Pacing Electrophysiol J. 2016;16 (4):126-133. https://doi.org/10.1016/j.ipej.2016.10.002

21. Bazett H. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353–370

22. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr. 2002;15 (2):167-184. https://doi.org/10.1067/mje.2002.120202

23. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020;5 (7):831-840. https://doi.org/10.1001/jamacardio.2020.1286

24. Corman VM, Muth D, Niemeyer D, Drosten C. Hosts and Sources of Endemic Human Coronaviruses. Adv Virus Res. 2018;100:163-188. https://doi.org/10.1016/bs.aivir.2018.01.001

25. The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. https:// www.escardio.org/Education/ COVID-19 and Cardiology/ESCCOVID-19-Guidance. [Last updated 10 June 2020]

26. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020 Apr;8 (4):420-422. Epub 2020 Feb 18. Erratum in: Lancet Respir Med. 2020 Feb 25;: https://doi.org/10.1016/S2213-2600 (20)30076-X.

27. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J. Am. Coll. Cardiol. 60(22), 2263–2270 (2012).

28. Liu T, Li G, Li L, Korantzopoulos P. Association between c-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. J. Am. Coll. Cardiol. 49, 1642–1648 (2007).

29. Lin YJ, Tsao HM, Chang SL, Lo LW, Tuan TC, Hu YF, et al. Prognostic implications of the high-sensitive c-reactive protein in the catheter ablation of atrial fibrillation. Am. J. Cardiol. 105, 495–501 (2010).

30. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020;50(4):332-334. https://doi.org/10.1016/j.medmal.2020.03.007.

31. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020;92(10):1733-1734. https://doi.org/10.1002/jmv.25819

32. Kelesoglu S, Yilmaz Y, Ozkan E, Calapkorur B, Gok M, Dursun ZB, et al. New onset atrial fibrilation and risk faktors in COVID-19. J Electrocardiol. 2021;65:76-81. https://doi.org/10.1016/j.jelectrocard.2020.12.005.

33. Canpolat U, Aytemir K, Yorgun H, Şahiner L, Kaya EB, Kabakçı G, et al. Role of preablation neutrophil/lymphocyte ratio on outcomes of cryoballoon-based atrial fibrillation ablation. Am. J. Cardiol. 112(4), 513–519 (2013).

34. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J. Thromb. Thrombolysis 34, 326–334 (2012).

35. Demirag MK, Bedir A. Evaluation of preoperative neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in patients undergoing major vascular surgery. Turk. Gogus. Kalp. Damar. 21, 930–935 (2013).

36. Gungor H, Babu AS, Zencir C, Akpek M, Selvi M, Erkan MH, et al. Association of preoperative platelet-to-lymphocyte ratio with atrial fibrillation after coronary artery bypass graft surgery. Med. Princ. Pract. 26(2), 164–168 (2017).

37. Magnani JW, Williamson MA, Ellinor PT, Monahan KM, Benjamin EJ. P wave indices: current status and future directions in epidemiology, clinical, and research applications. Circ Arrhythm Electrophysiol. 2009;2(1):72-79. https://doi.org/10.1161/CIRCEP.108.806828.

38. Yenerçağ M, Arslan U, Şeker OO, Dereli S, Kaya A, Doğduş M, et al. Evaluation of P-wave dispersion in patients with newly diagnosed coronavirus disease 2019. J Cardiovasc Med (Hagerstown). 2021 Mar 1;22(3):197-203 39-Yalta T, Yalta K. Systemic Inflammation and Arrhythmogenesis: A Review of Mechanistic and Clinical Perspectives. Angiology. 2018;69 (4):288-296. https://doi.org/10.1177/0003319717709380.

39. Korantzopoulos P, Letsas KP, Tse G, Fragakis N, Goudis CA, Liu T. Inflammation and atrial fibrillation: A comprehensive review. J Arrhythm. 2018;34 (4):394-401. Published 2018 Jun 4. https://doi.org/10.1002/joa3.12077.

40. Packer M. Characterization, Pathogenesis, and Clinical Implications of Inflammation-Related Atrial Myopathy as an Important Cause of Atrial Fibrillation. J Am Heart Assoc. 2020;9 (7):e015343. https://doi.org/10.1161/JAHA.119.015343

41. Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the Cardiologist: Basic Virology, Epidemiology, Cardiac Manifestations, and Potential Therapeutic Strategies. JACC Basic Transl Sci. 2020;5 (5):518-536. Published 2020 Apr 10. https://doi.org/10.1016/j.jacbts.2020.04.002

ORIGINAL RESEARCH

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Assessment of relationship between different communication methods and treatment compliance in orthodontic patients during Covid-19 pandemics

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Abstract

Objective: The aim of this study was to minimize impairment in oral hygiene and failure of brackets; therefore, effects of pandemic on treatment duration, by communicating our patients using 4 different methods during Covid-19 pandemic.

Method: In the study, 227 patients undergoing fixed orthodontic treatment were included. Five groups were designed: WhatsApp group, short message service (SMS) group, Teledentistry group, e-mail group and control group. During quarantine period, patients were contacted for 4 times and same text was sent to patients. After pandemics, the patients were assessed using mucogingival index (MGI), orthodontic plaque index (OPI) and failure of brackets was determined.

Results: In MGI, percentage of patients with healthy result were as follows: WhatsApp group, 83.7%; SMS group, 87.8%; Teledentistry group, 83.7%; E-mail group, 77.5%; control group, 72.2% and no significant difference was found ($p>0.05$). The OPI scores were as follows: 1.12±1.24 in WhatsApp group; 1.27±1.28 in SMS group; 1.24±1.38 in Teledentistry group; 1.00±1.22 in E-mail group; and 1.61±1.25 in the control group and no significant difference was found ($p>0.05$). The mean number of brackets broken was 0.47±0.88 in WhatsApp group, 0.39±0.83 in SMS group, 0.51±1.00 in Teledentistry group, 0.40±0.67 in E-mail group and 0.44±0.86 in the control group and no significant difference was found ($p>0.05$).

Conclusion: It was determined that communicating with patients in different ways did not make any difference in terms of the subjects investigated in the study. It was concluded that it would be more appropriate to conduct new studies including social and psychological evaluations.

Keywords: Telemedicine, Orthodontics, Compliance, Covid-19, Communication

INTRODUCTION

In December, 2019, a novel coronavirus was identified in China, which rapidly spread worldwide. It was initially denoted as novel coronavirus pneumonia; which was, in turn, termed as novel coronavirus 2019 (2019 nCoV or Covid-19) (1). The virus has become a major concern due to its high infectivity and morbidity as well as ability to evolve to a potentially fatal interstitial pneumonia (2). In many countries, preventive hygiene measures including social distancing, isolation or quarantine were taken in order to prevent varying degrees of viral spread (3). In January, 2020, the World Health Organization (WHO) declared Covid-19 as an international public health emergency (4).

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All dental procedures including professional hygiene sessions which cause droplet formation or time spent in waiting room can increase the spread of infection; so dental clinics are classified in high-risk category (5). Thus, there is an urgent need for strict and effective hygiene protocols to control infection in dental offices in order to prevent infection in dentists and patients (6). It is highly important to use personal protective equipment to prevent cross-infection between healthcare providers and patients during clinical practice (7, 8). In addition, it is thought that it will be important to avoid unnecessary visits for healthcare providers while maintaining follow-up for treatment outcomes and health status (6).

The successful orthodontic treatment requires patient compliance in many aspects of treatment including oral hygiene, diet, use and care of appliances and compliance to visits (9-12). Previous studies showed that missed visits, bond failure of brackets and behavioral factors such as poor oral hygiene may considerably prolong duration of orthodontic treatment. These factors can be explained by poor patient compliance (13, 14-18). Thus, it has become an important issue to relieve these factors, which are also important for oral health, in the orthodontics (19).

During pandemic, we aimed to minimize impairment in oral hygiene and failure of brackets; therefore, effects of pandemic on treatment duration, by communicating our patients using 4 different methods. The null hypothesis of this study was that there was no statistically significant difference between different communication methods in terms of oral hygiene and failure of braces.

METHOD

The study was approved by Ethics Committee on Clinical Trials of Hatay Mustafa Kemal University (approval: 2020/71) and informed consent was obtained from all participants. In this study, patient compliance was assessed in first visit after pandemics in patients in whom scheduled visits could not be realized and 4 different communication methods were used during pandemic. Five groups were designed: WhatsApp group, in which WhatsApp application was used for communication; short message service (SMS) group, in which SMS was used for communication; teledentistry group; in which phone interview was used for communication; e-mail group; electronic mail was used for communication; and control group, no communication was established.

Initially, gingival health in five study groups were compared using Modified Gingival Index (MGI). In priori power analysis by Gpower software using Chi-square test, effect size was estimated as medium (d=0.30), indicating need for 40 observations in each group. First, we screened files of 446 patients with ongoing treatment in our clinic. Among these, we included patients who were considered to be healthy according to MGI in last session and able to attend first control visit after pandemic. Also it was confirmed that, in patients included, no missing brackets were observed in last visit before pandemics. Patients were excluded if they [1] considered as unhealthy regarding periodontal aspect at baseline and during treatment, [2] had a history of previous periodontal treatment, [3] undergoing lingual orthodontic treatment, [4] undergoing second orthodontic treatment, [5] treated with aligners and ceramic brackets, had a systematic disease or medications and smoking. Patient allocation for groups was performed using a computer-generated randomization program.

If it is possible, contact details of patients were used, if contact with patient is not possible contact details of legal guards were used. Patients not using WhatsApp or electronic mail were excluded. 227 patients undergoing fixed orthodontic treatment with brackets in all teeth were randomized. Chart 1 presents inclusion process of the patients.

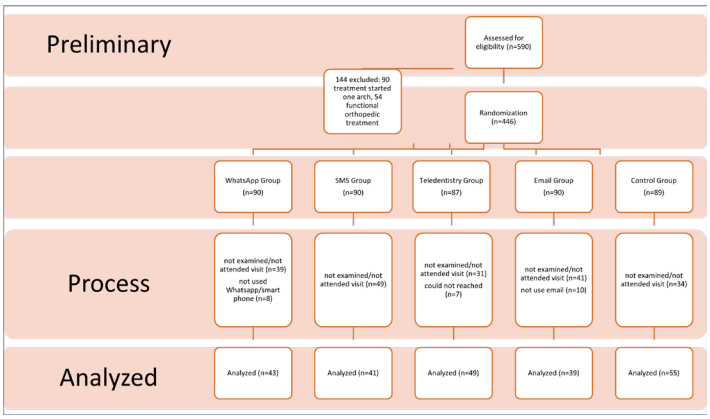

Chart 1. Inclusion process of the patients

All patients underwent orthodontic treatment using 3M Gemini MBT metal brackets (3M Unitek Orthodontic Products, Monrovia, CA, USA). The 3M Transbond XT light cure adhesive paste (3M Unitek Orthodontic Products, Monrovia, CA, USA) was used for bracket adhesion while the 3M Transbond XT light cure adhesive primer (3M Unitek Orthodontic Products, Monrovia, CA, USA) was used as bond. It was confirmed that,

in patients included, no missing brackets were observed in last visit before pandemics.

During quarantine period, patients were contacted for 4 times and same text was sent to patients. The text was sent as a message in E-mail, WhatsApp and SMS groups while it was read to patients in Teledentistry group. The text was as follows: "Please give attention to oral care in this period where visits could not be realized due to coronavirus pandemics. Please do not forget to brush your teeth after every meal. Please avoid acidic beverages and sticky foods that may harm our teeth. If fixed treatment is ongoing, please take care to use inter-dental brush and solid foods that may harm brackets. If you use an appliance or elastics, continue to use as recommended by your clinician". In acknowledgment message, we emphasized importance of tooth brushing and oral care, foods with risk for caries and careful consumption of foods to avoid loss of intraoral appliances. Patients were not asked for feedback regarding whether the message was read or not.

In the first control visit after pandemics, the patients were assessed using mucogingival index (MGI) (20) (Figure 1) and orthodontic plaque index (OPI) (21) (Figure 2) and failure of brackets was determined. Mucogingival scores are as follows: 0, no inflammation; 1, mild discoloration or slight changes in gingiva; 2, mild inflammation in gingival tissue surrounding tooth; 3, moderate inflammation in gingival tissue surrounding tooth; 4, severe inflammation in gingival tissue surrounding tooth. When assessing patients according to mucogingival index, scores 0 and 1 were defined as healthy while scores 2, 3 and 4 were defined as unhealthy. Orthodontic plague index was rated as follows: 0, if no visible plaque; 1, if there is plaque formation at one lateral of bracket; 2, if there is plaque formation at two lateral of brackets; 3, if moderate plaque formation at two lateral and cervical regions of brackets; 4, if one-third of area between bracket and gingiva is covered with plaque. Number of broken brackets was determined for each group.

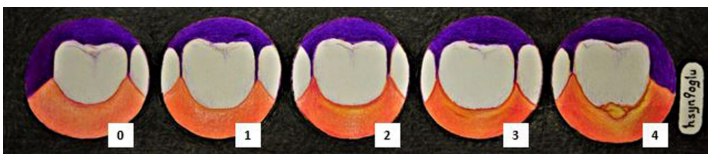

Figure 1: Mucogingival index

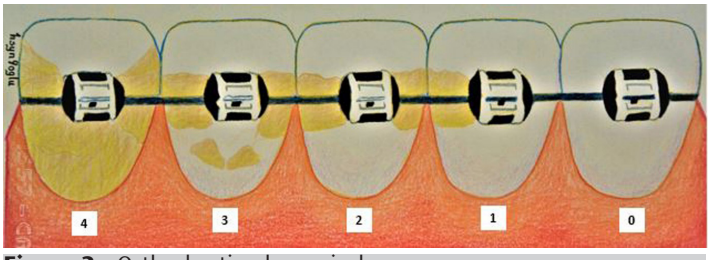

Figure 2: Orthodontic plaque index

Statistical Analysis

Shapiro-Wilk test was used to assess normality of data. Student's t test was used to compare data with normal distribution while Mann Whitney U test to compare data with skewed distribution between 2 independent groups. The correlations between categorical variables were analyzed using Pearson's correlation tests and Exact Chi-square test. Descriptive statistics are presented as mean± standard deviation for numeric data whereas count and percent for categorical data. All statistic analyses were performed using SPSS for Windows version 23.0. A p value <0.05 was considered as statistically significant.

RESULTS

Overall, 227 patients who suspended treatments between 13, March 2020 and 1, June 2020 were assessed in the study.

In MGI, percentage of patients with healthy result were as follows: WhatsApp group, 83.7%; SMS group, 87.8%; Teledentistry group, 83.7%; E-mail group, 77.5%; and control group, 72.2% (Table 2)._When groups were assessed, SMS group had best result in MGI (87.8%) while WhatsApp and Teledentistry groups had comparable results (83.7% in both groups) with higher percentage of patients with unhealthy results when compared to SMS group. These groups were followed by E-mail (77.5%) and control groups (72.2%). No significant difference was found among groups regarding MGI results (p>0.05).

Table 1. Distribution of general properties

		Min-Max	Mean ± SD
Age (year)		8-46	16.8±3.83
Treatment time (month)		6-43	11.65±6.36
Failure of bracket		0-4	0.44±0.86
OPI		0-4	1.27±1.28
		n	%
Gender	**Male**	78	34.4
	Female	149	65.6
MGI	**Healthy**	183	80.6
	Unhealthy	44	19.4
Group	**Whatsapp**	43	18.9
	SMS	41	18.1
	Teledentistry	49	21.6
	Email	40	17.6
	Control	54	23.8

SD: Standard deviation, OPI: Orthodontic plaque index, MGI: Mucogingival index

The OPI scores were as follows: 1.12±1.24 in WhatsApp group; 1.27±1.28 in SMS group; 1.24±1.38 in Teledentistry group; 1.00±1.22 in E-mail group; and 1.61±1.25 in the control group (Table 2). When groups were assessed, the best OPI result (lowest OPI score) was found in E-mail group (1.00±1.22); followed by WhatsApp group (1.12±1.24), Teledentistry group (1.24±1.38), SMS group (1.27±1.28) and control group (1.61±1.25). No significant difference was found among groups regarding OPI results (p>0.05).

Table 2. Examination of outcomes in groups

	Whatsapp		SMS		Teledentistry		E-Mail		Control		p-value
MGI	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Healthy	36	83.7	36	87.8	41	83.7	31	77.5	39	72.2	0.332
Unhealthy	7	16.3	5	12.2	8	16.3	9	22.5	15	27.8	
Gender											
Male	13	30.2	10	24.4	17	34.7	13	32.5	25	46.3	0.231
Female	30	69.8	31	75.6	32	65.3	27	67.5	29	53.7	
Failure of bracket (mean±sd)	0.47±0.88		0.39±0.83		0.51±1.00		0.40±0.67		0.44±0.86		0.986
OPI (mean±sd)	1.12±1,24		1.27±1.28		1.24±1.38		1.00±1.22		1.61±1.25		0.055
Treatment time (mean±sd)	11.30±5.36		11.73±4.84		11.00±6.88		10.45±5.28		13.33±8.00		0.137
Age	16.07±2.83		16.44±3.13		17.59±4.07		16.66±3.07		17.16±5.05		0.547

MGI: Mucogingival index, SD: Standard deviation, OPI: Orthodontic plaque index

The mean number of brackets broken was 0.47±0.88 in WhatsApp group, 0.39±0.83 in SMS group, 0.51±1.00 in Teledentistry group, 0.40±0.67 in E-mail group and 0.44±0.86 in the control group (Table 2). When groups were assessed, the SMS group had best result (0.39±0.83); followed by E-mail (0.40±0.67), control group (0.44±0.86), WhatsApp group (0.47±0.88) and Teledentistry group (0.51±1.00). No significant difference was found among groups regarding number of brackets broken (p>0.05). Table 2 demonstrates the outcomes of the study.

DISCUSSION

In our study, patients with interrupted visits were contacted using four different communication methods. The communication is highly important for quality and continuity of treatment in procedures such as orthodontic treatment which requires long-term treatment and follow-up. In healthcare industry, technological resources are employed in various areas for similar purposes. By widespread use of cell phones, technical tools such as SMS (short message services) have been widely attempted to use in healthcare services such as patient education and management of outpatient management (22,23). It was suggested that SMS support markedly improved treatment compliance in acquired immune deficiency syndrome (AIDS) patients and that it optimized blood pressure control in patients with hypertension (24,25). In dentistry, it was shown that attendance to visits can be considerably improved by sending a reminder of any kind (26-31). Similarly, reminders and educational messages are effective in improving oral hygiene and patient knowledge (32-36). Our study was conducted in 3-months of extraordinary period of Covid-19 pandemic where clinic control visits could not be maintained. In this period, main goals include to maintain oral hygiene, brackets and successful treatment outcomes. When groups were assessed, it was seen that an improvement was achieved in MGI and OPI indexes in study groups when compared to controls while number of brackets broken was higher in WhatsApp and Teledentistry groups than controls. However, the results did not reach statistical significance. Therefore, the null hypothesis of this study was accepted. In a similar study, oral hygiene was successfully improved in orthodontic patients. In the study, WhatsApp application was used as a social tool rather than reminders and educational messages and patients were encouraged to talk with each other in a chat room (37). In addition, a favorable effect was observed on oral hygiene in studies using SMS reminders (32, 33). We attributed comparable data obtained from groups to standardized procedures used in our facility. In our clinic, a strict oral hygiene education is provided to patients before starting treatment and treatment is postponed in patients considered as unhealthy according to mucogingival index. In case of periodontal problems occurring treatment period, treatment is withdrawn until the patient being healthy. The problems that may be caused by incompliance are explained to patients and patients are verbally acknowledged that they should contribute to treatment process in the start of treatment and each session. In several studies, it has been suggested that successful orthodontic treatment requires patient compliance in many issues such as oral hygiene, diet, use and maintenance of appliances and adherence to prescheduled visits (1-4).

In a study using reminders and informative message via a messenger application from start to end of treatment, no significant difference was found in baseline and post-treatment OPI and MGI values between study and control groups in agreement with our study. However, authors found that there was less bracket loss in the study group when compared to controls on contrary to our study where no significant difference was found in the number of brackets broken during study period (19).

The primary difference is that 3-months of pandemic was evaluated where treatments were withdrawn in our study while whole orthodontic treatment period was evaluated in the above-mentioned study.

Before pandemics, visits were scheduled by 4 or 5 weeks intervals in our clinic. In the study, communication was maintained by 2 weeks intervals since it is thought that message, mail or teledentistry communication will be less effective than warnings given during normal sessions. In a similar study, reminders about tooth brushing and solid foods were sent by twice weekly while educational messages about how tooth brushing will be performed or how periodontal pain will be relieved were sent once or twice weekly (19). We did not increase frequency of messages and teledentistry calls as in the above-mentioned study not to cause desensitization in our patients. The optimum frequency of communication with patients remains to be elucidated and requires further studies.

The fact that the study was performed during pandemics and that communication was established with patients during this period provided positive feedback in many aspects. Relieving patients concerns enhanced their trust to our clinicians. This is an issue that should be investigated by studies using psychological assessments. In our clinic, it is planned to implement such processes in addition to routine treatment procedure. The limitations of this study are that the bonding process and treatments of the patients were performed by different clinicians.

CONCLUSION

The communication is a highly important issue in the orthodontic treatment. According to the results of our study, particularly in extraordinary periods such as pandemic, it was required to communicate with patients to maintain normal therapeutic process. And also, oral hygiene monitoring can be performed via remote communication in any situation where patient control cannot be done. However, it was determined that communicating with patients in different ways did not make any difference in terms of the subjects investigated in the study. Despite this, it was verbally stated in the feedback that the trust of the patients in the institution increased. It was concluded that it would be more appropriate to conduct new studies including social and psychological evaluations.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical approval was obtained from Hatay Mustafa Kemal University Clinical Research Ethical Committee with date 2020 and number 2020/71, and Helsinki Declaration rules were followed to conduct this study.

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: HY, Design: HY, Supervising: FBZ, Financing and equipment: HY, Data collection and entry:İBK, Analysis and interpretation: FBZ, Literature search: İBK, Writing: HY, Critical review: FBZ

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REFERENCES

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270–273.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novelcoronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 2020;382:727-733.
3. Phelan AL, Katz R, Gostin LO. The Novel Coronavirus Originating inWuhan, China: Challenges for Global Health Governance. JAMA J. Am. Med. Assoc. 2020;323:709–710.
4. Mahase E. China coronavirus: WHO declares international emergency as death toll exceeds 200. BMJ. 2020; 368. HTTPS://DOI.ORG/10.1136/bmj.m408
5. Coulthard P. Dentistry and coronavirus (COVID-19)-moral decision-making. Br. Dent. J. 2020;228:503–505.
6. Maspero C, Abate A, Cavagnetto D, El Morsi M, Fama A, Farronato M. Available Technologies, Applications and Benefits of Teleorthodontics. A Literature Review and Possible Applications during the COVID-19 Pandemic. J. Clin. Med.

2020;9:1891.

7. Maspero C, Fama A, Cavagnetto D, Abate A, Farronato M. Treatment of dental dilacerations. J. Biol. Regul. Homeost. Agents. 2019; 33:1623–1627.

8. Farronato G, Giannini L, Galbiati G, Maspero C. Comparison of the dental and skeletal effects of two different rapid palatal expansion appliances for the correction of the maxillary asymmetric transverse discrepancies. Minerva Stomatol. 2012;61:45–55.

9. Fox N. Longer orthodontic treatment may result in greater external apical root resorption. Evid Based Dent. 2005;6:21.

10. El-Mangoury NH. Orthodontic cooperation. Am J Orthod. 1981;80:604-22.

11. Nanda RS, Kierl MJ. Prediction of cooperation in orthodontic treatment. Am J Orthod Dentofacial Orthop. 1992;102:15-21.

12. Daniels AS, Seacat JD, Inglehart MR. Orthodontic treatment motivation and cooperation: A cross-sectional analysis of adolescent patients' and parents' responses. Am J Orthod Dentofacial Orthop. 2009;136:780-7.

13. Skidmore KJ, Brook KJ, Thomson WM, Harding WJ. Factors influencing treatment time in orthodontic patients. Am J Orthod Dentofacial Orthop. 2006;129(2):230–238. https://doi.org/10.1016/j.ajodo.2005.10.003

14. Mavreas D, Athanasiou AE. Factors affecting the duration of orthodontic treatment: a systematic review. Eur J Orthod. 2008;30(4):386–395. https://doi.org/10.1093/ejo/cjn018

15. Beckwith FR, Ackerman Jr RJ, Cobb CM, Tira DE. An evaluation of factors affecting duration of orthodontic treatment. Am J Orthod Dentofac Orthop. 1999;115(4):439–447.

16. Robb SI, Sadowsky C, Schneider BJ, BeGole EA. Effectiveness and duration of orthodontic treatment in adults and adolescents. Am J Orthod Dentofacial Orthop. 1998;114(4):383–386. https://doi.org/10.1016/S0889-5406(98)70182–9

17. Ma W, Xu T-M. An evaluation of factors influencing orthodontic treatment duration. J Orthod. 2009;16(3):147–150. https://doi.org/10.3760/cma.j.issn.1674-5760.2009.03.007

18. Loke S, Tan S. Factors influencing duration of orthodontic treatment: a 12-year retrospective study. Malays Dent J. 2012;34(2):16–30.

19. Li X, Xu ZR, Tang N, Ye C, Zhu X-L, Zhou T, et al. Effect of intervention using a messaging app on compliance and duration of treatment in orthodontic patients. Clin Oral Invest. 2016;20:1849–1859. https://doi.org/10.1007/s00784-015-1662-6

20. Lobene RR, Weathford T, Ross NM, Lamm RA, Menaker L. A modified gingival index for use in clinical trials. Clinical Preventive Dentistry. 1986;8:3-6.

21. Beberhold K, Sachse-Kulp A, Schwestka-Polly R, Hornecker E, Ziebolz D. The Orthodontic Plaque Index: an oral hygiene index for patients with multibracket appliances. ORTHODONTICS (Chic). 2012;13(1):94-99.

22. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses. Cochrane Database Syst Rev 2012;CD007459. https://doi.org/10.1002/14651858.CD007459.pub2

23. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2008;2:CD000011. https://doi.org/10.1002/14651858.CD000011.pub3

24. Logan AG, McIsaac WJ, Tisler A, IrvineMJ, Saunders A, Dunai A, et al. Mobile phone-based remote patient monitoring system for management of hypertension in diabetic patients. Am J Hypertens. 2007;20(9):942–948. https://doi.org/10.1016/j.amjhyper.2007.03.020

25. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet. 2010;376(9755):1838–1845. https://doi.org/10.1016/S0140-6736(10)61997-6

26. Reekie D, Devlin H. Preventing failed appointments in general dental practice: a comparison of reminder methods. Br Dent J. 1998;185(9):472–474. https://doi.org/10.1038/sj.bdj.4809840

27. Can S, Macfarlane T, O'Brien KD. The use of postal reminders to reduce non-attendance at an orthodontic clinic: a randomised controlled trial. Br Dent J. 2003;195(4):199–201. https://doi.org/10.1038/sj.bdj.4810443

28. Thomas D. Postal reminders can improve attendance at orthodontic clinics. Evid Based Dent. 2004;5(1):14. https://doi.org/10.1038/sj.ebd. 6400244

29. Prasad S, Anand R. Use of mobile telephone short message service as a reminder: the effect on patient attendance. Int Dent J. 2012;62(1):21–26. https://doi.org/10.1111/j.1875-595X.2011.00081.x

30. Roth JP, Kula Jr TJ, Glaros A, Kula K. Effect of a computer-generated telephone reminder system on appointment attendance. Semin Orthod. 2004;10(3):190–193. https://doi.org/10.1053/j.sodo.2004.05.001

31. Nelson TM, Berg JH, Bell JF, Leggott PJ, Seminario AL. Assessing the effectiveness of text messages as appointment reminders in a pediatric dental setting. J Am Dent Assoc. 2011;142(4):397–405.

32. Brent Bowen T, Rinchuse DJ, Zullo T, DeMaria ME. The influence of text messaging on oral hygiene effectiveness. Angle Orthod. 2015;85(4):543–548. https://doi.org/10.2319/071514-495.1

33. Eppright M, Shroff B, Best AM, Barcoma E, Lindauer SJ. Influence of active reminders on oral hygiene compliance in orthodontic patients. Angle Orthod. 2014;84(2):208–213. https://doi.org/10.2319/062813-481.1

34. Jejurikar H, Nene S, Kalia A, Gupta G, Mirdehghan N. Does text messaging reminder help in the orthodontic compliance of patients to maintain their oral hygiene. Oral Hyg Health. 2014;2(5):152.

35. Hashemian TS, Kritz-Silverstein D, Baker R. Text2Floss: the feasibility and acceptability of a text messaging intervention to improve oral health behavior and knowledge. J Public Health Dent. 2015;75(1):34–41. https://doi.org/10.1111/jphd.12068

36. Sharma R, Hebbal M, Ankola AV, Murugabupathy V. Mobile-phone text messaging (SMS) for providing oral health education to mothers of preschool children in Belgaum city. J Telemed Telecare. 2011;17(8):432–436. https://doi.org/10.1258/jtt.2011.110416

37. Zotti F, Dalessandri D, Salgarello S, Piancino M, Bonetti S, Visconti L, et al. Usefulness of an app in improving oral hygiene compliance in adolescent orthodontic patients. Angle Orthod. 2016;86(1):101–107. https://doi.org/10.2319/010915-19.1

ORIGINAL RESEARCH

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Can the risk of hypocalcemia be detected with intact parathyroid hormone level after total thyroidectomy?

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Abstract

Objective: Nowadays, thyroidectomy is performed in patients with various indications. However, transient or permanent hypocalcemia occurs after surgery. In this case, the duration of hospitalization of the patients is prolonged. In this study, we aimed to detect hypocalcemia in the early phase with intact parathyroid hormone (iPTH), a biochemical marker.

Method: Hospital records of patients who had undergone standard bilateral total thyroidectomy for thyroid disease were retrospectively analyzed between September 2018 and April 2019 at the Department of General Surgery, Gaziantep University.

Results: Of the 114 patients included in the study, 91 were female (79.8%), and 23 were male (23%). Calcium levels of ≤8.5 mg/dL were found in 49 of 114 patients. Clinical symptoms of hypocalcemia were observed in 19 of these 49 patients. There was a significant correlation between the patients' iPTH levels at 3-6 hours postoperatively and the calcium values at 24 hours postoperatively ($p<0.05$). In addition, a significant, positive and weak correlation was found between the iPTH level and the iPTH level at 24 hours postoperatively and the Ca level at 24 hours postoperatively ($p<0.05$). The iPTH level measured between 3 and 6 hours postoperatively can predict hypocalcemia with a sensitivity of 77.5% and a specificity of 40.3%.

Conclusion: Postoperative hypocalcemia can be predicted with iPTH in the early period. The serum iPTH value has been concluded to be an effective parameter that can be used to predict postoperative hypocalcemia.

Keywords: Intact Parathyroid Hormone, Hypocalcemia, Thyroidectomy

INTRODUCTION

The thyroid gland is a vital endocrine organ that secretes thyroid hormones and is often operated on for many reasons (1). The most common complication following total thyroidectomy for thyroid disease is transient hypocalcemia (2). This clinical condition prolongs the patient's duration of hospitalization. Hypocalcemia may develop due to various factors, such as impaired blood supply to the parathyroid gland and injury to the parathyroid gland during dissection with the experience of the surgeon performing the surgery. However, thanks to developments in medicine, the risk of complications has been minimized through the use of advanced surgical instruments, good preoperative preparation of patients, and the development of anesthetic techniques. In parallel with these developments, the risk of morbidity, mortality, and complications in patients decreased.

Evaluating hypocalcemia with serum calcium value by looking at the clinical manifestation of the patients after surgery causes the diagnosis of hypocalcemia to be delayed and the duration of hospitalization to be prolonged. Hypocalcemia

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can be asymptomatic and sometimes lead to life-threatening clinical consequences (3). Early identification of risk factors for hypocalcemia is all the more important to reduce the potential risks and duration of hospitalization associated with hypocalcemia. Hypocalcemia can be predicted in the early postoperative period with iPTH (intact parathyroid hormone), which is tested immediately after surgery. This can also prevent prophylactic Ca (calcium) and vitamin D treatment in the early postoperative period (3).

Hypocalcemia and Hypoparathyroidism

Hypocalcemia that persists for less than one year after thyroidectomy is called transient hypocalcemia. If this condition persists for more than one year and requires calcium replacement, it is called persistent hypocalcemia.

The incidence of transient hypocalcemia is 3-80%, whereas permanent hypocalcemia occurs in society with an incidence of 0.4-13% (1,2).

Temporary hypocalcemia is not observed for a variety of reasons, such as complete ischemia or ischemic damage to the parathyroid glands due to thyroidectomy, hypothermia of the parathyroid glands, ET-1 (endothelin-1) secretion, hematomas formed adjacent to the parathyroid gland, calcitonin secretion due to surgical manipulation of the thyroid gland, fasting bone syndrome, hemodilution, hypothermia, decreased calcium absorption by the kidneys, removal of the parathyroid glands and necrosis due to vascular injury (4–9).

Serious complications such as cataracts, calcifications in the basal ganglia of the brain and cerebellum, and papilledema may occur in hypocalcemic patients who have waited for a long time and are delayed (10). Therefore, in hypocalcemic patients, calcium measurement should be performed in the postoperative period, regardless of the clinical picture. In this study, we aimed to detect hypocalcemia in the early phase with intact parathyroid hormone (iPTH), a biochemical marker.

METHOD

Ethical permission was obtained from the Gaziantep University, Medical Faculty Clinical Research Ethics Committee for this study with date 09.01.2019 and number 2019/34, and Helsinki Declaration rules were followed to conduct this study. Hospital records of 114 patients over 18 years of age who had undergone standard bilateral total thyroidectomy due to thyroid diseases (Graves' disease, multinodular goiter, benign and malignant thyroid diseases) were retrospectively analyzed between September 2018 and April 2019 at the Department of General Surgery, Faculty of Medicine, Gaziantep University. With the joint council meetings held with general surgery, endocrinology, nuclear medicine, and pathology, surgery was decided for these patients. The surgeries of the patients were performed by the same surgical team. Patients who underwent central or lateral lymph node dissection during surgery, patients with recurrent multinodular goiter, patients with parathyroid disease, pregnant patients, and patients with renal failure were excluded from the study. In these patients, age, gender, comorbidities, preoperative calcium, and parathyroid hormone levels, and postoperative calcium and parathyroid hormone levels measured in the blood between 3-6 hours, and calcium and parathyroid hormone levels measured 24 hours later were. The normal calcium range was assessed to be 8.5-10.5 mg/dL (milligrams/deciliter) when analyzed. Hypocalcemia was defined as a calcium value below 8.5 mg/dL. The intact parathormone (iPTH) levels were measured using an autoanalyzer with the spectrophotometric and chemiluminescent methods (Beckman Coulter Unicel DxI 800). The normal serum iPTH value was considered to be in the range of 15-65 pg/mL. In the postoperative period, numbness in the body, hand or foot, numbness, muscle spasms, positive Chvostek or Trousseau findings and cardiac arrhythmia were accepted as symptoms of hypocalcemia. Patients in whom these symptoms were not observed and whose calcium levels were decreased were evaluated as asymptomatic hypocalcemic patients.

Statistical Analysis

The analyses were performed with the SPSS 22.0 program. Repeated measurements analysis of variance test was used to compare the differences of iPTH and calcium values obtained at different measurement times. In order to determine from which measurement time the statistically significant difference originates, the LSD (Least significant difference) test, one of the multiple comparison tests, was used. The relationship between iPTH and calcium values obtained at different measurement times was analyzed by Pearson correlation analysis. In addition, patients were divided into two groups as hypocalcemia and normocalcemia according to the postoperative 24th hour calcium value. The T test was used to test the difference between the post op 3-6 hour iPTH values of these two groups. ROC analysis was used to determine the cut-off point for the variables. In all analyses, $p<0.05$ was considered significant.

RESULTS

A total of 114 male and female patients aged 18-82 years who underwent standard bilateral total thyroidectomy for thyroid disease (Graves', multinodular goiter, benign and malignant thyroid diseases) were included in the study. Ninety-one of the patients were female (79.8%), and 23 were male (23%). The mean age of the patients was 48 years.

In the study, the pathology results of the thyroidectomy material of the patients included in the surgery were analyzed (Table 1). Pathological examination revealed follicular

adenoma in 1 patient (0.9%), follicular neoplasia in 3 patients (2.6%), Graves' disease in 9 patients (7.9%), nodular goiter in 1 patient (0.9%), suspected hurthle cell neoplasia in 2 patients (1.8%), hurthle cell neoplasia in 1 patient (0.9%), medullary thyroid carcinoma in 1 patient (0.9%), medullary carcinoma in situ in 1 patient (0.9%), multinodular goiter in 45 patients (39.5%), NIFTP in 1 patient (0.9%), papillary microcarcinoma in 27 patients (23.7%), and papillary carcinoma in 22 patients (19.3%).

Table 1. Pathology diagnoses of patients after surgery

Pathology Pieces	n	%
Follicular Adenoma	1	0.9
Follicular Neoplasia	3	2.6
Graves	9	7.9
Nodular Goiter	1	0.9
Hurthle Cell Neoplasia Suspicious	2	1.8
Hurthle Cell Neoplasia	1	0.9
Medullary Carcinoma	1	0.9
Medullary Carcinoma in situ	1	0.9
Multinodular Goiter	45	39.5
NIFTP	1	0.9
Papillary Microcarcinoma	27	23.7
Papillary Thyroid Carcinoma	22	19.3
Total	114	100.0

NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features, n: number of patients

A calcium level of ≤8.5 mg/dL was found in 49 of 114 patients included in the study. Clinical symptoms of hypocalcemia were observed in 19 of these 49 patients. However, although the calcium value was >8.5 mg/dL, hypocalcemia symptoms were observed in 4 patients. Calcium replacement was performed in 19 patients with symptoms of hypocalcemia. In addition, although the calcium value was >8.5 mg/dL, calcium replacement was performed in 4 patients who developed hypocalcemia in the clinic.

Table 2. Age and hypocalcemia relationship

Calcium	n	Average age	Standard deviation	p value
≤ 8.5 mg/dL	49	47.76	11.60	0.815
> 8.5 mg/dL	65	48.34	14.14	

n: number of patients, p<0.05

When the data between the age of 114 patients included in the study and hypocalcemia were analyzed, the mean age of 49 patients with Ca≤8.5 mg/dL in the postoperative period was 47.7, while the mean age of 65 patients with Ca>8.5 mg/dL was 48.3 (Table 2). No significant correlation was found between age and hypocalcemia (p>0.05).

The relationship between sex and calcium studied in the postoperative period was analyzed. While Ca ≤8.5 mg/dL in 4 (17.4%) of 23 male patients, the number of males with Ca>8.5 mg/dL was 19 (82.6%). While Ca≤8.5 mg/dL was detected in 45 (49.5%) of 91 female patients included in the study in the postoperative period, Ca >8.5 mg/dL was detected in 46 (50.5%) female patients (Table 3). The risk of hypocalcemia in females was found to be higher than that in males and was found to be statistically significant (p<0.05).

Table 3. Gender and calcium relationship

			Calcium (mg/dL)		Total	p value
			Ca≤8.5 mg/dL	Ca>8.5 mg/dL		
Gender	M	n	4	19	23	0.006*
		%	17.4%	82.6%	100.0%	
	F	n	45	46	91	
		%	49.5%	50.5%	100.0%	
Total		n	49	65	114	
		%	43%	57%	100.0%	

P<0.05, Ca: calcium, M: male, F: female, n: number of patients

Patients' preoperative and postoperative 3-6 h and 24 h iPTH levels were analyzed (Table 4). The preoperative iPTH levels were found to be higher than postoperative iPTH levels that measured between 3-6 hours and 24th hours. Statistical analysis revealed that the preoperative and postoperative iPTH levels were statistically significant compared to the measurement times (p<0.05).

Table 4. Comparison of iPTH values according to measurement times.

Sample Time:	n	Mean ± standard deviation	p
Preoperative iPTH	114	53.64±26.25	0.001*
Postoperative iPTH (3-6 hours)	114	32.66±23.99	
Postoperative iPTH (24th hour)	114	33.39±25.83	

*p<0.05, n: number of patients, iPTH: intact parathyroid hormone, t-test

The patients' preoperative and postoperative Ca levels were analyzed at 3-6 hours and 24 hours (Table 5). The preoperative Ca values were higher than postoperatively 3-6 hours Ca levels and 24th hours Ca levels. Statistical analysis revealed that the preoperative and postoperative Ca levels were significant compared to the measurement times (p<0.05).

Patients' iPTH levels were analyzed between 3-6 hours postoperatively, and the calcium levels were analyzed at 24 hours postoperatively (Table 6). Patients who were found

to have hypocalcemia at the 24th hour postoperatively were also found to have low iPTH levels between 3-6 hours postoperatively. There was a significant correlation between the iPTH levels of the patients at 3-6 hours postoperatively and the calcium levels at 24 hours postoperatively ($p<0.05$).

Table 5. Comparison of calcium values according to measurement times

Sample Time:	n	Mean ± standard deviation (mg/dl)	p
Preoperative Ca	114	9.50±0.59[a]	0.001*
Postoperative Ca (3-6 hours)	114	8.51±0.97[b]	
Postoperative Ca (24th hour)	114	8.69±0.70[b]	

*p<0.05, n: number of patients, Ca: blood calcium level, t-test

Table 6. 3-6/h iPTH-postoperative and 24/h calcium relationship in the postoperative period

n	Postoperative 24th hour calcium value(mg/dl)	Postoperative 3-6/h iPTH mean Values	p value
49	≤8 5	27.31	0.038*
65	>8.5	36.72	

p<0.05, n: number of patients, h: hour, iPTH: intact parathyroid hormone

Table 7. Relationship between iPTH and calcium values

		Preoperative Ca p value	Postoperative Ca 3-6 hours p value	Postoperative Ca 24th hour p value
Preoperative iPTH	Pearson Correlation	-0.029	-0.051	0.016
	Sig. (2-tailed)	0.759	0.592	0.863
	n	114	114	114
Postoperative iPTH 3-6 hours	Pearson Correlation	0.060	0.079	0.287**
	Sig. (2-tailed)	0.529	0.402	0.002*
	n	114	114	114
Postoperative iPTH 24th hour	Pearson Correlation	0.122	0.053	0.308**
	Sig. (2-tailed)	0.197	0.577	0.001*
	n	114	114	114

P<0.05, n: number of patients, iPTH: intact parathyroid hormone, Ca: calcium, Pearson correlation analysis

The relationship between preoperative and postoperative iPTH and calcium levels was investigated using Pearson correlation analysis (Table 7). Accordingly, a statistically significant, positive and weak relationship was found between the iPTH level measured between 3-6 hours postoperatively and the iPTH level measured at 24 hours postoperatively and the Ca level measured at 24 hours postoperatively ($p<0.05$). Hypocalcemia can be predicted in the 24th postoperative hour by examining the iPTH level in the 3-6 hours postoperatively.

When the relationship between the iPTH level measured in the 3rd to 6th postoperative hour and hypocalcemia was investigated, the ROC diagram obtained for the postoperative iPTH level is shown in Figure 1. This is the 39.6 pg/ml cut-off point for the postoperative iPTH level. The area under the ROC curve for the iPTH level measured between 3-6 hours postoperatively was 0.611, and the iPTH level measured between 3-6 hours postoperatively was significant in predicting hypocalcemia (95% confidence interval: 63.4-88;

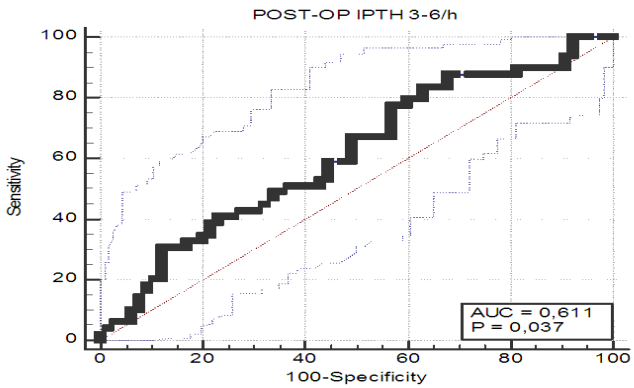

Figure 1: ROC curve obtained for iPTH value at 3-6 hours postoperatively

$p<0.05$). When the serum iPTH value was below 39.6 pg/ml between 3 and 6 hours postoperatively, it was found that it could predict hypocalcemia with a sensitivity of 77.55% and specificity of 40.3%.

DISCUSSION

Thyroidectomy is the most commonly performed endocrine surgical procedure worldwide. Thyroidectomy procedures can lead to various complications. The most common complication is hypocalcemia. Due to these complications, the medical treatments of the patients are prolonged, and the duration of hospitalization is prolonged. Accordingly, many biochemical and hormonal tests are required. While the rate of transient hypocalcemia is 10-50%, the rate of permanent hypocalcemia lasting more than 6 months is 0.5-2% (11–13). A total of 114 patients were included in our study, and 49 (42.3%) of these patients had transient hypocalcemia. The rate of development of hypocalcemia is similar to the literature (11–16).

The cause of hypocalcemia after thyroidectomy is not fully known. However, it was thought that there were reasons such as impaired blood supply to the parathyroid glands due to manipulations during surgery, the development of ischemia in the glands or accidental removal of the glands during surgery. Therefore, the physician performing thyroid surgery should have sufficient information about the anatomy of

the parathyroid glands and the changes in the parathyroid glands. The surgeon should stay away from interventions that will affect the blood supply to the glands. In many studies in the literature, it has been suggested that postoperative hypocalcemia may be due to surgical technique (11,17,18). In a prospective study conducted by Acun et al. (19), it was reported that there was no difference between experienced surgeons and residents in terms of damage to the parathyroid gland during surgery and related hypocalcemia. Since all the surgeries included in our study were performed with the same surgical team and the same surgical technique by the same residents, hypocalcemia that may occur due to surgical technique was standardized.

In the statistical analysis conducted for the relationship between hypocalcemia and gender, we observed a statistically significant higher susceptibility to hypocalcemia among females. A study by Bove et. al (8) similarly reported an increased risk of hypocalcemia associated with the female gender.

Early detection of the risk of hypocalcemia is important to avoid prophylactic medical treatment so that patients can be discharged early and avoid the risk of hypocalcemia that may occur. Calcium metabolism is slow and shows no signs and symptoms in postoperative early hour measurements. These findings occur at 24-72 hours postoperatively (20). The half-life in intact PTH blood is 2-5 minutes. Because of the short half-life of PTH, its drop in the early postoperative period has been used as a marker for transient hypocalcemia (14–16,21,22). In some studies, measurement of postoperative parathyroid hormone levels has been shown to reduce the incidence of hypocalcemia and the duration of hospitalization with early calcium replacement therapy by predicting hypocalcemia (14,23,24). In various studies conducted to predict hypocalcemia in the early period, the timing of iPTH measurement, the method and the thresholds obtained have been presented (16,23,25).

As the most common complication after total thyroidectomy is transient hypocalcemia, many centers prophylactically administer low-dose calcium and vitamin D to patients. However, studies have shown that low-dose calcium prophylaxis does not prevent the symptoms of hypocalcemia (20,26). According to these studies, more than 50% of the patients received unnecessary Ca prophylaxis, which caused an increase in health expenses. However, in our study, calcium replacement was performed at the appropriate dose according to the calcium values at the 24th postoperative hour and in patients with hypocalcemia symptoms. By comparing the iPTH and calcium levels examined in patients between the postoperative 3-6 hours before and after the surgery and at the postoperative 24th hour, we aimed to determine the relationship between the changes that may occur in the iPTH levels and the changes that may occur in the calcium levels and to predict hypocalcemia at a much earlier time. The aim was to prevent the symptoms of hypocalcemia that may develop by initiating early medical treatment in patients with postoperative hypocalcemia and to shorten the patients' duration of hospitalization.

In our study, the cut-off value was determined to be 39.6 pg/mL (picogram/milliliter) according to the ROC curve for the iPTH level measured between 3-6 hours postoperatively. When the iPTH value measured between the postoperative 3-6 hours was less than 39.6 pg/ml, the risk of hypocalcemia at the 24th hour was predicted with an accuracy of 77.5% and a specificity of 40.3%. Many similar studies are available in the literature. In a study of 260 patients published by Davide Inversini et al. (25) in 2016, the iPTH cut-off value of 10.0 pg/ml was shown to have a sensitivity of 76% and a specificity of 83% for the assessment of postoperative hypocalcemia. In this study, it was shown that there was a statistically strong relationship between iPTH and serum calcium levels at the 24th and 48th postoperative hours. In a prospective study conducted by Montana Suwannasarn et al. (26) in 2017 involving 65 patients, preoperative and postoperative 4th-hour iPTH values of the patients were measured, and hypocalcemia was detected in 25 (38.5%) patients. When the postoperative 4th-hour iPTH value was below 12.5 pg/mL and the iPTH decrease was above 72%, hypocalcemia was predicted in patients with a sensitivity of 92%, specificity of 87.5%, and accuracy of 82.1%.

In a study of 112 patients conducted by Adolfo Pisanu et al. (23) between 2010 and 2011, it was observed that the preoperative serum iPTH level decreased by 80.2% at the 6th postoperative hour and increased by 37% at the 48th postoperative hour in 33 patients who developed hypocalcemia. This difference was found to be significant in repeated iPTH measurements. As a result of the studies, a treatment algorithm was established with serum iPTH and calcium levels at the 6th and 24th postoperative hours (23). In our study, it was found that there was a statistically significant difference between the iPTH values of the groups formed according to the calcium value on the first postoperative day between 3 and 6 hours postoperatively ($p<0.05$). It was found that the iPTH levels of hypocalcemic patients were lower than those of normocalcemic patients between 3 and 6 hours postoperatively. We aimed to establish a hypocalcemia treatment algorithm with appropriate treatment by predicting postoperative hypocalcemia with iPTH between 3-6 hours postoperatively and at the 24th postoperative hour.

In a multicenter prospective study conducted by Saleh F. Al-Dhahri et al. (27) between 2009 and 2012, 168 patients were evaluated. The decrease in PTH value at the first postoperative hour was found to be significant in terms

of predicting hypocalcemia. Patients with symptoms of hypocalcemia had a greater reduction in PTH than those without. A positive correlation was found between the length of hospital stay and a decrease in PTH value of more than 73% postoperatively. In another study conducted by Azmi Lale et al. (28), 818 adult patients were discussed. The length of hospital stay of patients who developed postoperative hypocalcemia was found to be longer than that of normal patients. In our study, we aimed to reduce the duration of hospitalization of the patients by predicting the hypocalcemic picture that developed postoperatively with the decrease in iPTH and initiating appropriate calcium replacement on time.

In a study conducted by A. Bove et al. (29) examined preoperative PTH, postoperative 1st-hour PTH and postoperative 24th-hour serum calcium values in 96 patients between 2012 and 2013. The serum PTH level at the 1st postoperative hour was found to be 39.8 pg/dl for the detection of postoperative hypocalcemia and was found to predict hypocalcemia with a sensitivity of 50% and a specificity of 87%. Similar to this study, the cut-off value for iPTH measured between 3-6 hours postoperatively in our study was also 39.6 pg/ml. Thus, when the iPTH level was below 39.6 pg/ml, hypocalcemia could be predicted with a sensitivity of 77.55% and a specificity of 40.3%.

Limitations of The Study

The limitation of our study is that the long-term results of these patients are not known.

CONCLUSION

Postoperative hypocalcemia can be predicted with iPTH in the early period. Performing the necessary treatment at the appropriate time by predicting hypocalcemia early with the iPTH value measured from the blood between 3-6 hours postoperatively and at the 24th hour postoperatively shortens the length of hospital stay. There was a statistically significant relationship between the iPTH value measured from the blood between 3-6 hours postoperatively and at 24 hours postoperatively and the serum calcium levels of patients who developed hypocalcemia. Serum iPTH level was found to be an effective parameter for predicting postoperative hypocalcemia. Further comprehensive studies are needed to predict hypocalcemia in the early postoperative period.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Previously Presented

This study was prepared by rearrangement of the specialty thesis by first author, entitled as “total tiroidektomi sonrası intakt parathormon düzeyi ile hipokalsemi riski saptanabilir mi? ” and dated 2019.

Ethical Declaration:

Ethical permission was obtained from the Gaziantep University, Medical Faculty Clinical Research Ethics Committee for this study with date 09.01.2019 and number 2019/34, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: AA, Design: AA, AH, NB, Supervising: AA, AH, LY, AB, Financing and equipment: AA, LY, Data collection and entry: AH, AA, NB, Analysis and interpretation: AA, LY, NB, AB, Literature search: AH, AA, AB Writing: AH, AA, NB, Critical review: AA, LY, AB

REFERENCES

1. Zhu S, Pang Y, Xu J, Chen X, Zhang C, Wu B, et al. Endocrine Regulation on Bone by Thyroid. Frontiers in endocrinology. 2022;13:873820. https://doi.org/10.3389/fendo.2022.873820
2. Gac EP, Cabané TP, Amat VJ, Huidobro GF, Rossi FR, Rodríguez FF, et al. [Incidence of hypocalcemia after total thyroidectomy]. Revista medica de Chile. 2007;135(1):26-30. https://doi.org/10.4067/S0034-98872007000100004
3. Pepe J, Colangelo L, Biamonte F, Sonato C, Danese VC, Cecchetti V, et al. Diagnosis and management of hypocalcemia. Endocrine. 2020;69(3):485-95. https://doi.org/10.1007/s12020-020-02324-2
4. Warren FM, Andersen PE, Wax MK, Cohen JI. Perioperative parathyroid hormone levels in thyroid surgery: preliminary report. The Laryngoscope. 2004;114(4):689-93. https://doi.org/10.1097/00005537-200404000-00017
5. Husein M, Hier MP, Al-Abdulhadi K, Black M. Predicting calcium status post thyroidectomy with early calcium levels. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2002;127(4):289-93. https://doi.org/10.1067/mhn.2002.127891
6. Shaha AR, Burnett C, Jaffe BM. Parathyroid autotransplantation during thyroid surgery. Journal of surgical oncology. 1991;46(1):21-4. https://doi.org/10.1002/jso.2930460106
7. Fahmy FF, Gillett D, Lolen Y, Shotton JC. Management of serum calcium levels in post-thyroidectomy patients. Clinical otolaryngology and allied sciences. 2004;29(6):735-9. https://doi.org/10.1111/j.1365-2273.2004.00895.x

8. Bove A, Bongarzoni G, Dragani G, Serafini F, Di Iorio A, Palone G, et al. Should female patients undergoing parathyroid-sparing total thyroidectomy receive routine prophylaxis for transient hypocalcemia? The American surgeon. 2004;70(6):533-6. https://doi.org/10.1177/000313480407000615

9. Erickson L. A. and Lloyd R. V. Pathology of the thyroid gland. Surg. Pathol. Head Neck 3rd Edn Inf. Healthc. N. Y.,2009;pp.1385-1428. https://doi.org/10.3109/9781420020373-22

10. Adams J, Andersen P, Everts E, Cohen J. Early postoperative calcium levels as predictors of hypocalcemia. The Laryngoscope. 1998;108(12):1829-31. https://doi.org/10.1097/00005537-199812000-00012

11. Erbil Y, Bozbora A, Ozbey N, Issever H, Aral F, Ozarmagan S, et al. Predictive value of age and serum parathormone and vitamin d3 levels for postoperative hypocalcemia after total thyroidectomy for nontoxic multinodular goiter. Archives of surgery (Chicago, Ill : 1960). 2007;142(12):1182-7. https://doi.org/10.1001/archsurg.142.12.1182

12. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B. Hypoparathyroidism after total thyroidectomy: a prospective study. Archives of surgery (Chicago, Ill : 1960). 2008;143(2):132-7; discussion 8. https://doi.org/10.1001/archsurg.2007.55

13. Lefevre JH, Tresallet C, Leenhardt L, Jublanc C, Chigot JP, Menegaux F. Reoperative surgery for thyroid disease. Langenbeck's archives of surgery. 2007;392(6):685-91. https://doi.org/10.1007/s00423-007-0201-6

14. AlQahtani A, Parsyan A, Payne R, Tabah R. Parathyroid hormone levels 1 hour after thyroidectomy: an early predictor of postoperative hypocalcemia. Canadian journal of surgery Journal canadien de chirurgie. 2014;57(4):237-40. https://doi.org/10.1503/cjs.008013

15. Schlottmann F, Arbulú AL, Sadava EE, Mendez P, Pereyra L, Fernández Vila JM, et al. Algorithm for early discharge after total thyroidectomy using PTH to predict hypocalcemia: prospective study. Langenbeck's archives of surgery. 2015;400(7):831-6. https://doi.org/10.1007/s00423-015-1341-8

16. Karatzanis AD, Ierodiakonou DP, Fountakis ES, Velegrakis SG, Doulaptsi MV, Prokopakis EP, et al. Postoperative day 1 levels of parathyroid as predictor of occurrence and severity of hypocalcaemia after total thyroidectomy. Head & neck. 2018;40(5):1040-5. https://doi.org/10.1002/hed.25081

17. Uruno T, Miyauchi A, Shimizu K, Tomoda C, Takamura Y, Ito Y, et al. A prophylactic infusion of calcium solution reduces the risk of symptomatic hypocalcemia in patients after total thyroidectomy. World journal of surgery. 2006;30(3):304-8. https://doi.org/10.1007/s00268-005-0374-5

18. Pattou F, Combemale F, Fabre S, Carnaille B, Decoulx M, Wemeau JL, et al. Hypocalcemia following thyroid surgery: incidence and prediction of outcome. World journal of surgery. 1998;22(7):718-24. https://doi.org/10.1007/s002689900459

19. Acun Z, Cihan A, Ulukent SC, Comert M, Ucan B, Cakmak GK, et al. A randomized prospective study of complications between general surgery residents and attending surgeons in near-total thyroidectomies. Surgery today. 2004;34(12):997-1001. https://doi.org/10.1007/s00595-004-2857-7

20. Orloff LA, Wiseman SM, Bernet VJ, Fahey TJ, 3rd, Shaha AR, Shindo ML, et al. American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults. Thyroid : official journal of the American Thyroid Association. 2018;28(7):830-41. https://doi.org/10.1089/thy.2017.0309

21. Murray TM, Rao LG, Divieti P, Bringhurst FR. Parathyroid hormone secretion and action: evidence for discrete receptors for the carboxyl-terminal region and related biological actions of carboxyl- terminal ligands. Endocrine reviews. 2005;26(1):78-113. https://doi.org/10.1210/er.2003-0024

22. Vescan A, Witterick I, Freeman J. Parathyroid hormone as a predictor of hypocalcemia after thyroidectomy. The Laryngoscope. 2005;115(12):2105-8. https://doi.org/10.1097/01.MLG.0000181504.69230.87

23. Saba A, Podda M, Messina Campanella A, Pisanu A. Early prediction of hypocalcemia following thyroid surgery. A prospective randomized clinical trial. Langenbeck's archives of surgery. 2017;402(7):1119-25. https://doi.org/10.1007/s00423-017-1586-5

24. Lecerf P, Orry D, Perrodeau E, Lhommet C, Charretier C, Mor C, et al. Parathyroid hormone decline 4 hours after total thyroidectomy accurately predicts hypocalcemia. Surgery. 2012;152(5):863-8. https://doi.org/10.1016/j.surg.2012.03.011

25. Inversini D, Rausei S, Ferrari CC, Frattini F, Anuwong A, Kim HY, et al. Early intact PTH (iPTH) is an early predictor of postoperative hypocalcemia for a safer and earlier hospital discharge: an analysis on 260 total thyroidectomies. Gland surgery. 2016;5(5):522-8. https://doi.org/10.21037/gs.2016.09.08

26. Suwannasarn M, Jongjaroenprasert W, Chayangsu P, Suvikapakornkul R, Sriphrapradang C. Single measurement of intact parathyroid hormone after thyroidectomy can predict transient and permanent hypoparathyroidism: a prospective study. Asian journal of surgery. 2017;40(5):350-6. https://doi.org/10.1016/j.asjsur.2015.11.005

27. Al-Dhahri SF, Mubasher M, Al-Muhawas F, Alessa M, Terkawi RS, Terkawi AS. Early prediction of oral calcium and vitamin D requirements in post-thyroidectomy hypocalcemia. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2014;151(3):407-14. https://doi.org/10.1177/0194599814536848

28. Lale A, Öz B, Akcan AC, Sözüer EM, Arıkan TB, Gök M. Determination of risk factors causing hypocalcaemia after thyroid surgery. Asian journal of surgery. 2019;42(9):883-9. https://doi.org/10.1016/j.asjsur.2018.12.009

29. Bove A, Di Renzo RM, Palone G, D'Addetta V, Percario R, Panaccio P, et al. Early biomarkers of hypocalcemia following total thyroidectomy. International journal of surgery (London, England). 2014;12 Suppl 1:S202-4. https://doi.org/10.1016/j.ijsu.2014.05.008

CASE REPORT

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Vena cava inferior agenesis recognized by incidentally in a patient under cholecystectomy

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Abstract

Inferior Vena cava (IVC) agenesis is a rare congenital anomaly, which may cause significant consequences with regard to morbidity and mortality. In this case report, a patient diagnosed with IVC agenesis which was seen intraabdominal intensive venous collateral during surgery for cholecystectomy is presented.

Keywords: Inferior Vena Cava, Agenesis, Venous Anomalies, Abnormal Varicosities.

INTRODUCTION

Inferior vena cava (IVC) is the major venous collecting system that brings venous blood from the legs, pelvis, and abdominal organs to the right atrium. Changes in the development process of the IVC between the 6th and 8th weeks of intrauterine life give rise to some developmental anomalies (1). The congenital anomalies of the IVC affect approximately 0.5% of the general population (2). Congenital IVC agenesis is a rare anomaly, and its incidence is 0.0005%-1% (3).

In patients with IVC agenesis, venous drainage from the lower extremities is provided via the well-developed ascending lumbar veins within the azygos and hemiazygos system (4, 5). When preoperatively undiagnosed anomalies are found incidentally intraoperatively, the management of the surgical procedure is vital. Intraoperative bleeding caused by venous anomalies can be life threatening. The bleeding complications increase up to 40% when abnormal venous formations are recognized intraoperatively (6).

IVC agenesis may be associated with cardiovascular, tracheobronchial, and other visceral malformations (7), but may also show a silent course symptom until advanced ages (3). In cardiovascular surgery, this anomaly often causes pelvic congestion symptoms, deep vein thrombosis (3,8), and rarely pulmonary thromboembolism (3). In addition, it may be accidentally detected during abdominal surgeries (6) or may occur as an unexpected technical problem at cannulation during thoracic cardiovascular surgery. Thus, IVC agenesis may be a cause of morbidity, and mortality and negatively affect the surgical results. We present a patient who underwent surgery for cholecystectomy with intense venous collateral vascularization in the abdominal region.

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CASE REPORT

A 60-year-old female patient with a history of cholecystectomy was admitted to our clinic. Her patient file indicated that intense vascular formations were incidentally observed in the intraabdominal area during the operation for cholecystectomy. The surgery was initially planned laparoscopically. Open surgery was performed due to bleeding due to traumatization of venous collaterals during the laparoscopic procedure, which disrupted the surgical procedures. The gallbladder was reached by tying or clipping the venous collaterals observed during exploration. There were no additional complications except for non-major bleeding. Physical examination of the patient showed intense venous collaterals development on the right side of the abdominal area. Contrast-Enhanced Computed Tomography (CECT) scanning in venous phase for further examination was performed. The scanning revealed the complete absence of IVC. IVC was partially observed at the infra-renal level and was not observed at more proximal levels. Then, the IVC was observed normally at the diaphragm level and it opens into the right atrium. There were widespread collateral venous structures in the abdomen. The superior and inferior mesenteric veins drain through the collaterals to the portal vein, from there to the hepatic veins, and then to the IVC. IVC diameter was measured as 16-17mm at the crus diaphragm level. The portal vein diameter was measured as 22.2mm at the hepatic hilus level and it was larger than normal. Hepatic veins were dilated. Ovarian veins drained into the right and left renal veins on both sides, and the left renal vein was dilated. Widespread, dilated vascular structures were noted at the base of the superior and inferior mesenteric veins, in the left lower quadrant, at the pelvic level, in the subcutaneous fatty tissue on the abdominal wall. Heterogeneity was observed in the uterine parenchyma, and widespread vascularization in the myometrium was noted (Figures1- 4).

Informed consent was obtained from the patient.

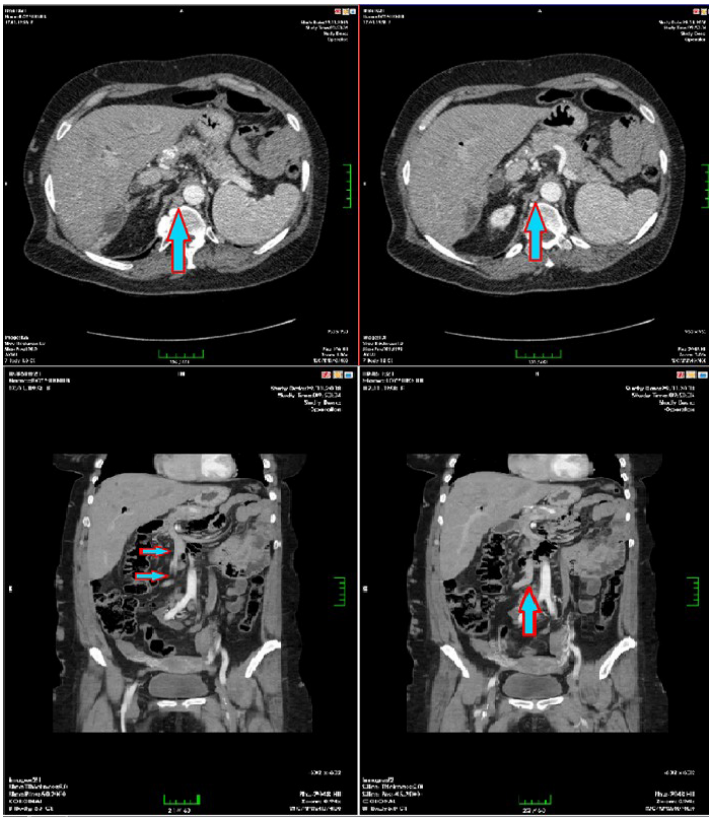

Figure 1: In I.V. contrast-enhanced CT sections; The IVC calibration narrows starting from below the diaphragm level; Its lumen below the level of the right vena renalis shows completely stenotic atresia (Partial IVC Agenesis).

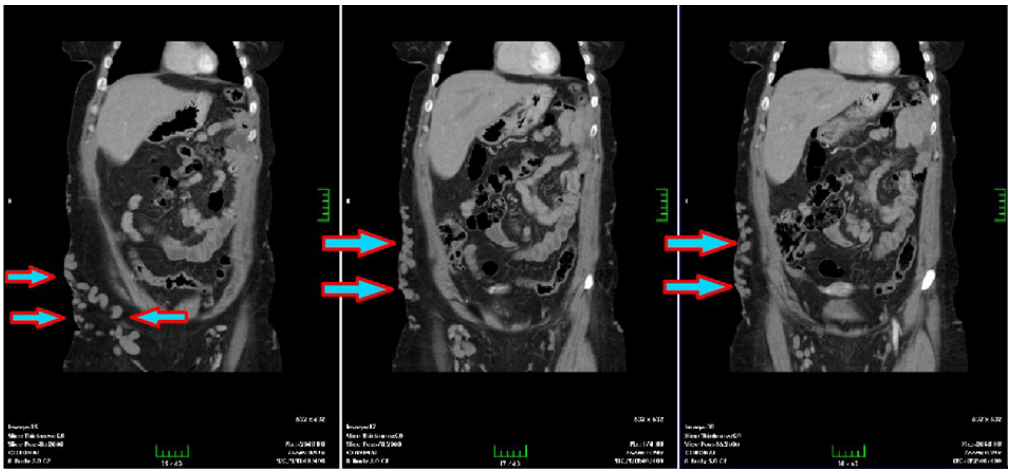

Figure 2: In I.V. contrast-enhanced CT sections taken in the axial plane; In order to provide venous system drainage secondary to infra-renal IVC partial agenesis, widespread tortuous venous vascular structures with increasing calibration and ectatic dilatation attract attention within subcutaneous adipose tissue planes in the right abdominal lower quadrant and pelvic level abdominal walls.

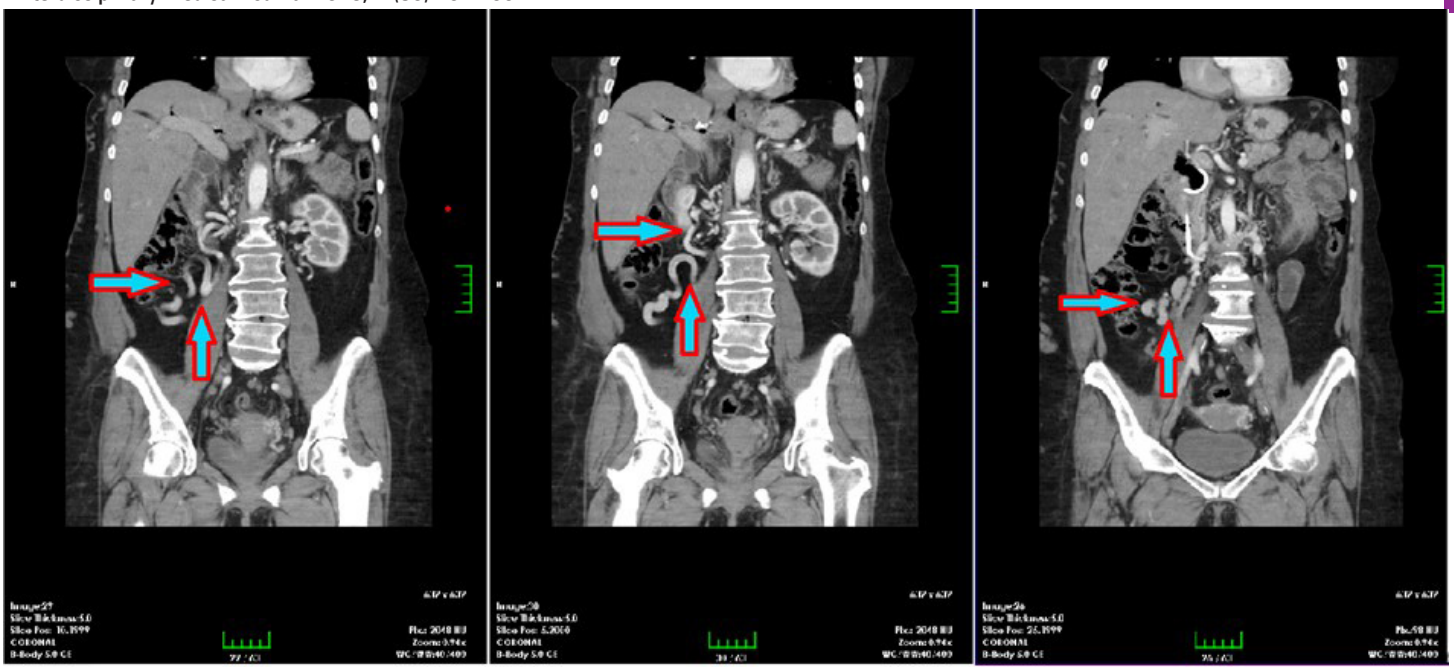

Figure 3: In I.V. contrast-enhanced CT sections taken in the axial plane; Venous vascular structures with ectatic dilatation increasing calibration to provide venous system drainage secondary to infra-renal IVC agenesis/atresia and diffusely tortuous varicose appearance at the levels of SMV and IMV roots are shown with arrows. The superior and inferior mesenteric veins drain into the vena porta via collaterals, then into the hepatic veins and then into the IVC.

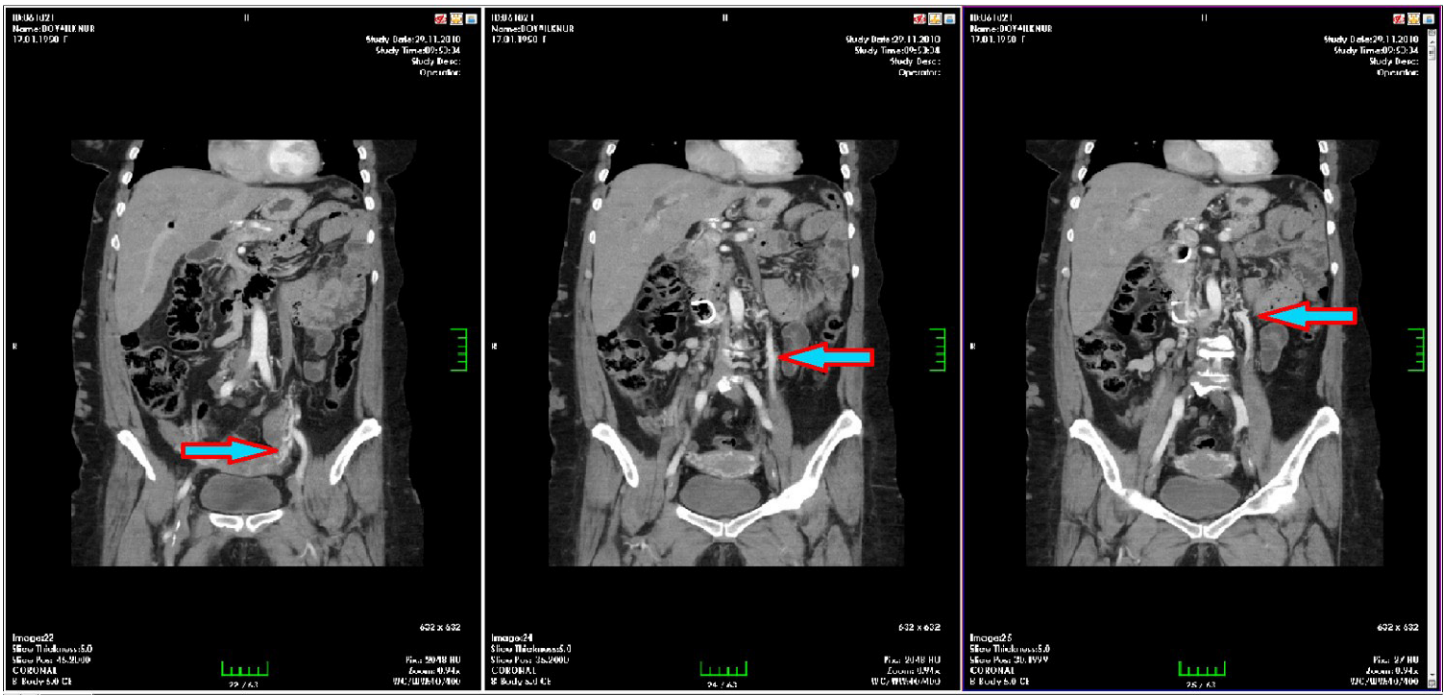

Figure 4: In Contrasted CT Sections; Secondary to infra-renal IVC agenesis, tortuous left ovarian vein, showing ectatic dilatation by increasing calibration to provide venous system drainage, and pouring into the left vena renal.

DISCUSSION

IVC agenesis is a rare anomaly which is usually asymptomatic until advanced ages and it is often incidentally detected during cross-sectional imaging in healthy subjects (4). In IVC agenesis, venous system drainage is usually provided the suprarenal cava, superior vena cava, portal vein, and subclavian veins through the gonadal venous system, paravertebral venous plexus, hemorrhoidal plexus, and the superficial pathway (2). Symptoms may vary according to the localization of these networks (9,10).

Recognition of IVC anomalies is important as they may cause complications related to accompanying anomalies

and possible complications during interventional procedures (7). This anomaly may cause retroperitoneal hemorrhage secondary to large venous aneurysms (10). Occasionally, however, this anomaly is incidentally recognized during abdominal surgery or retroperitoneal surgeries (6) and may affect the method or outcome of surgery by causing technical difficulties (6,11). It can cause major hemorrhages due to vascular injury during the surgical procedure (6,11). In addition, abnormally developing veins in the thoracic area may be mimicked for aortic dissection, lymphadenopathy, and mediastinal tumors and by mistake a percutaneous biopsy may be performed (12). In our case, no preoperative diagnosis was provided. This anomaly was diagnosed via triphasic CT angiography in the venous phase in the postoperative period, due to the suspicion of dense venous collateral formations observed during surgery. In our case, although the surgical procedure was started laparoscopically, it was converted to open surgery due to bleeding. Thus, major bleeding that could be life-threatening was avoided. In such cases, even if it was not diagnosed before the operation, it is essential to manage the process carefully during the operation to avoid an injury that could cause excessive bleeding.

In the literature, transjugular insertion of IVC filter caused difficulties during the process due to IVC anomaly (13). It should be kept in mind that IVC anomalies may cause various complications during the invasive procedure for the treatment of deep venous thrombosis (DVT) and may have predisposing effects for DVT (14,15). In addition, an undiagnosed IVC agenesis can be detected incidentally during IVC cannulation in a patient undergoing open heart surgery and may result in vascular injury (5). Therefore, it is important to diagnose this condition before the cardiopulmonary bypass, which is vital, and before other cardiothoracic procedures (4,5).

Pelvic congestion syndrome is a chronic pelvic pain event caused by increased congestion in the pelvic area due to impaired venous drainage as a result of insufficiency of the pelvic veins (3). A rare cause of this syndrome is IVC agenesis (3,16). IVC agenesis should be considered in patients presenting with pelvic pain. In addition, IVC agenesis can present with venous stasis in the lower limbs and may cause deep vein thrombosis due to increased venous pressure in the lower extremity veins (7,17). IVC anomalies are most commonly presented with DVT in the lower extremities. Congenital IVC anomalies are detected in 5% of patients with lower limb DVT below 30 years of age (17). Especially, in young patients, this anomaly should be taken into consideration during the investigation of the etiology of DVT (18). Although these patients can often present with lower extremity proximal DVT, the risk of pulmonary embolism is very low as the thrombus is difficult to reach the lungs through the extensive compensatory collateral circulation network (2). Besides all these, patients with IVC agenesis may present with symptoms such as paresthesia and neural deficits due to neural compression or obstructive pyelonephritis due to compression to surrounding tissues of highly dilated veins (2).

The CECT scanning and contrast-enhanced MRI in the venous phase provide information on the exact type of IVC anomaly and also describe the extent and compressive effect of deep venous thrombosis and hypertrophic varicose veins. The direct venography via femoral access is a widely used diagnostic test; however, it cannot describe the compressive effects of thrombosed and hypertrophic vessels (3). The treatment of these patients is evaluated individually. In addition to traditional venous insufficiency treatment in patients with signs of venous stasis, anticoagulation therapy can be performed in the treatment to prevent DVT (7, 8). Also, thrombectomy can be performed with invasive procedures in cases with acute DVT. There are cases undergoing endovascular reconstruction and prosthetic graft interposition for interrupted IVC anomaly (19,20).

CONCLUSION

IVC agenesis is a rare entity and clinical suspicion is important in the diagnosis of the disease. Triphasic CT angiography, contrast-enhanced MRI, and direct venography are useful for definitive diagnosis. Besides the use of anticoagulants in the treatment, surgical or endovascular interventions may come into prominence according to the patient's symptoms. The preoperative screening of vascular anomalies and considering IVC anomalies are important to be successful in planned operations and to prevent possible injuries and excessive bleeding. Pre-surgical screening for IVC anomalies can assist in planning safe abdominal and cardiovascular surgery as well as interventional or diagnostic procedures such as IVC filter placement.

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REFERENCES

1. Eldefrawy A, Arianayagam M, Kanagarajah P, Acosta K, Manoharan M. Anomalies of the inferior vena cava and renal veins and implications for renal surgery. Cent European J Urol 2011;64(1):4-8. https://doi.org/10.5173/ceju.2011.01.art1
2. Yugueros X, Alvarez B, Fernández E, Boqué M, Matas M. Compressive symptoms due to thrombosed or hypertrophic collateral circulation in infrarenal Inferior Vena Cava Agenesis. Ann Vasc Surg 2013;27:238.e9-238.e13. https://doi.org/10.1016/j.avsg.2012.06.014.
3. Singh SN, Bhatt, TC. Inferior Vena Cava Agenesis: A Rare Cause of Pelvic Congestion Syndrome. J Clin Diagn Res 2017;11(3):6-8. https://doi.org/10.7860/JCDR/2017/24123.9554
4. González J, Gaynor JJ, Albéniz LF, Ciancio G. Inferior Vena Cava System Anomalies: Surgical Implications. Curr Urol Rep 2017;18(2):10. https://doi.org/10.1007/s11934-017-0658-y.
5. Mazzucco A, Bortolotti U, Stellin G, Gallucci V. Anomalies of the systemic venous return: a review. J Card Surg 1990;5(2):122-33. https://doi.org/10.1111/j.1540-8191.1990.tb00749.x.
6. Truty MJ, Bower TC. Congenital anomalies of the inferior vena cava and left renal vein: implications during open abdominal aortic aneurysm reconstruction. Ann Vasc Surg 2007;21(2):186-97. https://doi.org/10.1016/j.avsg.2006.10.014.
7. Hamoud S, Nitecky S, Engel A, Goldsher D, Hayek T. Hypoplasia of the inferior vena cava with azygous continuation presenting as recurrent leg deep vein thrombosis. Am J Med Sci 2000;319(6):414-6. https://doi.org/10.1097/00000441-200006000-00013.
8. Lawless RA, Dangleben DA. Caval agenesis with a hypoplastic left kidney in a patient with trauma on warfarin for deep vein thrombosis. Vasc Endovascular Surg 2012;46(1):75-6. https://doi.org/10.1177/1538574411425107.
9. Dudeck O, Zeile M, Poellinger A, Kluhs L, Ludwig WD, Hamm B. Epidural venous enlargements presenting with intractable lower back pain and sciatica in a patient with absence of the infrarenal inferior vena cava and bilateral deep venous thrombosis. Spine 2007;32(23):688-91. https://doi.org/10.1097/BRS.0b013e318158cf94.
10. Balze KM, Pillny M, Luther B, Grabitz K, Sandmann W. Spontaneous rupture of collateral venous aneurysm in a patient with agenesis of the inferior vena cava: a case report. J Vasc Surg 2002;36(5):1053-7. https://doi.org/10.1067/mva.2002.128939.
11. Jimenez Gil R, Morant Gimeno F. Major venous anomalies and abdominal aortic surgery. Interact Cardiovasc Thorac Surg 2010;10(4):631-633. https://doi.org/10.1510/icvts.2009.225565.
12. Nishie A, Barloon T, Schreiber A. Preaortic interazygous vein; mimicker of other pathologies. Clin Imaging 2009;33(2):144-5. https://doi.org/10.1016/j.clinimag.2008.11.002.
13. Savader SJ, Ronsivalle JA. Permanent inferior vena cava filters. In: Savader SJ, editor. Venous interventional radiology with clinical perspectives. 2nd ed. New York: Thieme; 2000. p. 511e27.
14. Sontakke YA, Gladwin V, Chand P. Anatomic Variant of Liver, Gall Bladder and Inferior Vena Cava. J Clin Diagn Res 2016;10(7):AD03-5. https://doi.org/10.7860/JCDR/2016/20059.8174
15. Tuncer ON, Onk OA, Karahan Ü, Erkut B. Deep Venous Thrombosis in a Patient with Inferior Vena Cava Agenesi. JAREM 2017; 7: 102-4
16. Menezes T, Haider EA, Al-Douri F, El-Khodary M, Al-Salmia I. Pelvic congestion syndrome due to agenesis of the infrarenal inferior vena cava. Radiol Case Rep 2019;14(1):36-40. https://doi.org/10.1016/j.radcr.2018.04.004
17. Parsa P, Lane JS 3rd, Barleben AR, Owens EL, Bandyk D. Congenital agenesis of inferior vena cava: a rare cause of unprovoked deep venous thrombosis. Ann Vasc Surg 2015;29(5):1017.e15-8. https://doi.org/10.1016/j.avsg.2015.01.003.
18. Guanella R, Glauser F, Bounameaux H, Mazzolai L. Inferior vena cava agenesis: association with bilateral lower-limb deep vein thrombosis in young males. Thromb Haemost 2009;102(4):795-8. https://doi.org/10.1160/TH09-04-0254.
19. Thomas SD, Ofri A, Tang T, Englund R. Endovascular reconstruction of an interrupted inferior vena cava. Int J Surg Case Rep 2014;5(2):59-62. https://doi.org/10.1016/j.ijscr.2013.12.016.
20. Dougherty MJ, Calligaro KD, DeLaurentis DA. Congenitally absent inferior vena cava presenting in adulthood with venous stasis and ulceration: A surgically treated case. J Vasc Surg 1996;23(1):141-6. https://doi.org/10.1016/s0741-5214(05)80044-8.

CASE REPORT

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A rare malignity observed in the appearance of angiomyolipoma; tubulocystic renal cell carcinoma after partial nephrectomy

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Abstract

Cystic neoplasms of the kidney are quite rare. Because they contain various differential diagnoses and their radiological features are not specific, their diagnosis is very difficult except for histopathological data. Usually, they can be confused radiologically with benign cysts of the kidney or angiomyolipoma. Radical or partial nephrectomy is the most commonly preferred curative treatment method when it shows features like rapidly growing or malignancy. Histopathological examination is required for definitive diagnosis. In this article, we aimed to present a rare case of tubulocystic renal cell carcinoma after partial nephrectomy in our clinic, who was followed up in another center for years with the pre-diagnosis of angiomyolipoma, in the light of the literature.

Keywords: Renal Cell Carcinoma, Angiomyolipoma, Tubulocystic Renal Cell Carcinoma

INTRODUCTION

Cystic neoplasms of the kidney, which comprise diagnostic challenges as they include various differential diagnoses and lack of specific radiological features, that represent approximately 10% of renal cell carcinomas (RCC), are rare (1). These neoplasms are followed up until their size increases since they are usually reported as benign cysts or angiomyolipomas in radiological imaging techniques such as tomography and ultrasonography. Radical or partial nephrectomy is usually a preferred surgical treatment method when these neoplasms become symptomatic that generally emerge with a flank pain or a palpable mass in the abdomen. In this article, we aimed to present a case whose histopathology was reported as tubulocystic renal cell carcinoma after partial nephrectomy performed in our clinic due to the enlargement and pain of the mass over time, followed up for years with the diagnosis of angiomyolipoma in another center.

CASE

A 53-year-old male patient first applied to an external center in 2011 due to left flank pain. Urinary system ultrasonography (USG) showed a 25×20 mm renal mass compatible with angiomyolipoma in the lower pole of the left kidney. Upon the finding, a contrast enhanced computed tomography (CT) of the abdomen was performed and the mass was interpreted as a 25×20 mm simple cortical cyst in the lower pole of the left kidney. The patient was followed up every 6 months with the diagnosis of angiomyolipoma with increased fat density. In these follow-ups, the mass had limited growth up to 35×40 mm in size. The patient applied to our clinic in 2019 with the complaint of progressive left flank pain. We performed an USG

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which indicated an exophytic 40×42 mm angiomyolipoma-compatible cystic mass in the lower pole of the left kidney. Dynamic contrast-enhanced CT was performed because the cystic mass had reached twice the size of the first measures during follow-up, and an endophytic, interpolar that located in the lower pole, Bosniak type III renal cyst was noticed in the abovementioned kidney (Figure 1). Due to the clinical condition of the patient and the high risk of malignancy of the cystic mass, this situation was explained to the patient in detail and open partial nephrectomy was planned for the patient.

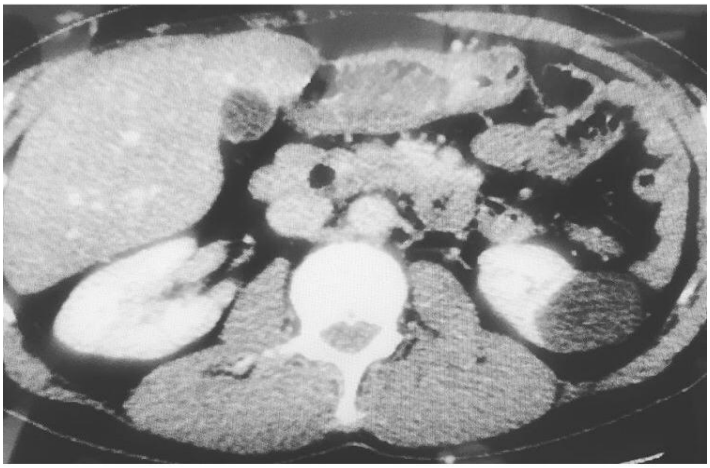

Figure 1. Pre-operative contrast-enhanced CT image of the patient (indicated by the arrow)

Pathological Diagnosis and Histochemistry

The patient underwent open left partial nephrectomy. Partial nephrectomy material examining histopathologically; 4×4×4.5 cm in size, with a macroscopically observable parenchymal surgical margin (Figure 2). Clustered smooth-walled cysts accompanied by few smooth areas recognised during analysis macroscopically. In the course of histological examination, the tumoral tissue demonstrated enlarged tubules occured with limited proliferation and cystic formation. Each cysts contained papillary structures and crusty, flat, cubic shaped cells covered the tubules and wall of the cysts as a single layer partition. In the incision made, at a distance of 0.2 cm closest to the surgical margin, nodular lesions with a thin fibrous capsular appearance, 4.6×4×4 cm in size, gray-white cross-sectional surface, and numerous cystic areas, the largest of which was 0.6 cm in diameter, were observed. It was noticed that the cysts were often single layered, sometimes multi-layered, appearing with eosinophilic cytoplasm in fluctuative amounts. and lined with a cuboidal, squamous or hobnail-like single-layered epithelium (Figure 3). An immunohistochemical analysis was obtained to affirm the diagnosis. Tumor cells were found to be CK7 and HMWCK focal positive, while AMACR and Vimentin were diffusely positive. Although there was no loss of fumarate hydratase in the tissues, S100 and CD117 were typically negative and CD10 positive. However, mutational and molecular genetic parameters could not be studied due to the lack of necessary kits in our pathology department at that time. Based on these histopathological findings, the mass resected from the lower pole of the left kidney was diagnosed as "Tubulocystic Renal Cell Carcinoma". The patient has been followed for two years without any evidence of local recurrence or distant metastasis.

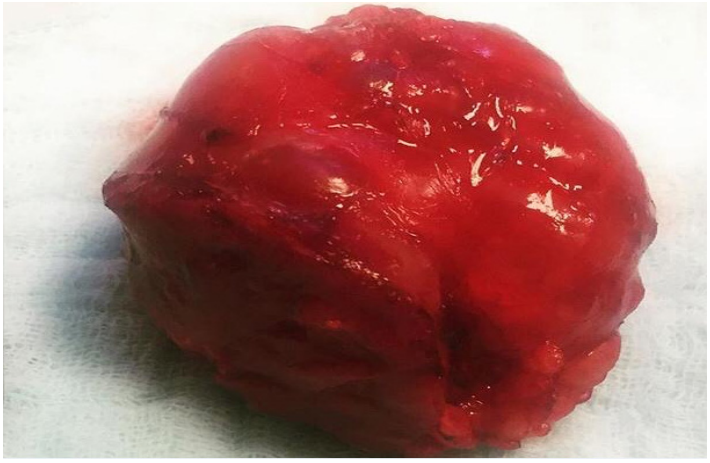

Figure 2. Partial nephrectomy material, macroscopic view.

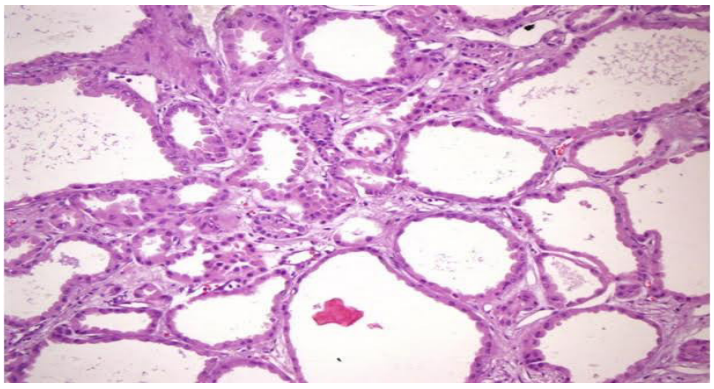

Figure 3. Tubulocystic renal cell carcinoma microscopic image (40x).

DISCUSSION

TC-RCC is defined as an uncommon kidney cancer with a tendency to behave less aggressively when compared to other urologic malignancies. Although most of these tumors enlarge slowly, they rarely progress, recur or metastasize. In clinical practice, frequently, with a male predominance (male:female ratio 7:1) and almost 60% of occurrence in the left kidney, these tumors reported more or less by the fifth or sixth decade of individuals presence (2). Although infrequent, important clinical findings such as abdominal pain, abdominal distension and hematuria might be encountered, patients are usually asymptomatic (3,4). The sizes of TC-RCCs are generally

small at the time of presentation, and approximately 40% of reported cases are less than 2 cm (5). However, patients with larger tumors or metastatic masses might experience complaints of abdominal pain, abdominal feel of distention come along with hematuria (6). The differential diagnosis of TC-RCC is likely vary and mostly includes tumors such as multilocular cystic RCC, cystic nephroma, mixed epithelial and stromal tumors, cystic oncocytoma, angiomyolipoma, and cystic form of RCC (6,7). Our patient was also followed up with the diagnosis of angiomyolipoma for years and the mass showed slow growth over time and radiological findings in subsequent examinations was reported as compatible with Bosniak type III renal cyst. Bosniak category type III-IV renal cysts are lesions with progressive malignancy rates, and hence a surgical resection is usually recommended as the main treatment method (8). Likewise, the recommended curative treatment for TC-RCC is radical nephrectomy, and the surgical procedure can be performed with an open or laparoscopic approach. However, partial nephrectomy can be performed for small tumors located superficially or peripherally. In our case, the tumor was located in the lower pole with a suitable size and location for partial nephrectomy that we performed accordingly.

Renal Cystic neoplasms comprise a few types of entities, including those newly described. A proper analysis of immunohistochemical markers is a necessity to obtain an accurate diagnosis (5). Since the biological behavior of cystic neoplasms in newly diagnosed patients is still uncertain, these patients should be monitored closely and the results should be reported properly. Considering the mild but certain risk of metastasis, all cases diagnosed with TC-RCC should be precisely followed up (5). The CT findings of TC-RCC indicate a solid mass with a thickened septum shaped as multiloculated neoplasia considered as Bosniak type II, IIF, III, or IV cysts. Moreover, considering the Bosniak classification system, MRI is more advantageous to accurately determine and categorize the cystic mass (2,9).

Cystic genre of TC-RCC challenge clinicians to distinguish it from alternate cystic masses that are considered benign such as simple renal cyst, MDK (multicystic dysplastic kidney), renal abscess, and malignant tumors, including complex renal cyst, multilocular cystic RCC, adult cystic nephroma, even MEST (mixed epithelial and stromal tumor). Simple renal cysts, particularly in the form of a complex structure, carry some radiological features identical to thin, non-contrast-enhancing inner septa accompanied by wall calcifications and lack of wall nodules that complicate the differential diagnosis. MDK, on the other hand, is characterized by multiple cysts of assorted extent unbonded with each other covering the renal parenchyma and shows minimal or no contrast enhancement. Multilocular cystic RCC is composed of multiple cysts with clear cytoplasm and lined with septal epithelial cells of fibrous tissue.

TC-RCC is observed as a well confined tumor that is non-encapsulated on macroscopic pathological examination; It is white or gray in color, Swiss cheese-like or wrapped balloon-like aspect due to spongy cysts of dissimilar extents. In Histological examination, it contains cysts of various sizes as well as tubules coated by a sole layer of hobnail, cubic cells. In some cases, it also includes cylindrical and columnar neoplastic cells specifically with eosinophilic cytoplasm. Evident nucleoli appear with a round nuclei (2). In Immunohistochemical scanning, protein expression can be demonstrated by neoplastic cells in both proximal tubules (CD10, P504S and CA-IX) and distal tubules and collecting ducts (CK7, CK19, keratin 903 and parvalbumin) in a weak and focal staining pattern of CK7. In the immunohistochemical examination of our case, the tumor cells were CK7 and HMWCK focal positive, while AMACR and Vimentin were diffusely positive. TC-RCC, previously called “Bellinian epithelioma” particularly. Besides, owing features of proximal and distal nephron differentiation and because of its morphological similarity, it was also named as “low-grade collecting ductal carcinoma”. Consequently, TC-RCC and collecting duct carcinoma, having evident histopathological diagnosis, are distinct from other neoplasms in regard to gene expression, clinical results and in the basis of immunohistochemistry.

Recent studies reveal similarities between TC-RCC and type 2 papillary RCC regarding morphological and immunohistochemically (10). Besides, both neoplasms can occasionally be encountered in the very identical lesion. Papillary form of RCC is considered to have a more aggressive course. Hence the association between papillary RCC and TC-RCC, radical nephrectomy is mainly suggested treatment method. Partial nephrectomy could be considered as an alternative option for suitable tumors. In our case, we also performed a partial nephrectomy because of the small size mass that is located in the lower pole of the polar pole.

Although a few case reports showed an inadequate response to Sunitinib (tyrosine kinase inhibitor) and Everolimus (mTOR inhibitor), Targeted therapy in Metastatic TC-RCC have not been reliably documented yet (2,11). In addition, liver and bone metastases were defined in a TC-RCC case presented by Salvatori et al., and Pazopanib and Nivolumab were administered for treatment (12). In our case, we did not consider counseling oncology, as no evidence of recurrence or metastasis was observed in the patient, whom we followed up regularly for about two years after surgery.

The biological behavior of these tumors is still not well known. Most of the tumors represent variable behavior, besides metastases to lymph nodes, liver, bone and brain have been described as well as local recurrences (13,14). Our patient was followed up for years considering it as a simple renal cyst with a benign course, afterwards surgery was required due to emerging growth in size and pain. No findings of recurrence or metastasis were detected for two-year follow-up after treatment. Some small masses reported as cysts or angiolipomas on radiological imaging should be followed closely and treated when these masses grow rapidly. TC-RCC, which can be seen rarely, should also be considered in the differential diagnosis.

CONCLUSION

TC-RCCs are tumors that predominate in males and, when examined in experienced centers, comprise remarkable distinctive features like bubble wrap aspect in macroscopy, and cysts detached by a thin fibrotic stroma that is covered by hobnail cells in microscopic appearance. However, TC-RCCs represent as cystic renal masses like Bosniak type II-IV cysts and are difficult to distinguish from other renal cystic tumors by using conventional imaging methods. Such renal cysts should undergo particular ultrasonographic examination, and lesions with these imaging features should be highlighted and noted by the radiologist to encourage earlier intervention. In order to determine the prognosis, select the appropriate treatment, and better understand the biology of these rare tumors, we believe that larger series of cases with long-term follow-up are necessary.

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REFERENCES

1. Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. ISUP renal tumor panel: The international society of urological pathology (ISUP) Vancouver classification of renal neoplasia. Am J Surg Pathol. 2013;37:1469–89. https://doi.org/10.1097/PAS.0b013e318299f2d1

2. Honda Y, Nakamura Y, Goto K, Terada H, Sentani K, Yasui W, et al. Tubulocystic renal cell carcinoma: a review of literature focused on radiological findings for differential diagnosis. Abdom Radiol 2018; 43: 1540–1545. https://doi.org/10.1007/s00261-018-1643-8

3. Amin MB, MacLennan GT, Gupta R, Grignon D, Paraf F, Vieillefond A, et al. Tubulocystic carcinoma of the kidney: Clinicopathological analysis of 31 cases of a distinctive rare subtype of renal cell carcinoma. Am J Surg Pathol. 2009;33:384–92. https://doi.org/10.1097/PAS.0b013e3181872d3f

4. Zhou M, Yang XJ, Lopez JI, Shah RB, Hes O, Shen SS, et al. Renal tubulocystic carcinoma is closely related to papillary renal cell carcinoma: Implications for pathologic classification. Am J Surg Pathol. 2009;33:1840–9. https://doi.org/10.1097/PAS.0b013e3181be22d1

5. Kakkar A, Sharma MC, Uppal M, Chumber S. Tubulocystic renal cell carcinoma: Report of a rare case. Can Urol Assoc J. 2015;9(9-10):E654-E657. https://doi.org/10.5489/cuaj.2935

6. Srigley JR, Delahunt B. Uncommon and recently described renal carcinomas. Mod Pathol. 2009;22:S2–S23. https://doi.org/10.1038/modpathol.2009.70

7. Kuroda N, Matsumoto H, Ohe C, Mikami S, Nagashima Y, Inoue

K, et al. Review of tubulocystic carcinoma of the kidney with focus on clinical and pathobiological aspects. Pol J Pathol. 2013 Dec;64(4):233-7. https://doi.org/10.5114/pjp.2013.39329

8. Nouhaud FX, Bernhard JC, Bigot P, Khene ZE, Audenet F, Lang H, et al. Contemporary assessment of the correlation between Bosniak classification and histological characteristics of surgically removed atypical renal cysts (UroCCR-12 study). World J Urol. 2018 Oct;36(10):1643-1649. https://doi.org/10.1007/s00345-018-2307-6

9. Narayanasamy S, Krishna S, Prasad Shanbhogue AK, Flood TA, Sadoughi N, Sathiadoss P, et al. Contemporary update on imaging of cystic renal masses with histopathological correlation and emphasis on patient management. Clin Radiol. 2019 Feb;74(2):83-94. https://doi.org/10.1016/j.crad.2018.09.003

10. Zhao M, Teng X, Ru G, Zhao Z, Hu Q, Han L, et al. Tubulocystic renal cell carcinoma with poorly differentiated foci is indicative of aggressive behavior: clinicopathologic study of two cases and review of the literature. Int J Clin Exp Pathol. 2015;8(9):11124-11131. Published 2015 Sep 1.

11. Bhullar JS, Bindroo S, Varshney N, Mittal V. A new type of renal cancer—tubulocystic carcinoma of the kidney: a review of the literature. Int J Surg Pathol 2014; 22(4): 297–302. https://doi.org/10.15586/jkcvhl.2014.13

12. Salvatori F, Macchini M, Misericordia M, Paci E, Giovagnoni A, Candelari R. A simple cyst is not always simply a cyst: A case of cystic recurrence after nephrectomy for tubulocystic renal cell carcinoma and literature review. Urologia Journal. 2020;87(3):119-124. https://doi.org/10.1177/0391560319870091

13. Sangle NA, Mao R, Shetty S, Schiffman JD, Dechet C, Layfield L, et al. Novel molecular aberrations and pathologic findings in a tubulocystic variant of renal cell carcinoma. Indian J Pathol Microbiol. 2013;56:428–33

14. Iakovleva G, Iakovlev V, Ordon M, Srigley J, Yousef GM. Tubulocystic carcinoma of kidney: a challenging diagnostic entity mimicking multicystic kidney and presenting with bone metastasis. Histopathology. 2015 May;66(6):892-894. https://doi.org/10.1111/his.12502

CASE REPORT

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Modified Konno Procedure for left ventricular outflow tract obstruction: report of two cases

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Abstract

Left ventricular outflow tract obstruction with a systolic anterior motion of the mitral valve is a challenging pathology. An intervention, either surgically or with a percutaneous technique is taken into consideration when the pressure gradient reaches critical levels. Subaortic myectomy is still the gold standard treatment modality in these particular patients. Modified Konno procedure may be added to the procedure when a significant gradient persists following subaortic resection, because of its association with increased outflow tract obstruction relief.

We herein present our experiences with two cases that underwent modified Konno procedures for the treatment of hypertrophic obstructive cardiomyopathy.

Keywords: Left Ventricular Outflow Tract Obstruction, Hypertrophic Obstructive Cardiomyopathy, Surgical Treatment, Modified Konno Procedure

INTRODUCTION

Left ventricular outflow tract (LVOT) obstructions that occur at the subvalvular level are divided into two groups. The first group consists of congenital discrete subvalvular aortic stenosis. This particular obstruction is localized by fibrosis, or a fibromuscular membrane, and may involve the entire subvalvular region in the form of a fibromuscular tunnel. The second group presents as hypertrophic obstructive cardiomyopathy consisting of a dynamic obstruction at the subvalvular level. Gold standard treatment option for both groups is still surgical muscular resection although percutaneous ablation methods are also attempted in selected cases. Unfortunately, the pathology is associated with increased incidence of recurrence and/or incomplete resection revealing significant persisting left ventricular outflow tract gradient (1).

The modified Konno procedure is an alternative option which may be added to the surgical subaortic muscle resection to provide better outflow. It is indicated in patients with diffuse subaortic stenosis consisting of a normal aortic orifice in patients with severe forms of hypertrophic obstructive cardiomyopathy and children with tunnel subaortic stenosis (2). Although

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the procedure is challenging and requires expertise, it allows adequate relief of diffuse subaortic obstruction, significantly decreases pressure gradient.

In this manuscript, we present our experiences with modified Konno procedure on two cases to treat hypertrophic obstructive cardiomyopathy.

Patient I

A 7-year-old male patient with chest pain, exertional dyspnea, and fatigue had been referred to our institution. In his history, there surgical treatment for subaortic stenosis at the age of 2.

The patient weighed 28,4 kg and was 142 cm tall with a heart rate of 84 beats per minute. Body surface area was calculated as 1.24 m^2. On physical examination, S1-S2 were rhythmic, 4-5/6 systolic murmur at the mesocardiac focus was heard, femoral arterial pulse was symmetrically palpable, respiratory sounds were normal and a sternotomy incision mark was present from previous procedures. Blood pressure of the patient was 102/54 mmHg. The electrocardiogram showed an increase in voltage in the chest leads, along with non-specific abnormalities in the ST segment and T-waves. Additionally, deep, narrow Q waves were observed in the lateral leads I, aVL, V5-6. The cardiothoracic index was increased on plain chest X-ray. Echocardiography indicated left ventricular outflow tract obstruction due to interventricular septal hypertrophy and systolic anterior motion of the mitral valve with an asymmetric septal hypertrophy of 29 mm and there was a pressure gradient of 100 mmHg. The aortic valve was tricuspid and there was no stenosis. The patient was scheduled for a surgical treatment following the consent of family after being informed about the risks and benefits in details.

Patient II

An 18-year-old female patient with the diagnosis of idiopathic hypertrophic obstructive cardiomyopathy was referred to our institution. Her history revealed septal myectomy and intracardiac defibrillator implantation 3 years ago. She complained of chest pain, exertional dyspnea, and fatigue.

The patient weighed 79.2 kg and was 165 cm tall with a heart rate of 68 beats per minute. Body surface area was calculated as 1.91 m2. On physical examination, S1-S2 were rhythmic, 3-4/6 systolic murmur at the mesocardiac focus was heard, femoral arteries were symmetrically palpable, respiratory sounds were normal, an implantable cardioverter-defibrillator pocket was present on the left pectoral area, and a sternotomy incision mark was present from the previous procedure. Blood pressure of the patient was 120/70 mmHg. Electrocardiography indicated a normal sinus rhythm, left bundle branch block with a QRS of 170 msn. The cardiothoracic index was increased on plain chest X-ray. Echocardiography indicated LVOT obstruction due to interventricular septal hypertrophy of 3.5 cm, moderate mitral valve insufficiency, a mild tricuspid insufficiency, and the outline of an implantable cardioverted-defibrillator lead. The aortic valve was tricuspid and there was no stenosis. A Valsalva manoeuvre provoked pressure gradient of 75 mmHg was detected. The patient with IHSS who an operative candidate was severely symptomatic was not significantly improved by optimal nonoperative treatment. Thus, the patient was operated after being informed about the risks and benefits of the procedure and following her consent.

Surgical Technique

The operations began with a redo midline sternotomy. The Aorta, both cavae, pulmonary artery, right ventricular outflow tract was prepared. Extracorporeal circulation was initiated after aortic and bicaval cannulation. Cardiac arrest was achieved at 32°C with infusion of antegrade hypothermic cold blood cardioplegia. Left ventricular outflow tract was inspected through aortotomy. The hypertrophied bands were resected. The septum was very hypertrophic and we thought the resections have not been sufficient. A transverse right infundibulotomy was also made long the right ventricular outflow tract (Figure 1). Further myectomy was performed. The septum was severely hypertrophied till the apex. A ventricular septal defect was created with linear incision till the level of the papillary muscles (Figure 2). The ventricular septal defect was closed with an oval shaped PTFE patch (Modified Konno), (Figure 3). The infundibulotomy was repaired with another piece of PTFE patch (Figure 4).

Intraoperative SAM evaluation was performed with TEE and temporary pacemaker was implanted in both patients. Operations were finalized uneventfully. Cardiopulmonary bypass and cross clamp times were 84 minutes and 62 minutes, respectively in the first patient and corresponding values were 95 minutes and 76 minutes, respectively in the second patient. Postoperative transaortic gradients were maximum of 25mmHg in the first patient and insignificant (none) in the case. Trivial to mild degree of mitral insufficiency was detected in patients after the operation. Both patients were transferred to the intensive care unit, weaned off ventilator in 6 hours, taken to the ward the next day and discharged from the hospital in 6 days. They have been followed asymptomatic for more than 6 months. The first patient was scheduled for and implantable cardiac defibrillator.

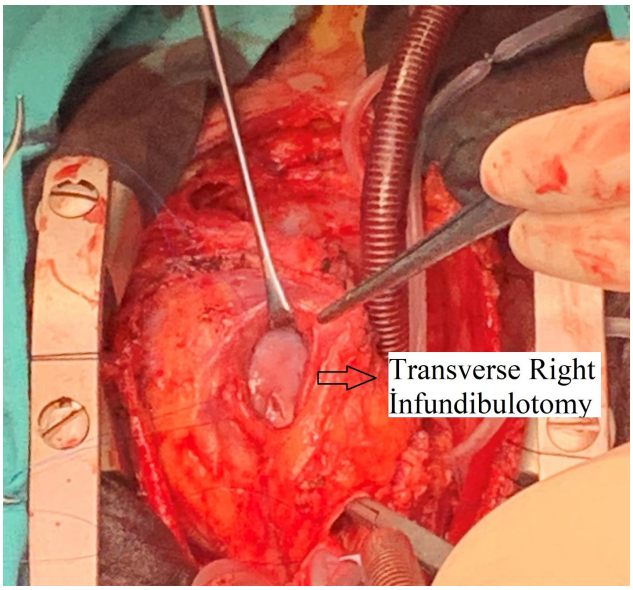

Figure 1: Transverse right infundibulotomy

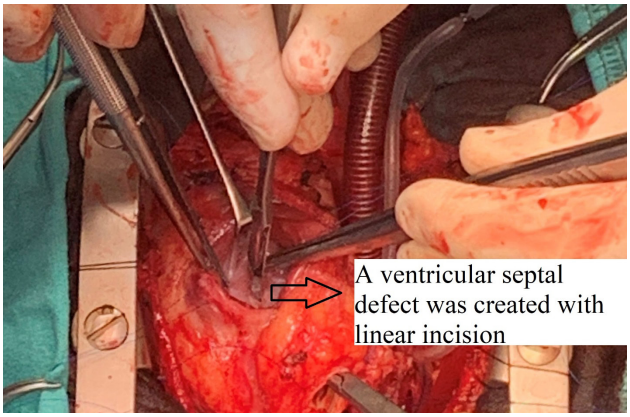

Figure 2: A ventricular septal defect was created with linear incision

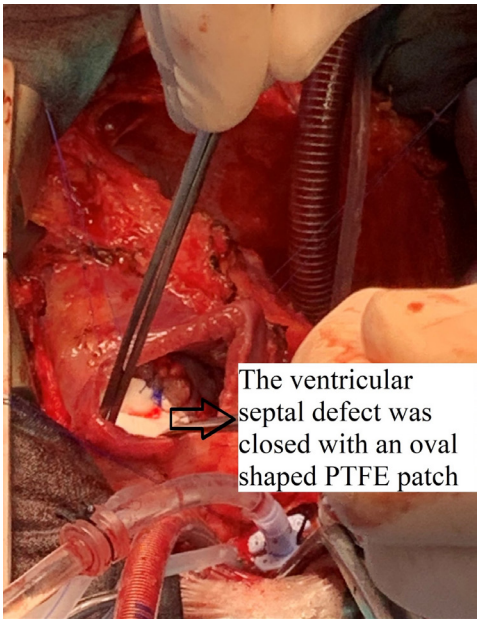

Figure 3: The ventricular septal defect was closed with an oval shaped PTFE patch

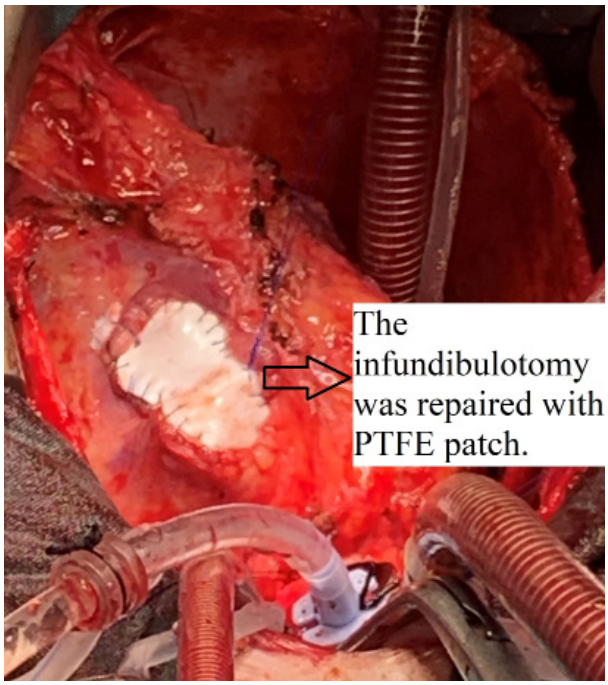

Figure 4: The infundibulotomy was repaired with PTFE patch

DISCUSSION

Idiopathic hypertrophic subaortic stenosis is an intense ventricular hypertrophy which is characterized with myocardial fibrous tissue disorders concentrated in the ventricular septum leading to dynamic obstruction in the subaortic region (3). Left ventricular outflow tract obstruction in this pathology is related with both systolic anterior motion of the anterior leaflet of the mitral valve and the hypertrophied interventricular septum.

Left ventricular outflow tract obstruction leads to acute decline of cardiac output, elevated left ventricular filling pressures, and myocardial ischemia, which can present with symptoms of chest pain, exertional dyspnea, presyncope, and syncope (4). Approximately one-third of patients with hypertrophic obstructive cardiomyopathy have left ventricular outflow tract obstruction at rest which is defined when gradients ≥30 mmHg. Another one third may present without outflow obstruction at rest; however, become symptomatic when provoked with physiologic and pharmacologic interventions that decrease left ventricular end-diastolic volume or increase left ventricular contractility such as during Valsalva maneuver or on exertion (<30 mmHg at rest and ≥30 mmHg at stress conditions). This is also known as latent left ventricular outflow tract obstruction. The third group of patients possess nonobstructive form of hypertrophic obstructive cardiomyopathy having gradients <30 mmHg at rest and stress. Marked gradients of ≥50 mmHg, either at rest or with stress represent the conventional threshold for surgical or percutaneous intervention if symptoms cannot be

controlled with medical measures (5). The treatment method of LVOT due to hypertrophic cardiomyopathy is achieved mainly through subaortic myectomy. When significant LVOT pressure gradient cannot be obtained with simple septal muscular resection, the modified Konno procedure (subaortic ventriculoplasty) which was first described by Cooley and Garrett in1986, provides excellent LVOT obstruction relief. This complex procedure is conducted to relieve tunnel or complex subaortic stenosis while preserving the aortic valve. With this technique, an extensive subaortic interventricular septum resection is performed, creating an artificial ventricular septal defect. The ventricular septal incision during modified Konno procedure should reach level of the papillary muscle level to overcome the other component of LVOT obstruction, the systolic anterior motion of the mitral valve. The artificially created ventricular septal defect is usually closed with a patch which can simply bulge away from the subaortic area, creating a spacious environment and allowing smooth flow from the left ventricle outflow tract. On the other hand, one of the disadvantages of the ventricular septal defect patch is right ventricular outflow tract (RVOT) obstruction. Hence, RVOT incision also requires special care during closure.

The modified Konno procedure is designed to address aortic and subaortic issues while minimizing the potential for aortic valve problems. Creation of an artificial ventricular septal defect poses certain risks such as injury to the mitral and the aortic valve as well as the conduction system. Therefore, the area of safe resection becomes limited. Aortotomy and right infundibulotomy is performed during the procedure to carefully inspect and consider the septum before resection. Resection of the septum adjacent to the aortic valve annulus is performed (6).

Cooley performed a simple resection and myectomy in a patient with subaortic stenosis; however, due to the recurrence of the case, decision to conduct the method known today as the modified Konno procedure was executed. However, he believed that following a ventriculotomy, a change in the morphology of the ventricle would lead to a RVOT obstruction, therefore placed another patch to reconstruct the RVOT (7). In our cases we performed the same procedure as Cooley, postoperative measurement of pressures indicated no signs of an obstruction, the operation was a success.

One other risk of modified Konno procedure is conduction disturbances related with septal myocardial resection and ventricular septal defect creation. The conduction tissue is generally located at the right side of the commissure between right and left aortic leaflets. The region of the conduction tissue is identified, located to the right of a line between the nadir of the right coronary aortic cusp and the septal attachments of the septal leaflet of the tricuspid valve. Resection at this level requires good cardiac anatomy knowledge, experience, and meticulous care (8). We did not experience conduction disturbances in our patients. However, we were more aggressive with resection in the second case whom already had an implantable cardioverter-defibrillator implanted and surgery resulted with nearly no LVOT gradient.

In IHSS, along with previously mentioned mechanisms, functional mitral insufficiency may also be seen. Whether it be an aortoventriculoplasty or a modified Konno procedure, since the left ventricular pressure decreases and the systolic anterior motion is resolved following a surgical treatment modality , functional mitral regurgitation becomes minimal or in some cases completely resolves (9). As mentioned, both of our patients who had mitral insufficiency prior to surgery, indicated no sign of mitral insufficiency following surgical treatment Whether it be an aortoventriculoplasty or a modified Konno procedure, since the left ventricular pressure decreases and the systolic anterior motion is resolved following a surgical treatment modality by intraoperative TEE. On the other hand, despite aggressive LVOT reconstruction with septal myectomy and modified Konno septal enhancement, mitral insufficiency and SAM may still persist. In such an occasion, mitral valve replacement may be an option. Another method may be simple edge to edge type repair of mitral valve which secures the anterior leaflet and prevents its systolic anterior subaortic displacement as well as subaortic obstruction (10).

In 1983, Vouhe and his colleagues, performed a similar surgery to that of a modified Konno procedure. To eliminate left ventricular outflow tract obstructions (especially IHSS and tunnel stenosis types), they performed a procedure they called the aortoseptal approach. In this method, a septal incision is made in the commissure between the aortic anulus and the right and left coronary cusps. The diffuse stenotic segment is resected, and the septum and opening of the aortic annulus is repaired. In addition, since the septum is primarily sutured without using a patch, the possibility of recurrence remains high (11). Hence, comparably, the modified Konno procedure seems more advantageous. Also, dual chamber pacing does remain a useful therapy for patients at very high risk for surgical or transcatheter therapy, or in whom these options are not available.

Following an idiopathic hypertrophic subaortic stenosis treatment with the modified Konno procedure, due to increased risk of arrhythmias and malignant fibrillation in such patients, the İmplantation of a cardioverted defibrillator is performed to prevent such complications. After postoperative rhythm evaluation, ICD insertion can be planned. One of our patients had an implanted cardioverter-defibrillator in place, however the other patient didn't, so we planned a placement of an implanted cardioverter-defibrillator.

In conclusion, the aim of treatment of hypertrophic

obstructive cardiomyopathy is to relieve subaortic occlusion. The most simple subaortic muscular resection may be associated with insignificant outflow tract relief and recurrence. In such cases modified Konno procedure seems a reliable alternative; however, technique is challenging and requires expertise and knowledge.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: EO, GS, MTB, OK, YY,MU, HT Design: EO,OK Supervising: MU,HT Financing and equipment: MU,HT, Data collection and entry: EO,GS,MTB,OK,YY,MU,HT Analysis and interpretation: EO,OK, Literature search: EO,OK, Writing: EÖ, Critical review: GS,MTB.

REFERENCES

1. Akçevin A, Sarıoğlu T, Süzer K, Polat B, Sarıoğlu A, Aytaç A. Subaortik stenozların cerrahi tedavisinde yeni bir yöntem: Modifiye Konno ameliyatı. Türk Göğüs Kalp Damar Cer Derg. 1991;1:63-7.
2. Metton O, Ali WB, Raisky O, Vouhe PR. Modified Konno operation for diffuse subaortic stenosis. Multimedia Manual of Cardio Thoracic Surgery. 2008 Jan 1.https://doi.org/10.1510/mmcts.2008.003426.
3. Henry WL, clark CE, epstein SE. Asymmetric septal hypertrophy: echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. Circulation. 1973 Feb;47(2):225-33. https://doi.org/10.1161/01.cir.47.2.225
4. Norrish, Gabrielle, and Juan Pablo Kaski. "Congenital heart disease: An ageing problem." British Journal of Cardiology 25.2 (2018): 46-47. https://doi.org/10.5837/bjc.2018.015
5. Mitevksa IP. Focus on echocardiography in hypertrophic cardiomyopathy-fourth in series. Article eJ ESC Council Cardiol Practice. 2015;13:20-14.
6. Bichell DP. Modified Konno procedure for left ventricular outflow tract obstruction. Operative Techniques in Thoracic and Cardiovascular Surgery. 2011 Mar 1;16(1):62-9. https://doi.org/10.1053/j.optechstcvs.2010.09.001
7. Cooley DA, Garrett JR. Septoplasty for left ventricular outflow obstruction without aortic valve replacement: a new technique. The Annals of thoracic surgery. 1986 Oct 1;42(4):445-8. https://doi.org/10.1016/s0003-4975(10)60556-5
8. Kouchoukos NT, Blackstone EH, Hanley FL, Kirklin JK. Kirklin/Barratt-Boyes Cardiac Surgery E-Book. Elsevier Health Sciences; 2012 Sep 27.
9. Rastan H, Koncz J. Aortoventriculoplasty: a new technique for the treatment of left ventricular outflow tract obstruction. The Journal of thoracic and cardiovascular surgery. 1976 Jun 1;71(6):920-7.
10. Misbach GA, Turley K, Ullyot DJ, Ebert PA. Left ventricular outflow enlargement by the Konno procedure. The Journal of Thoracic and Cardiovascular Surgery. 1982 Nov 1;84(5):696-703.
11. Vouhè PR, Poulain H, Bloch G, Loisance DY, Gamain J, Lombaert M, Quiret JC, Lesbre JP, Bernasconi P, Pièrtri J, Cachera JP. Aortoseptal approach for optimal resection of diffuse subvalvular aortic stenosis. The Journal of Thoracic and Cardiovascular Surgery. 1984 Jun 1;87(6):887-93.

The corrected article of the MKU Medical Jorunal (Interdisciplinary Medical Journal) issue 2022;13(45) has been added.

ÖZGÜN ARAŞTIRMA / ORIGINAL RESEARCH

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MKÜ Tıp Dergisi 2022;13(45):1-5

COVID-19 pnömonisinde prokalsitonin düzeylerinin önemi

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Öz

COVID-19 pnömonisinde prokalsitonin düzeylerinin önemi

Amaç: Bu çalışmadaki amacımız, RT-PCR (Real-Time Polymerase Chain Reaction) pozitif COVID-19 pömonisinde prokalsitonin seviyelerinin nasıl etkilendiğini tespit etmektir. Bu parametrenin tanı ve tedavide klinik açıdan değerini araştırmak, konuyla ilgili yeni görüşler ileri sürebilmektir.
Yöntem: Çalışmamıza hastaneye başvuran 18 yaş üstü RT-PCR testi pozitif olup servise yatışı olan 100 COVİD-19 hasta dahil edildi. Hastaların verileri hastanenin sisteminden geriye dönük olarak toplandı. RT-PCR pozitif hastalar toraks BT (bilgisayarlı tomografi) pozitif ve BT negatif diye iki gruba ayrıldı ve bu iki grup arasında prokalsitonin değerleri araştırıldı. Elde elden sonuçlar SPSS 25 programında değerlendirildi.
Bulgular: RT-PCR testi pozitif olan 100 hastanın 42'sinde BT negatif, 58'inde BT pozitifti. BT pozitif hasta grubunda ölçülen prokalsitonin düzeyleri, BT negatif hasta grubuna göre yüksek olmasına rağmen istatiksel olarak anlamlı bulunmadı (0.113±0.154 ng/mL, 0.064±0.058 ng/mL, p=0.510).
Sonuç: Elde ettiğimiz sonuçlar prokalsitonin düzeyinin RT-PCR pozitif hastalarda COVID-19 pnömonisinin varlığını ayırt edemeyeceğini göstermektedir. Prokalsitonin düzeyindeki yükseklik hastalığın daha komplike bir hale geldiğini öngörebilir.
Anahtar Kelimeler: COVID-19, Pnömoni, Prokalsitonin

Abstract

The importance of procalcitonin levels in COVID-19 pneumonia

Objective: Our aim in this study is to determine how procalcitonin levels are affected in RT-PCR (Real-Time Polymerase Chain Reaction) positive COVID-19 pneumonia. To investigate the clinical value of this parameter in diagnosis and treatment and to propose new opinions on the subject.
Methods: One hundred COVID-19 patients admitted to the hospital with positive RT-PCR test and above the age of 18 were included in our study. The data of the patients were collected retrospectively from the hospital system. RT-PCR positive patients were divided into two groups as thoracic CT (computed tomography) positive and CT negative, and procalcitonin values were investigated between these two groups. The obtained results were evaluated in the SPSS 25 program.
Results: Of the 100 patients with positive RT-PCR tests, 42 patients were CT negative and 58 patients were CT positive. Although the procalcitonin levels measured in the CT positive patient group were higher than the CT negative group, it was not statistically significant (0.113 ± 0.154 ng / mL, 0.064 ± 0.058 ng / mL, p = 0.510).
Conclusion: Our results show that the procalcitonin level cannot distinguish the presence of COVID-19 pneumonia in RT-PCR positive patients. High procalcitonin levels may predict that the disease becomes more complicated.
Keywords: COVID-19, Pneumonia, Procalcitonin

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GİRİŞ

Çin›in Hubei Eyaleti, Vuhan şehrinde 31 Aralık 2019'da etiyolojisi bilinmeyen pnömoni vakalarının görüldüğü bildirildi. Hastalık etkeninin daha önce insanlarda tespit edilmemiş yeni bir koronavirüs (2019-nCoV) olduğu, 7 Ocak 2020'de tanımlandı. Hastalığın adı daha sonra coronavirus disease-19 (COVID-19) olarak, etkeni de SARS CoV'e yakın benzerliğinden dolayı SARS-CoV-2 olarak isimlendirildi (1). Hastalığın etkeni olan SARS-CoV-2, koronavirüs ailesinin tipik özelliklerine sahiptir ve Betacoronavirus 2b soyunda yer almaktadır. Tek zincirli, pozitif polariteli, zarflı bir RNA virüsüdür (2). Hastalığın enfeksiyon kaynağı henüz netlik kazanmamıştır. Vuhan'da yapılan ilk epidemiyolojik araştırmalara göre, salgının başlangıcında hastaların çoğunun deniz ürünleri ve canlı hayvan satan bir pazarda çalışma veya ziyaret etme öyküsüne sahip olmaları nedeniyle hastalığın hayvanlarla ilişkisi olduğu düşünülmüştür (3). İlk olguların ardından hastalığın bulaşma yolu, insandan insana doğrudan temas yoluyla olmuştur. Hastalık esas olarak damlacık yoluyla bulaşmaktadır. Damlacık yolu ile enfeksiyonu olan bir kişi öksürdüğünde, hapşırdığında veya konuştuğunda solunum salgılarında bulunan virüs, mukozayla temas ederse başka bir kişiye bulaşabilir (4).

İnkübasyon dönemi sonrasında COVID-19'da en sık görülen klinik bulgular ateş, kuru öksürük, halsizliktir. Daha ağır olgularda nefes darlığı, solunum yetmezliği ile acute respiratory distress syndrome (ARDS)'ye giden klinik tabloya neden olabilir (5). Klasik üst solunum yolu enfeksiyon bulgularının (rinore, nazal konjesyon, boğaz ağrısı vb.) varlığı COVID-19'da nadiren bildirilmiştir, ancak varlığı da tanıyı reddettirmez. Birçok çalışmada anozmi ve hipozmi gibi koku almada değişiklik erken hastalık semptomları olarak bildirilmiştir. Daha nadir olarak nörolojik semptomlar (baş ağrısı, konfüzyon, bilinç değişikliği vb.) ve özellikle çocuklarda diyare gibi gastrointestinal semptomlar COVID-19 enfeksiyonunda tanımlanmıştır (5-7).

COVID-19 tanısında en sık kullanılan yöntem RT-PCR olmakla birlikte, testin sensitivitesinin düşük olmasıyla ilgili olarak yalancı negatif sonuçlarla karşılaşılabilmektedir. Bu nedenle hastaların tanısal açıdan klinik, laboratuvar ve toraks BT bulgularıyla birlikte değerlendirilmesi gerekmektedir (8-11).

Kalsitonin hormonunun bir peptit öncüsü olan prokalsitonin, bir bakteriyel enfeksiyonun ilk araştırmasında umut verici bir biyobelirteç olarak geniş çapta araştırılmıştır (12). Serum prokalsitonin konsantrasyonları birçok inflamatuvar durumda artmakta olup, sepsis, ağır bakteriyel ve fungal enfeksiyonlarda, bakteriyel menenjit, bakteriyel süperenfeksiyon, akut pankreatit gibi durumlarda yararlı bir prognostik göstergedir (13). Serum prokalsitonin konsantrasyonun hızla yükselmesi veya yüksek seyretmesi kötü prognoz veya devam eden inflamatuar aktivite durumlarında görülür. Prokalsitoninin bakteriyel veya viral pnömoniyi doğru bir şekilde ayırt edip edemeyeceği hala tartışmalı olmakla birlikte, akut solunum yolu enfeksiyonlarında prokalsitonin kılavuzluğunda tedavinin antibiyotik maruziyetini ve yan etkileri azalttığı ve hayatta kalma oranını iyileştirdiği bulunmuştur (14-15).

Bu çalışmada, RT-PCR pozitif hastaların prokalsitonin seviyeleri incelendi. COVID-19 pömonisinde prokalsitonin seviyelerinin rolü araştırıldı.

YÖNTEM

Çalışmamız retrospektif bir çalışmadır. Çalışmamıza hastaneye başvuran 18 yaş RT-PCR testi pozitif olup servise yatışı olan 100 COVİD-19 hastası dahil edildi. Hastaların verileri hastane sisteminden geriye dönük olarak toplanmış olup pandeminin ilk aylarındaki hasta verileridir. Bu veriler, hastaların hastaneye ilk başvuru sırasındaki laboratuvar ve radyolojik bulgularını içermektedir. Bu çalışmada prokalsitonin seviyeleri, diğer demografik veriler toplandı ve akciğer BT taraması yapıldı. RT-PCR pozitif hastalar BT pozitif ve BT negatif diye iki gruba ayrıldı ve bu iki grup arasında prokalsitonin değerlerinin değişiklikleri araştırıldı.

İstatistiksel analiz IBM SPSS 25.0 (SPSS for Windows, SPSS Inc., Chicago, IL, ABD) kullanılarak yapıldı. Prokalsitonin seviyeleri normallik testi için Kolmogorow–Smirnov testi kullanıldı. Gruplar normal dağılım göstermedi. Gruplar arasında önemli farklılıklar olup olmadığını araştırmak için parametrik olmayan testlerden Mann-Whitney U Testi kullanıldı. $P < 0.05$ istatistiksel olarak anlamlı kabul edildi.

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BULGULAR

RT-PCR testi pozitif olan 100 hastanın 42'sinda BT negatif, 58'inde BT pozitifti. Çalışmamıza dahil edilen BT negatif grup ve BT pozitif demografik ve bazı laboratuvar verileri Tablo 1'de gösterilmektedir.

BT negatif hastalarımızın 20'si kadın, 22'si erkekti ve yaş ortalaması 39.15±13.28 idi. BT pozitif hastalarımızın 30'u erkek 28'i kadındı ve yaş ortalaması 42.23±12.67 idi. BT pozitif

hastalarımızın %32'sinde ateş, %67'sinde öksürük, %41'inde dispne, %33'ünde boğaz ağrısı, %48'inde kırgınlık, %33'ünde miyalji saptanırken BT negatif hastalarımızın%15'inde ateş, %38'inde öksürük, %5'inde dispne, %21'inde boğaz ağrısı, %28'inde kırgınlık, %15'inde miyalji saptanmıştır. BT pozitif hastaların %36'sında, BT negatif hastaların ise %18'inde diyabet, hipertansiyon, KOAH, astım, kalp yetmezliği ve kanser gibi ek hastalıklardan bir veya daha fazlası mevcuttu. BT pozitif ve BT negatif hasta grubunda ölçülen prokalsitonin seviyeleri Tablo-2'de gösterilmiştir. BT pozitif hasta grubunda ölçülen prokalsitonin düzeyleri (0.113±0.154 ng/mL), BT negatif hasta grubuna (0.064±0.058 ng/mL) göre yüksek olmasına rağmen istatiksel olarak anlamlı bulunmadı.

Tablo-1 BT pozitif ve BT negatif COVİD-19 hastalarının demografik ve laboratuvar verileri.

Gruplar		BT Pozitif	BT Negatif
Cinsiyet	Erkek	30	22
	Kadın	28	20
Yaş (yıl)		42.23±12.67	39.15±13.28
Üre (mg/dL)		34.96±32.10	27.12±15.83
Kreatinin (mg/dL)		1.12±0.98	0.87±0,34
Albümin (g/dL)		4.21±0.54	4.48±0.41
WBC (10^3/uL)		6.69±2.95	6.39±2.44
Crp (mg/L)		38.06±62	9.11±23
D-dimer (ug/mL)		0.58±1.04	0.33±0.92
Ferritin (ng/mL)		512.15±1118.12	91.12±89.93

Tablo 2. BT negatif ve BT pozitif COVİD-19 hastalarının Prokalsitonin değerlerinin istatistiksel karşılaştırılması

Gruplar	Prokalsitonin (ng/mL)	P değeri
BT Negatif	0.064±0.058	0.510
BT Pozitif	0.113±0.154	

TARTIŞMA

Herhangi bir rutin laboratuvar biyobelirteci, tek başına bir tanı testi olarak kullanılması birçok hastalığın tanısında yeterince iyi performans göstermez. Pnömoni, COVID-19'un sık görülen ve ciddi komplikasyonlarından birisidir. Hastalığın tanısında RT-PCR öncelikle kullanılmakla birlikte, hatalı negatiflik durumunda akciğer BT görüntülemesi COVID-19 hastalığının tedavisinde önemli bir rol oynamaktadır (16). COVID-19 ile hastanede yatan hastalarda çok sayıda biyobelirteç ölçülmüştür. Çin'den gelen ilk raporlar, COVID-19 hastalarının çoğunda yüksek prokalsitonin (> 0.5 µg/L) olmadığını göstermiştir (17-18). Liu ve ark. yaptığı COVID-19 hastalarında interlökin-6, C-reaktif protein ve prokalsitoninin prognostik değeri adlı çalışmada COVID-19 hastaları şiddetli (nefes darlığı, solunum hızı dakikada ≥30 atış, dinlenme durumunda oksijen satürasyonu -%93, arteryel oksijen kısmi basıncı (PEP 2)/oksijen konsantrasyonu (FiO 2) ≤300 mmHg (1 mmHg = 0.133 K Pa), 24-48 saat içinde>% 50 lezyon boyutunda bariz ilerleme gösteren akciğer görüntüleri olan hastalar) ve hafif (hafif klinik semptomlar veya görüntüleme bulgularında hafif lezyonlar veya hiç lezyon yok) olarak iki gruba ayırarak incelemiştir. Şiddetli COVID-19 gurubunda hafif COVID-19 grubuna göre başvuru anındaki prokalsitonin düzeyi yüksek bulunmuştur. Prokalsitonin düzeyinde artış olan hastaların oranı şiddetli grupta anlamlı olarak daha yüksek saptanmıştır (19). Hu ve ark. yaptığı COVID-19 hastalarında prokalsitonin seviyeleri adlı çalışmada ise sadece COVID-19 pnömonisi olan hastalar dahil edilerek orta, şiddetli ve kritik olarak üç gruba ayırmıştır. Sonuç olarak ortalama serum prokalsitonin düzeylerinin, şiddetli hastalarda orta şiddette hastalara göre yaklaşık dört kat daha yüksek olduğu ve kritik hastalarda yaklaşık sekiz kat daha yüksek olduğu gösterilmiştir. Birlikte enfeksiyon oranı, orta derecede olan hastalarda (~%10) yüksek prokalsitonin seviyelerinin oranına yakın olduğu için, prokalsitonin seviyelerinin hastalığın şiddetine bağlı olduğu ve bakteriyel ko-enfeksiyon ile ilişkili olabileceği saptanmıştır (20). Lippi ve ark. yaptığı meta-analiz çalışması ise seri prokalsitonin ölçümünün, daha şiddetli bir hastalık biçimine doğru ilerlemeyi öngörmede bir rol oynayabileceğini ortaya koymuştur (21). Ancak eşzamanlı bakteriyel bir enfeksiyon bu sonuçları saptırabilir ve kafa karıştırıcı faktör olarak hareket edebilir. Yapılan başka bir meta analizde prokalsitonini yüksek olan 256 hastanın 163›ü ciddi hastalığa sahipti (%63.7). Şiddetli seyir ve ters sonuç olan hastaların sırasıyla %22.8'inde ve %30.6'sında prokalsitonin yükselmiştir. Sekonder bakteriyel enfeksiyon oranları %4.7 ile %19.5 arasında değişmekteydi ve ciddi seyir veya ölümcül sonuç riskinde artış ile ilişkiliydi. Sonuç olarak yüksek prokalsitonin seviyeleri, artan ciddi hastalık ve olumsuz sonuç riski taşıyan COVID-19 hastalarının bir alt grubunu tanımlayabilir (22). Yapılan başka bir çalışmada, kritik ve şiddetli klinik seyri olanların, orta şiddettekilere kıyasla yüksek prokalsitonin seviyelerine sahip oldukları; yüksek prokalsitonin seviyesine sahip olan vakaların hastalığı daha şiddetli geçirdiği gözlenmiş ve bu vakaların büyük çoğunluğunun da yaşlılar olduğu bildirilmiştir (23). Heesom ve arkadaşlarının 52 COVID-19 vakasını değerlendirdikleri çalışmalarında düşük (<0.5ng/ml) prokalsitonin grubuyla karşılaştırıldığında, yüksek (>0.5ng/ml) prokalsitonin grubunda ventilasyon gereksiniminin daha fazla olduğu ve yüksek prokalsitonin seviyesine sahip olan vakalar arasında daha fazla ölüm gerçekleştiği bildirilmiştir (24). Elshazli ve ark. tarafından yapılan ve şiddetli ve hafif COVID-19 vakalarının laboratuvar parametrelerinin karşılaştırıldığı bir çalışmaya 52 makale ve 6320 vaka dahil edilmiş; hastalığı şiddetli geçiren vakaların prokalsitonin düzeyinin hafif geçirenlere göre daha yüksek

olduğu; prokalsitonin seviyesinin hastalığın morbiditesi ve mortalitesiyle ilişkili olduğu üzerinde durulmuştur (25). Li ve ark. COVID-19 vakalarında laboratuvar parametrelerini karşılaştıran 12 çalışmanın dahil edildiği bir başka metaanaliz çalışmasında hastalığı ağır seyreden vakaların prokalsitonin seviyelerinin, hastalığı normal seyreden vakalara kıyasla daha yüksek olduğunu ve prokalsitonin seviyesinin hastalığın şiddetiyle ilişkili olduğu bildirmiştir (26).

Prokalsitonin, bakteri ve diğer patojenleri ayırt etmek için umut verici biyobelirteçlerden biri olarak önerilmiş olsa da COVID-19 hastalarındaki faydası belirsizliğini koruyor. Biz yaptığımız çalışmada sadece RT-PCR testi pozitif olup servise yatışı olan hastaları dahil edildi. Hastaları BT pozitif ve BT negatif olarak iki gruba ayrıldı. BT pozitif olan hastaların prokalsitonin düzeylerini BT negatif hastalara göre daha yüksek saptamamıza rağmen istatistiksel olarak anlamlı bulunmadı. Prokalsitonin seviyelerindeki değişiklik, daha önce bakteriyel enfeksiyona işaret eden önemli bir artışla, toplumdan edinilmiş pnömoni ve sepsisteki bakteriyel orijinli sistemik inflamasyonu viral orijinden ayırt etmek için önerilmişti (27-28). Ekstratiroidal kaynaklardan prokalsitonin üretimi ve dolaşımına salınması, bakteriyel enfeksiyonlar sırasında büyük ölçüde güçlendirilir. Bununla birlikte, prokalsitonin sentezi, viral enfeksiyonlar sırasında konsantrasyonu artan interferon (INF) -γ tarafından inhibe edilir (29). Yaptığımız çalışmada BT pozitif hastalarda BT negatif hastalara göre artan enfeksiyonla birlikte prokalsitonin artışı inhibe edilmiş olabilir.

SONUÇ

Şimdiye kadar COVID-19 pozitif ve negatif hastalar arasında bir dizi rutin laboratuvar biyobelirteçlerinde farklılıklar tespit edildi. Elde ettiğimiz sonuçlar prokalsitonin düzeyinin RT-PCR pozitif hastalarda COVID-19 pnömonisinin varlığını ayırt edemeyeceğini göstermektedir. Hasta sayısının az olması ve diyabet, hipertansiyon, KOAH, astım, kalp yetmezliği ve kanser gibi ek hastalıkların ekarte edilmemiş olması çalışmamızın kısıtlılıkları arasındadır. Ancak şu ana kadar yapılan çalışmalar da göz önünde bulundurulursa, prokalsitonin düzeyindeki yüksekliğin hastalığın daha komplike bir hale geldiğini öngörmede yardımcı olacağını düşünmekteyiz.

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KAYNAKLAR

1. Metintas S. Epidemiology of COVID-19. Eurasian J Pulmonol 2020;22, Suppl S1:2-7
2. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü: COVID-19 (SARS-CoV-2 ENFEKSİYONU) REHBERİ. Bilim Kurulu Çalışması, T.C. Sağlık Bakanlığı 12 Nisan 2020, Ankara.
3. Nishiura, H.; Linton, N.M.; Akhmetzhanov, A.R. Initial Cluster of Novel Coronavirus (2019-nCoV) Infections in Wuhan, China Is Consistent with Substantial Human-to-Human Transmission. J. Clin. Med. 2020, 9, 488. https://doi.org/10.3390/jcm9020488
4. McIntosh K. Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention. UpToDate. (https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-epidemiology-virology-clinical-features-diagnosis-and-prevention).
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;NEJMoa2002032. https://doi.org/10.1101/2020.02.06.20020974.
6. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis 2020;ciaa272. https://doi.org/10.1093/cid/ciaa272.
7. Wang C, Horby P, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395:470-473. https://doi.org/10.1016/S0140-6736(20)30185-9.
8. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. 2020. 27:25727. https://doi.org/10.1002/jmv.25727.
9. Hao W, Li M. Clinical diagnostic value of CT imaging in COVID-19 with multiple negative RT-PCR testing. Travel Med Infect Dis. 2020; 34: 101627. https://doi.org/10.1016/j.tmaid.2020.101627.
10. Wang S, Kang B, Ma, J, Zeng X, Xiao, M, Guo J, et al. A deep learning algorithm using CT images to screen for corona virus disease (COVID-19). medRxiv 2020.02.14.20023028. https://doi.org/10.1101/2020.02.14.20023028.
11. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020; 55(5): 105955. https://doi.org/10.1016/j.