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Interdiscip Med J 2023;14(49)

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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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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

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INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2023;14(49)

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.

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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.

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

Article Format

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.

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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.

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INTERDISCIPLINARY MEDICAL JOURNAL
Interdiscip Med J 2023;14(49)

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.

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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?

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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=

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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).

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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?

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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?

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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

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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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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(49)

CONTENTS

Volume: 14, Issue 49, Year: 2023

ORIGINAL RESEARCH
DOI: 10.17944/interdiscip.1320530
Interdisciplinary Medical Journal 2023;14(49):69-73.

Evaluation of dermatology consultations requested for inpatients in a tertiary institution from Türkiye

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Abstract

Objective: To investigate and present the features of the consultations requested for inpatients in a tertiary institution retrospectively.

Methods: Archive of our tertiary institution located in the South Marmara Region of Turkiye was reviewed and every single consultation responded by Dermatology Department was investigated.

Results: The mean age of the 421 consulted patients (191 females, 230 males) was 62 ± 17 (1-95) years. The most frequently consultation requesting departments were Cardiology (18.8%), Neurology (11.4%) and Physical medicine and Rehabilitation (8.3%). The most common lesions resulting in consultation were rashes (22.3%), erythematous lesions (14.5%) and wounds (14%). The most common dermatologic diagnoses were contact dermatitis (10.7%), tinea pedis (8%) and cellulitis (5.2%). Among 421 patients, 62 (14.7%) patients required a histopathologic diagnosis and underwent biopsy. Most frequent histopathologic diagnoses were non-specific findings 14 (22.6%), basal cell carcinoma (12.9%), maculopapular drug reaction (12.9%) and contact dermatitis (9.7%).

Conclusion: The perspective of interdisciplinary approach leads physicians request dermatology consultations frequently for inpatients particularly having systemic diseases and reviewing and reporting the features of consulted patients periodically might provide a satisfactory contribution to the current literature.

Keywords: Dermatology, Consultation, Interdisciplinary, Inpatient, Rash, Contact Dermatitis

INTRODUCTION

Tertiary medical institutions generally admit many patients having various systemic diseases in Turkiye. Patients having any systemic disease may manifest with a dermatologic symptom or may have an accompanying dermatologic disease. Although Dermatology and Venerology is a department admitting many outpatients, consultations are frequently requested from other services because of frequent skin findings of systemic diseases, accompanying dermatologic symptoms and dermatologic side effects of the medications used (1). In daily dermatology practice, high- mortality conditions like acute graft versus host disease (GVHD) and purpura fulminans might not be common among outpatient clinic admissions, however, high- mortality diseases are commonly seen among inpatient consultations (1).

Based on this perspective, this study aimed to investigate and present the features of the consultations requested for inpatients in a tertiary institution retrospectively.

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METHODS

This retrospective- archival investigation was conducted in line with the dictates of Helsinki Declaration by World Medical association. After the approval of the local ethical committee of Balıkesir University, Clinical / Human (IRB Number: 2022/71) the medical archive of our tertiary institution located in the South Marmara Region of Turkiye was reviewed and every single consultation responded by Dermatology Department was investigated. The ages, genders, consultation requesting departments, dermatologic diagnoses and histopathologic diagnoses of the patients underwent biopsy were analyzed and noted. Findings of the study were presented as number (percentage).

RESULTS

In total, 421 consultations were requested between January 2022 and January 2023, for inpatients of our tertiary institution. The mean age of the patients was 62 ± 17 (1-95) years (Eight children in total, 5 children from Department of Pediatrics). Additionally, 191 (45.4%) patients were female, and 230 (54.6%) patients were male. The distribution of the departments that requested consultations were presented in Table 1. The most frequently consultation requesting departments were Cardiology (18.8%), Neurology (11.4%) and Physical medicine and Rehabilitation (8.3%). Table 2 presents the distribution of the reasons for dermatology consultation. The most common lesions resulting in consultation were rashes (22.3%), erythematous lesions (14.5%) and wounds (14%). Table 3 presents the distribution of dermatologic diagnosis of consulted patients. Out of 421 patients, 24 (5.7%) had no dermatologic diagnosis. The most common dermatologic diagnoses were contact dermatitis (10.7%),

Table 1. The distribution of the departments that requested consultations.

Department	n	(%)
Cardiology	79	(18.8%)
Neurology	48	(11.4%)
Physical Medicine and Rehabilitation	35	(8.3%)
Otolaryngology	31	(7.4%)
Anesthesiology and Reanimation	27	(6.4%)
Internal Medicine	25	(5.9%)
Infectious diseases	22	(5.2%)
Gastroenterology	20	(4.8%)
Pulmonary Diseases	20	(4.8%)
Urology	16	(3.8%)
Orthopedics	15	(3.6%)
Cardiovascular Surgery	14	(3.3%)
Psychiatry	13	(3.1%)
General Surgery	11	(2.6%)
Neurosurgery	11	(2.6%)
Gynecology and Obstetrics	7	(1.7%)
Plastic and Reconstructive Surgery	6	(1.4%)
Pediatrics	5	(1.2%)
Ophthalmology	5	(1.2%)
Geriatrics	4	(1%)
Endocrinology and Metabolism	4	(1%)
Nephrology	2	(0.5%)
Immunology and Allergy	1	(0.2%)
Total	421	(100%)

Table 2. Distribution of Dermatology consultation reasons.

Reason for consultation	n	(%)
Rash	94	(22.3%)
Erythematous lesions	61	(14.5%)
Wound	59	(14%)
Pruritis	43	(10.2%)
Rash with pruritis	19	(4.5%)
Rash with erythema	19	(4.5%)
Bullous lesions	13	(3%)
Oral lesions	13	(3%)
Suspicion of Behcet Disease	12	(2.9%)
For any additional suggestions for treatment	11	(2.6%)
Re-consultation for control	11	(2.6%)
Papulous lesions	11	(2.6%)
Discharged lesions	9	(2.1%)
Erythema with warmth	8	(1.9%)
Erythema with pruritis	8	(1.9%)
Nail disorders	4	(1%)
Acne	4	(1%)
Ulcer	4	(1%)
Painful lesions	3	(0.7%)
Consultation for biopsy results	3	(0.7%)
Stain on skin	3	(0.7%)
Alopecia	2	(0.5%)
Rash with warmth	2	(0.5%)
Subcutaneous nodule	1	(0.2%)
Edema	1	(0.2%)
For melanoma scan	1	(0.2%)
Ecchymosis	1	(0.2%)
Suspicion of Dermatomyositis	1	(0.2%)
Total	421	(100%)

Table 3. The distribution of dermatologic diagnosis of consulted patients.		
Dermatologic diagnosis	n	(%)
Contact dermatitis	45	(10.7%)
Tinea pedis	34	(8%)
Cellulitis	22	(5.2%)
Maculopapular drug reaction	17	(4%)
Xerosis cutis	15	(3.5%)
Decubitus ulcer	15	(3.5%)
Urticaria	13	(3%)
Stasis dermatitis	13	(3%)
Vesicular dermatitis of herpes virus	12	(2.9%)
Intertrigo	12	(2.9%)
Pyoderma gangrenosum	12	(2.9%)
Traumatic ecchymosis	10	(2.4%)
Basal cell carcinoma	9	(2.1%)
Oral candidiasis	9	(2.1%)
Psoriasis	8	(1.9%)
Zona Zoster	7	(1.7%)
Tinea corporis	7	(1.7%)
Bullous pemphigoid	7	(1.7%)
Scabies	6	(1.4%)
Tinea cruris	5	(1.2%)
Acne vulgaris	5	(1.2%)
Pigmented purpuric dermatosis	4	(1%)
Lymphedema	4	(1%)
Seborrheic dermatitis	4	(1%)

Table 3. (continued) The distribution of dermatologic diagnosis of consulted patients.		
Verruca vulgaris	4	(1%)
Traumatic bulla	4	(1%)
Seborrheic keratosis	3	(0.7%)
Asteatotic eczema	3	(0.7%)
Atopic dermatitis	3	(0.7%)
Tinea unguium	3	(0.7%)
Diabetic ulcer	3	(0.7%)
Uremic pruritus	2	(0.5%)
Pigmented actinic keratosis	2	(0.5%)
Postherpetic neuralgy	2	(0.5%)
Toxic epidermal necrolysis	2	(0.5%)
Fixed drug eruption	2	(0.5%)
Dermatomyositis	2	(0.5%)
DRESS	2	(0.5%)
Liken amyloidosis	2	(0.5%)
Erythema multiforme	2	(0.5%)
Carcinoma metastasis	2	(0.5%)
Acute GVHD	1	(0.2%)
Anaphylaxis	1	(0.2%)
Atypical mycobacteria infection	1	(0.2%)
Behcet Disease	1	(0.2%)
Heparin induced thrombocytopenia	1	(0.2%)
Gardner Diamond syndrome	1	(0.2%)
Other diagnosis	53	(12.6%)
NONE	24	(5.7%)
Total	421	(100%)

tinea pedis (8%) and cellulitis (5.2%). Among 421 patients, 62 (14.7%) patients required a histopathologic diagnosis and underwent biopsy. The distribution of histopathologic diagnosis of 62 patients underwent biopsy was presented in table 4. Among 62 biopsy reports, 14 (22.6%) revealed non-specific findings. Following most frequent histopathologic diagnoses were basal cell carcinoma (12.9%), maculopapular drug reaction (12.9%) and contact dermatitis (9.7%).

DISCUSSION

Interdisciplinary approach to systemic diseases of inpatients is crucial for accurate treatment. Because many systemic diseases might manifest along with dermatologic symptoms, dermatology consultations are commonly requested for inpatients of other services. In this retrospective study, we aimed to review the features of the patients referred to Dermatology Department for consultation from other services. We basically found that the most frequently consultation requesting service was Cardiology, followed by Neurology and Physical Medicine. We can hypothesize that the systemic diseases seen in cardiology patients might be more likely to manifest with dermatologic findings.

The idea of reviewing the consultations is not novel for the current literature (2). Taşçı reported an analysis focusing psychiatry consultations in a city hospital (3). The consultations requested from otolaryngology department of a tertiary institution were analyzed and reported by Kayabasi et al previously (4). Moreover, many studies focusing on dermatology consultations are available in the prior literature. Walia et al reported that dermatologic consultations changed the diagnosis and treatment in more than 66% of the patients (5). In this study, the service requesting consultation more frequently was cardiology, however, Fernandes reported the most frequently consultation requesting service as internal medicine, from a tertiary institution in Portugal (6). According to Joseph et al, dermatology consultations were most often requested by medical teams from emergency service (7). Additionally, the most common dermatologic conditions found in the consulted patients were dermatitis and skin infections (7).

Table 4. The distribution of histopathologic diagnosis of the patients underwent biopsy.

Histopathologic diagnosis	n	(%)
Non- specific findings	14	(22.6%)
Basal cell carcinoma	8	(12.9%)
Maculopapular drug reaction	8	(12.9%)
Contact dermatitis	6	(9.7%)
Squamous cell carcinoma	4	(6.4%)
Steven-Johnson syndrome	3	(4.8%)
Fixed drug eruption	2	(3.2%)
Edematous inflamed minimal skin tissue	2	(3.2%)
Perforating dermatosis	2	(3.2%)
Superficial perivascular psoriasiform dermatitis	2	(3.2%)
Psoriasis vulgaris	1	(1.6%)
Dermatomyositis	1	(1.6%)
Erythema multiforme	1	(1.6%)
Gardner Diamond Syndrome	1	(1.6%)
Interphase dermatitis	1	(1.6%)
Carcinoma metastasis	1	(1.6%)
Lichenoid interface reaction pattern	1	(1.6%)
Necrosis	1	(1.6%)
Perivascular dermatitis	1	(1.6%)
Pigmented purpuric dermatosis	1	(1.6%)
Trichilemmal cyst	1	(1.6%)
Total	62	(100%)

According to report by Bauer et al from USA, the most common dermatologic diagnosis was dermatitis, skin infections and ulcer (8). In consistent with the prior literature, we found that the most common dermatologic diagnosis in consulted patients was contact dermatitis, followed by tinea pedis and cellulitis. However, Falanga et al reported that the most common dermatologic diagnosis was drug eruption in their study group (9).

The most common dermatologic symptoms leading the physicians ask for a consultation was skin rash according to the report by Chojer et al (10). Consistently, we found that the most common dermatologic symptoms leading the physicians ask for a consultation were rashes, erythematous lesions and wounds. Additionally, the mean age of consulted patients was 62 ± 17 (1-95) years and only 5 patients were referred from department of pediatrics. Çiçek et al reported that 3.57% percent of consulted patients required biopsy (11), however, 62 (14.7%) patients required biopsy in this study group.

CONCLUSION

The perspective of interdisciplinary approach leads physicians request dermatology consultations frequently for inpatients particularly having systemic diseases. Although current literature includes many studies focusing on reviewing consultations of various services, reviewing and reporting the features of consulted patients periodically might provide a satisfactory contribution to the current literature.

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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 permission was obtained from Balıkesir University, Clinical / Human Research Ethics Committee for this study with date 2022 and number 71, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: PH, Design: PH, Supervising: FAK, Financing and equipment: MES, Data collection and entry: MES, Analysis and interpretation: PH, MES, Literature search: PH Writing: PH, Critical review: FAK.

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ORIGINAL RESEARCH
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Can venous blood gas be used instead of arterial blood gas in emergency department?

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Abstract

Objective: In our study, we aimed to evaluate the usability of venous blood gas (VBG) in substitution for arterial blood gas (ABG).

Methods: In this study, 110 patients with respiratory complaints, who were brought intubated were evaluated prospectively. Arterial and venous blood gases were taken simultaneously shortly before the initiation of oxygen therapy in the emergency department. PH, pO2, pCO2, SaO2, HCO3, lactate (Lac) and BEecf values were recorded.

Results: Of the 110 patients included in the study, 75 were male (68.2%), 35 were female (31.8%), and they had a mean age of 53.7 ± 23.1 years. A strong positive correlation between PH, PCO2, HCO3-, BEecf, Lac values (p=0.001) and positive correlation between PO2 and SaO2 values (p= 0.002) were detected.

Conclusion: We can conclude that venous blood gas be used in substitution for arterial blood gas in patients who are presented to emergency service and it may reduce the need for arterial blood gas sampling.
Keywords: Arterial Blood Gas, Venous Blood Gas, Emergency Department

INTRODUCTION

Arterial blood gas (ABG) analysis is a commonly used laboratory method for the diagnosis, treatment and follow-up of respiratory and metabolic diseases, showing the acid base condition and giving useful findings for the clinical evaluation. Arterial blood gas analysis, which is frequently used for this purpose, is the gold standard. However arterial blood sampling is a painful method that causes vascular complications and poses a risk to health personnel in terms of contagious infections. Acquisition of ABG is a very difficult method due to disruption of patient comfort, pain, hematoma, embolism, ischemia and interventional practice.

Obtaining venous blood gas (VBG) sample is much easier than obtaining arterial blood gas sample and can also work concurrently with the blood sample taken for other laboratory studies. Therefore, the use of a venous blood gas sampling can prevent time loss caused by the arterial blood gas sampling and the risk of complications that may occur in the arterial puncture (1,2).

The ease of operation, practicality, speed and patient comfort are crucial in crowded and busy emergency services. The sooner the whole process is done, the sooner the diagnosis and conclusion can be made.

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In this work we have done, we aimed to evaluate the usability of venous blood gas in substitution for arterial blood gas because of the difficulty and risks of arterial blood sampling.

METHODS

The study included patients who were admitted to the Emergency Department as intubated and in need of intensive care, and congestive heart failure patients with respiratory distress. The research was conducted in an emergency department of a medium sized University Research Hospital, and 300 patients on average are admitted to our Emergency Department, daily. During the research period, 110 patients who were admitted to the Research Hospital of Hatay Mustafa Kemal University with respiratory complaints and with a poor general condition. They were evaluated prospectively in our study after obtaining the consent of the patients or their relatives. Arterial and venous blood gases were taken simultaneously (5 minutes at the latest) shortly before initiation of the oxygen therapy in the Emergency Department. First of all, Radial artery was used for arterial blood gas. Secondly, Femoral artery was preferred when blood could not have been taken from the radial artery and peripheral venules were used for venous blood gas. The blood samples were taken by the research assistants of the Emergency department on duty at the time of patient's admission. They were collected using a 2 ml blood gas injector with hypodermic needle containing 80 IU dry lithium heparin (Berika brand, Turkey). Without delay, samples were transferred to the biochemistry laboratory of the Research Hospital and analyzed there with GEM Premier 3000 analyzer (India).

Statistical Analysis

PH, pO_2, pCO_2, SaO_2, HCO_3, Lactate and BE_{ecf} values of blood gases taken for the study were recorded. Averages and safety intervals of arterial and venous variables were determined. The relationship between their values was determined and an equation was formulated to find arterial values from venous values by linear regression analysis.

Whether the data had normal distribution was analyzed using the Shapiro-Wilk test. The descriptive statistics for the blood gas parameters such as PH, pO_2, pCO_2, SaO_2, HCO_3, Lactate and BE_{ecf} were expressed as mean, minimum, maximum, and standard deviation The correlation between these variables were analyzed using Pearson's Correlation test, and correlation coefficient was calculated for them. Scatterplot method was used in graphic drawings. The statistical analysis was performed using the SPSS Statistics Software v21 and $p<0.05$ were considered as statistically significant.

Table 1. Blood gas values of patients

Blood gas	Arterial Blood Gas			Venous Blood Gas		
	Min	Max	Mean±SD	Min	Max	Mean±SD
SaO2	51	100	94.2±7.2	4	100	50.6±25.4
pO2	37	458	110.1±64.3	6	181	37.0±25.2
pH	6.80	7.54	7.33±0.14	6.80	7.56	7.27±0.15
pCO2	14	66	36.2±10.6	21	93	48.0±14.9
Lac	0.4	15.0	3.0±3.1	0.5	15.0	3.2±3.1
HCO3	6.4	37.3	19.9±5.8	6.0	40.5	22.7±6.5
BEecf	-24.1	13.5	-5.6±7.1	-26.3	16.7	-3.6±8.0

RESULTS

Of the 110 patients included in the study, 68.2% (n = 75) were male and 31.8% (n = 35) were female. The mean age was 53.7 ± 23.1 (4-92). At the time of admission, 65.5% (n = 72) had congestive heart failure (CHF) with respiratory distress, and 34.5% (n = 38) had poor overall condition, were unconscious and intubated by 112 ambulance crew. The blood gas values of the patients are shown in Table 1.

When the correlation values of arterial and venous blood gases are examined; mild positive correlation, (respectively r=0.395 and r=0.294) between arterial and venous SaO_2 and pO_2 values were detected. There was a strong correlation between the other parameters (Table 2). The strongest correlation was between HCO_3 values (Figure 1).

Table 2. Correlation values of arterial and venous blood gases

Parameter	r*	p
HCO_3	**0.915**	**0.001**
pH	**0.914**	**0.001**
Lac	0.909	0.001
BE_{ecf}	0.875	0.001
pCO_2	0.666	0.001
SaO_2	0.395	0.001
POI_2	0.294	0.002

* Pearson Correlation analysis, r: Pearson Correlation coefficient, p < .005

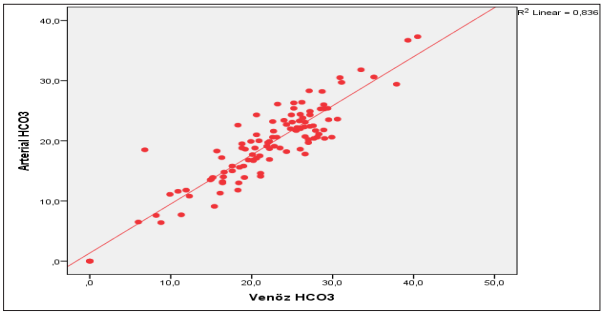

Figure 1. Correlation and linear regression line between arterial and venous HCO3

DISCUSSION

In a study conducted by Zahn and Weil to investigate the correlation between arterial and venous blood samples; it has been reported that there is an relation between arterial and venous PH values, and central venous blood samples could be used instead of arterial blood samples (4). Another study by Moore and Good, compared arterial and venous PH values in patients with hemorrhagic shock and hypothermia and reported that venous PH was a highly sensitive marker for assessing arterial PH (5).

Brandenburg and Dire investigated the effects of arterial blood gas results on diagnosis, treatment and follow-up of patients suspected of diabetic ketoacidosis. Correlations between arterial and venous PH, HCO_3^- values were calculated and they stated that the venous blood sample could be used easily if the PH value had to be known so that the patients in the emergency room could be evaluated (6).

Hale and Natrass, in the study they conducted on the cases with diabetic ketoacidosis, compared PH and PCO_2 values in arterial and venous blood gases and reported that venous blood samples could be used instead of arterial blood samples to assess the acid-base status in these cases (7). Although there were mostly studies comparing arterial and venous blood samples to evaluate metabolic acidosis in the literature; in 2001, Kelly et al. compared arterial and venous pH values in 196 patients with acute respiratory failure. They have stated that venous PH is an acceptable data to calculate arterial PH and thus may reduce complications that may arise, in terms of both patient and health personnel while taking arterial blood gas (3).

Zetos et al. evaluated the correlation between arterial and venous PH values in a study of 103 patients who referred to the emergency department of the Chest Diseases hospital with acute respiratory failure and they reported that venous PH could be used instead of arterial PH (8).

There are a lot of studies comparing direct arterial and venous PCO_2 values in the literature, and in these studies strong correlation between arterial and venous PCO_2 values were detected. It has been stated that the correlation found in these studies is not surprising, and this correlation is an expected finding because the arterial and venous PCO_2 values are part of the physiological system (9,10).

In the studies where Kelly et al. were searching for the availability of usage of venous PH and PCO_2 values instead of arterial PH and PCO_2 values in acute respiratory failure cases, they found out that venous PH could be used for that purpose safely, calculated that venous PCO_2 value is 5.8 mmHg higher than arterial PCO_2 and concluded that venous PCO_2 value is not sufficient to be used in place of arterial PCO_2. They stated that venous PCO_2 could only be used to monitor hypercarbia (11).

In another study conducted in 2004, Kelly et al. examined the compatibility of arterial and venous HCO_3^- values in patients who require blood gas analysis for metabolic or respiratory reasons and stated that venous HCO_3^- value could be calculated in place of arterial HCO_3^- (12). In a similar study, usability of venous blood samples in place of arterial blood samples in terms of PH, PCO2, HCO3- in cases of acute respiratory failure followed by mechanical ventilation in intensive care unit was examined and they found out that even in acute respiratory failure cases, venous blood samples can be used instead of arterial PH, PCO2 and HCO3- values (13).

In another study conducted in Turkey, correlation between PH, PO2, PCO2 and HCO3- values in arterial, vein and capillary blood samples in patients undergoing pediatric intensive care was examined and as a result, it was suggested that in the cases where follow up of regular blood pressure measurement and PO2 wasn't needed, capillary and venous blood gas samples could be alternatives to arterial samples (14).

In our study, when the correlation values of arterial and venous blood gases were examined, it was found that there is a very strong positive correlation between PH, HCO_3^-values. Venous HCO_3^- value was found to be on average 2.8 mmol/L (22.7-19.9 = 2.8) higher than arterial HCO_3^-. These values we have found are consistent with similar studies in the literature (15,16). Therefore, in accordance with the literature, we reached the conclusion that venous PH can be used in place of arterial PH and venous HCO_3^- values can be used instead of arterial HCO_3^-values.

Likewise, we have found that there was a very strong positive correlation between lactate and BE_{ecf} values. It shows that in emergency patients, venous blood lactate measurements could be used instead of arterial lactate measurements and venous blood BE_{ecf} measurements could be used instead of BE_{ecf} measurements. Venous blood samples can be used in substitution for arterial blood specimens to guess the arterial hyperlactacidemia and in situations where we need to assess base excess and deficit in patients, attended to emergency, in whom metabolic disorder is suspected.

In our study, a strong positive correlation between the PCO_2 values was detected. With these results we obtained, although we do not statistically support the use of venous PCO_2 value instead of arterial PCO_2 value, we think that venous PCO_2 value could give an idea about the assessment of respiratory functions.

Mild positive correlation was detected between the arterial-venous PO_2 and SaO_2 values. There aren't any reported findings in previous similar studies about the PO_2 and SaO_2. Reason

of the mild correlation between arterial and venous PO_2 and SaO_2 we have determined may be the effects of increased tissue oxygen uptake, decreased cardiac output, right-left shunts, low hemoglobin level etc. on venous oxygen pressure (17). In addition, rapid changes in concentrations during the time taken to acquire arterial and venous blood gas samples may also be the reason for the moderate correlation we have detected.

In the study we have conducted, in the cases where venous PO_2 value is higher than 40 mmHg, we have found that arterial SaO_2 value is higher than 90%. We have determined that arterial blood gas values are closer to normal limits in cases where venous PCO_2 values are lower than 40 mmHg. Therefore, we think that in cases where venous PO_2 values are higher than 40 mmHg and venous PCO_2 value is lower than 40 mmHg, arterial blood gas values can be considered to be within normal limits.

Limitations of the Study

The research didn't specifically include a patient spectrum with a certain disease. However, we consider it a limitation that we did not record the statistics of the clinical diagnosis of intubated patients in detail. Further, although the blood samples were collected just before the initiation of the oxygen therapy in the emergency room, most of the patients probably received nasal oxygen during transportation as they were brought by 112 ambulances. That could have affected the blood gas parameters of the patients.

CONCLUSION

Venous blood gas can be used in substitution for arterial blood gas in patients with suspected metabolic disorders. In assessment and close follow-up of respiratory functions, arterial blood gas is preferred. However, venous blood gas values may reduce the need for arterial blood gas when the information VBG gives about the respiratory functions and patient's clinic were evaluated.

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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 the Hatay Mustafa Kemal University, Medical Faculty Clinical Research Ethics Committee for this study with date 6.5.2015 and number 03, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: YKE, AK, Design: YKE, AK, Supervising: AK, Financing and equipment: YKE, AK, Data collection and entry: YKE, Analysis and interpretation YKE, AK, Literature search: YKE, AK, Writing: YKE, AK, Critical review: AK.

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Local and systemic side effects of the coronanovac vaccine

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Abstract

Objective: Vaccines are biological products that provide protection against diseases by stimulating the immune system. Our aim in this study is to examine local and systemic side effects after inactivated coronavirus vaccination. In addition, when these side effects started, how long they lasted and their effect on daily life were evaluated.

Methods: 224 healthcare workers who met the study criteria and were vaccinated against coronavirus in Adana City Training and Research Hospital were included in the study. A questionnaire prepared by us was filled in for these patients in which we inquired about the local and systemic side effects of the vaccine, the onset of side effects, their duration, whether they affect daily life, the need for drug use, and some demographic data. The survey results were evaluated with the SPSS statistical program. Local and systemic side effects were evaluated according to age, gender, allergy status, onset time, duration of effect, effect on daily life, and use of medical treatment.

Results: At least one side effect was observed in 73.2% of 224 patients, while no side effects were observed in 26.8%. Being under the age of 35, being female, and being allergic increased the side effects (p:0.0027, p:0.001, p.0.031). In the logistic regression analysis, it was seen that being a woman was more effective (p.0.002). The most common local side effect was at the injection site pain was 76.2%, the most common systemic side effect was weakness 40.9%. 85.6% of local side effects and 70.4% of systemic side effects were seen in the first 24 hours. 71.3% of local side effects and 70.1% of systemic side effects lasted less than 24 hours.

Conclusion: Inactivated covid-19 vaccine causes side effects in the majority of patients.In the otorhinolaryngology outpatient clinic, attention should be paid to the side effects of the coronovac vaccine in female patients under the age of 35 who have allergies.

Keywords: Vaccine, Side Effect, Coronovac, Allergy, Pain

INTRODUCTION

A number of unexplained cases of pneumonia were reported in December 2019 in Wuhan, China. The Chinese Centers for Disease Control and Prevention (CDC) identified a new type of B-coronavirus in the sample obtained from a throat swab on January 7th, 2020 (1). This virus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) by the World Health Organization (WHO) (2). SARS-COV-2 spread to countries such as Germany, Italy, Spain, and America in February 2020, and affected the entire world over time and the WHO announced SARS-CoV2 as a pandemic on March 11th, 2020, when Turkey announced that it had its first official case of coronavirus (3,4).

Coronaviruses are positive-polar, enveloped, and single-stranded RNA viruses with rod-like protrusions on their surface. According to their genomic structures, coronaviruses are divided into alpha (α), beta (β), gamma (ɣ) and delta (δ) subgroups. SARS-CoV-1, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 viruses are in the coronaviruses subgroup (I). It has four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). These proteins are very important in vaccine and drug studies in the treatment of COVID-19 (5).

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Vaccines are biologic products that protect against disease by stimulating the immune system. In vaccination, it is desired that the person's body creates immunity by encountering the agent, but not contracting the disease. The effect of the vaccine occurs when the immune system responds to the weakened or killed microorganism or parts thereof. Thus, when the person encounters the disease agent, the immune system will develop a rapid response by remembering the factor and the disease will pass before the disease occurs or with a mild picture. Vaccines are divided into two groups as live active and inactive vaccines (6). Local side effects such as pain, redness, burning, itching, rash, ulceration, abscess can be seen after vaccination, as well as systemic side effects such as fever, anaphylactic reaction, lymphadenopathy, convulsion, encephalopathy, weakness, nausea, vertigo, vomiting and thrombocytopenia. In Turkey in January 2021, inactivated Covid-19 vaccine (CoronaVac) vaccination started. First of all, healthcare workers were vaccinated (7).

Our aim in this study is to examine local and systemic side effects after inactivated coronavirus vaccination. In addition, when these side effects started, how long they lasted and their effect on daily life were evaluated.

METHODS

This study was conducted between February 1, 2021 and April 1, 2021. The study included 450 healthcare workers (doctor, nurse, assistant health personnel, technician) who were vaccinated against coronavirus at Adana City Training and Research Hospital. 125 patients who did not complete the questionnaire and 73 patients who wanted to withdraw from the study were excluded from the study. 28 patients under the age of 18 and over the age of 85 were excluded.

The questionnaire form prepared by us and containing the following questions was distributed to the patients. The patients filled out the questionnaire in the company of one of the researchers. Those who were illiterate and did not fully understand the questions in the questionnaire received support from the researchers. Volunteers completed the questionnaire containing the following information 1 week after the vaccination in the examination room.

1. Age, sex, chronic disease history, history of allergies, pregnancy status, breastfeeding, COVID-19 disease, whether antibodies were checked for COVID-19 and PCR positivity.

2. Local side effects: pain, redness, burning, stiffness, swelling, itching, bruising, rash.

3. Systemic side effects: weakness, headache, myalgia, fever, chills-chills, metallic taste in the mouth, nausea, dizziness, runny nose, numbness in legs and arms, sore throat, diarrhea, palpitations, cough, sweating, nasal congestion, chest pain, shortness of breath, blurred vision, vomiting, smell disorder, and anaphylactic shock.

4. Whether local and systemic side effects started in the first 24 hours.

5. Whether local and systemic side effects lasted longer or shorter than 24 hours.

6. Whether side effects affected daily life, if so, to what extent (such as eating, going to work, studying, doing housework, sleep patterns).

7. Whether the patient presented to the hospital due to side effects, whether they received medical treatment, the symptoms that caused a hospital visit, and symptoms requiring medical treatment.

Informed voluntary consent of all patients participating in the study was obtained.

Statistical analysis

All data were evaluated using the SPSS: 2.2 statistical program. Student's t-test, the Chi-square test, and Fisher's exact test were used for statistical analysis. Student's t test was used to evaluate whether the difference between the 2 dependent and independent groups was significant. Chi-square test was used to test the relationship between variables. In categorical data analysis, as an alternative to chi-square for small samples ($n<20$). Fisher Exact test was used to classify categorical data and examine the relationship between two types of classification.

RESULTS

A total of 224 patients were included in the study. One hundred sixty-four (73.2%) of 224 patients had at least one side effect, and 60 (26.8%) had no side effects (Figure 1).

The average age of the patients was 36.6 years.The rate of side effects was higher in those aged under 35 years compared with those aged over 35 years ($p = 0.027$). The rate of side effects was higher in women than in men ($p = 0.001$). Side effects were more common in those with allergies ($p = 0.031$) (Table 1).

Table 1: Demographic data of the patients

		Side effect (-) (n:60)		Side effect (+) (n:164)		Total (n:224)		p
Age (mean±sd) (min-max)		38.70±12.62 (23-77)		35.94±12.27 (22-84)		36.68±12.40 (22-84)		0.140[a]
		n	%	n	%	n	%	
Age n (%)	<35	20	(33.3)	82	(50)	102	(45.5)	0.027[b]
	≥35	40	(66.7)	82	(50)	122	(54.5)	
Gender n (%)	Male	25	(41.7)	33	(20.1)	58	(25.9)	0.001[b]
	Female	35	(58.3)	131	(79.9)	166	(74.1)	
Allergy n (%)	Yes	7	(11.7)	41	(25)	48	(21.4)	0.031[b]
	No	53	(88.3)	123	(75)	176	(78.6)	
Chronic disease n (%)	Yes	11	(18.3)	30	(18.3)	41	(18.3)	1.00[b]
	No	49	(81.7)	134	(81.7)	183	(81.7)	
Did you have Covid19 disease before the Covid19 vaccine? n (%)	Yes	5	(8.3)	24	(14.6)	29	(12.9)	0.214[b]
	No	55	(91.7)	140	(85.4)	195	(87.1)	
Was it PCR (+) when we had Covid 19 disease? (n:29) n (%)	Yes	5	(100)	19	(79.2)	24	(82.8)	0.358[c]
	No	0	(0)	5	(20.8)	5	(17.2)	
Have you checked antibodies for Covid19 before Covid19 vaccine? n (%)	Yes	8	(13.3)	19	(11.6)	27	(12.1)	0.722[b]
	No	52	(86.7)	145	(88.4)	197	(87.9)	
Are you breastfeeding? n (%)	Yes	1	(1.7)	2	(1.2)	3	(1.3)	1.00[c]
	No	59	(98.3)	162	(98.8)	221	(98.7)	

a: Student's t test, b: Chi-Square test, c: Fisher Exact test

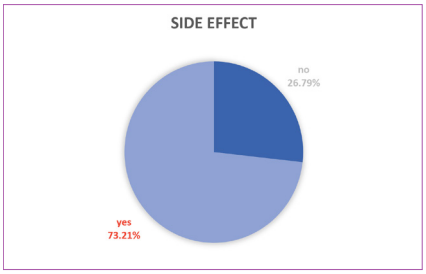

Figure 1. Incidence of side effects in patients

When age, gender and presence of allergy were evaluated together and multiple logistic regression analysis was performed, it was found that being female was 2.769 times more risky for those with side effect (odds ratio. 2.769) (Table 2).

The most common local side effect was pain at the injection site (76.2%). Other local side effects and their frequency are shown in Table 3. %64 of pain side effect started in the first 24 hours and %48.8 lasted less than 24 hours. Most of the local side effects started in the first 24 hours and lasted less than 24 hours (Table 3).

Table 2: Effect of age. gender and allergy on side effects

	Odds Ratio	95% C.I. for Odds Ratio		
		Lower	Upper	p
Age (<35)	1.891	0.999	3.581	0.050
Gender (female)	2.769	1.442	5.317	0.002
Allergy (yes)	2.324	0.955	5.657	0.063
Constant	0.890			0.704

p: Multiple Logistic Regression

Table 3: Frequency, onset time and duration of local side effects

			Time for side effects to start				Duration of Side Effects			
	Total (n:164)		First 24 hours		After 24 hours		Less than 24 hours		More than 24 hours	
	n	%	n	%	n	%	n	%	n	%
Pain	125	76.2	105	64.0	20	12.2	80	48.8	45	27.4
Redness	14	8.5	13	7.9	1	0.6	13	7.9	1	0.6
Burning	11	6.7	11	6.7	0	0.0	11	6.7	0	0.0
Stiffness	10	6.1	9	5.5	1	0.6	8	4.9	2	1.2
Swelling	6	3.7	5	3.0	1	0.6	6	3.7	0	0.0
İtching	6	3.7	4	2.4	2	1.2	4	2.4	2	1.2
Bruise	1	0.6	1	0.6	0	0.0	1	0.6	0	0.0
Rash	1	0.6	1	0.6	0	0.0	1	0.6	0	0.0

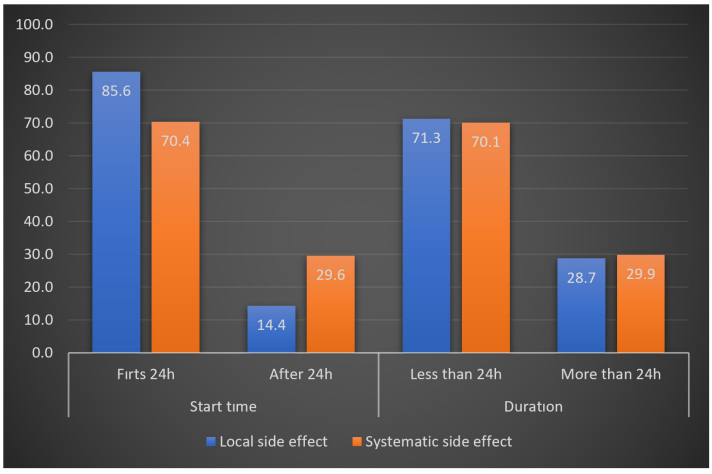

Figure 2. Onset time and duration of local and systemic side effects

The most common systemic side effect was weakness with a rate of 67 (40.9%). 55 weakness started in the first 24 hours and 38 lasted less than 24 hours. Most of the systemic side effects were seen in the first 24 hours and the symptom duration was less than 24 hours. The onset time and duration of other systemic side effects are shown in Table 4.

Anaphylactic reaction and lymphadenopathy were questioned but not observed in any patients. Other symptoms were redness in the eyes low back pain and change in the menstrual cycle in one person.

Table 4: Frequency, onset time and duration of systemic side effects

			Time for side effects to start				Duration of Side Effects			
	Total (n:164)		First 24 hours		After 24 hours		Less than 24 hours		More than 24 hours	
	n	%	n	%	n	%	n	%	n	%
Weakness	67	40.9	55	33.5	12	7.3	38	23.2	29	17.7
Headache	50	30.5	35	21.3	15	9.1	41	25.0	9	5.5
Myalgia	47	28.7	31	18.9	16	9.8	21	12.8	26	15.9
Fever	26	15.9	23	14.0	3	1.8	22	13.4	4	2.4
Chills and chills	16	9.8	12	7.3	4	2.4	12	7.3	4	2.4
Metallic taste in the mouth	14	8.5	12	7.3	2	1.2	9	5.5	5	3.0
Nausea	12	7.3	11	6.7	1	0.6	12	7.3	0	0.0
Vertigo	12	7.3	8	4.9	4	2.4	12	7.3	0	0.0
Runny nose	11	6.7	6	3.7	5	3.0	9	5.5	2	1.2
Numbness in the legs and arms	10	6.1	7	4.3	3	1.8	10	6.1	0	0.0
Sore throat	10	6.1	5	3.0	5	3.0	7	4.3	3	1.8
Diarrhea	9	5.5	5	3.0	4	2.4	5	3.0	4	2.4
Palpitation	9	5.5	5	3.0	4	2.4	8	4.9	1	0.6
Cough	9	5.5	5	3.0	4	2.4	6	3.7	3	1.8
Sweating	9	5.5	3	1.8	6	3.7	6	3.7	3	1.8
Nasal congestion	8	4.9	4	2.4	4	2.4	5	3.0	3	1.8
Chest pain	4	2.4	1	0.6	3	1.8	2	1.2	2	1.2
Shortness of breath	3	1.8	2	1.2	1	0.6	3	1.8	0	0.0
Blurred vision	3	1.8	2	1.2	1	0.6	3	1.8	0	0.0
Vomiting	1	0.6	1	0.6	0	0.0	1	0.6	0	0.0
Smell disorder	1	0.6	0	0.0	1	0.6	0	0.0	1	0.6

The majority (85.6%) of the local side effects and 70.4% of systemic side effects were seen in the first 24 hours. Most (71.3%) of local side effects and 70.1% of systemic side effects lasted 24 hours or less (Figure 2).

Pain was the most common local side effect affecting daily life ($p<0.001$).In systemic side effects, it was observed that weakness, headache, muscle pain, fever, chills-chills, metallic taste in the mouth, nausea, dizziness, runny nose, sore throat, diarrhea, palpitations, cough, nasal congestion, and chest pain affected daily life ($p<0.05$). The most affecting systemic side effect on daily life was weakness ($p<0.001$) (Table 5).

Two (1.2%) of the 164 patients who had side effects went to a hospital, and 31 (18.9%) received medical treatment. The daily life of 42.7% of the patients was not affected by these side effects (Table 6). The daily life of the patients was affected mildly at a rate of 38.4%, moderately at 16.65%, and severely at 2.4% according to the volunteers' answers (Figure 3).

Patients with pain, shortness of breath, numbness in the arms and legs, and blurred vision were admitted to the hospital.

The patients mostly received medical treatment due to pain at the injection site, headache, and weakness (Figure 4)

DISCUSSION

In our study, at least one side effect was observed in 164 (73.2%) of 224 patients. The rate of side effects was found to be significantly higher in women, those with a history of allergies, and those aged under 35 years. The most common local side effect was pain, and the most common systemic side effect was weakness. The majority (85.6%) of local side effects and 70.4% of the systemic side effects were seen in the first 24 hours. Most (71.3%) of local side effects and 70.1% of the systemic side effects lasted less than 24 hours. Of the patients with side effects, 1.2% went to the hospital, 18.9% received medical treatment due to these side effects, and the daily life of 57.3% was affected. The symptom that most affected daily life was weakness. The symptoms that caused patients to attend the hospital were usually pain, shortness of breath, numbness in the arms and legs, and blurred vision.

Against the SARS-COV-2 virus, DNA- and RNA-based formulas, viral episodes containing recombinant subunits, adenovirus-based vectors, and attenuated inactivated virus vaccines have been studied (8). Weakened inactivated virus vaccines are a traditional method used in safe and effective vaccine studies as in polio and influenza virus vaccines (9,10). A 2 µg/dose of BBIBP (Inactive SARS-Cov2 Vaccine) was used to protect against SARS-CoV-2 in mice, rats, guinea pigs, rabbits, and non-human primates. Vaccine studies using CorV (inactivated) showed that high-efficacy protection was provided and it was concluded that inactivated virus vaccines should be evaluated in further clinical studies (11).

Shengli et al. evaluated the safety and immunogenicity of the inactivated SARS-CoV-2 vaccine candidate BBIBP-CorV in humans. A randomized, double-blind, placebo-controlled, phase 1/2 trial was conducted at the CDC in Shangqiu City Liangyuan District in Henan Province, China. At least one

Table 5: The effect level of side effects on daily life

	Effect on Daily life											
	No (n:70)		Yes (n:94)			Mild (n:63)		Moderate (n:27)		Severe (n:4)		
	n	%	n	%	p	n	%	n	%	n	%	p
Pain	58	82.9	67	71.3	<0.001	46	73.0	17	63.0	4	100	0.115
redness	6	8.6	8	8.5	0.235	7	11.1	1	3.7	0	0.0	0.633
Burning	4	5.7	7	7.4	0.209*	4	6.3	3	11.1	0	0.0	0.742
Stiffness	6	8.6	4	4.3	1.000*	3	4.8	1	3.7	0	0.0	0.688
Swelling	3	4.3	3	3.2	0.697*	2	3.2	1	3.7	0	0.0	0.965
İtching	2	2.9	4	4.3	0.241*	2	3.2	2	7.4	0	0.0	0.706
Bruise	0	0.0	1	1.1	0.420*	1	1.6	0	0.0	0	0.0	0.656
Rash	0	0.0	1	1.1	0.420*	1	1.6	0	0.0	0	0.0	0.656
Weakness	9	12.9	58	61.7	<0.001	37	58.7[a]	19	70.4[a]	2	50[a]	<0.001
Headache	4	5.7	46	48.9	<0.001*	27	42.9[a]	17	63[a]	2	50[a]	<0.001
Abdominal pain	8	11.4	39	41.5	<0.001	25	39.7[a]	12	44.4[a]	2	50[a]	<0.001
Fever	4	5.7	22	23.4	<0.001*	12	19.0[a]	8	29.6[a]	2	50[a]	0.004
Chills and chills	0	0.0	16	17.0	<0.001*	8	12.7[a]	7	25.9[a]	1	25[a]	0.001
Metallic taste in the mouth	2	2.9	12	12.8	0.001*	9	14.3	3	11.1	0	0.0	0.104
Nausea	2	2.9	10	10.6	0.005*	7	11.1	3	11.1	0	0.0	0.233
Vertigo	3	4.3	9	9.6	0.031*	6	9.5	2	7.4	1	25	0.355
Runny nose	1	1.4	10	10.6	0.001*	6	9.5	3	11.1	1	25	0.075
Numbness in the legs and arms	3	4.3	7	7.4	0.099*	6	9.5	1	3.7	0	0.0	0.527
Sore throat	1	1.4	9	9.6	0.002*	4	6.3	4	14.8[a]	1	25[a]	0.033
Diarrhea	0	0.0	9	9.6	<0.001*	2	3.2	6	22.2[ab]	1	25[ab]	<0.001
Palpitation	1	1.4	8	8.5	0.005*	4	6.3	3	11.1	1	25	0.075
Cough	1	1.4	8	8.5	0.005*	3	4.8	5	18.5[ab]	0	0.0	0.010
Sweating	3	4.3	6	6.4	0.171*	1	1.6	5	18.5[ab]	0	0.0	0.011
Nasal congestion	0	0.0	8	8.5	0.001*	3	4.8	3	11.1[a]	2	50[ab]	<0.001
Chest pain	0	0.0	4	4.3	0.030*	0	0.0	2	7.4[ab]	2	50[abc]	<0.001
Shortness of breath	0	0.0	3	3.2	0.073*	3	4.8	0	0.0	0	0.0	0.179
Blurred vision	1	1.4	2	2.1	0.574*	1	1.6	0	0.0	1	25[abc]	0.006
Vomiting	0	0.0	1	1.1	0.420*	1	1.6	0	0.0	0	0.0	0.656
Smell disorder	0	0.0	1	1.1	0.420*	1	1.6	0	0.0	0	0.0	0.656

p: Chi-Square test *Fisher Exact test; represents the highest rate (a: none, b: mild, c: moderate) p<0.05

side-reaction was reported in the first 7 days of vaccination in 29% of vaccine recipients. The most common side effects were fever and pain at the injection site. All side effects were mild or moderate. No serious side-events were reported within 28 days of vaccination (12). In our study, we saw at least one side effect at a higher rate (73.2%) than Shenglis' study. The difference between the studies in terms of the frequency of side effects may be because the patients had different genetic structures in different countries, different age groups, and the humoral-cellular immune response varies between races. Similar to Shengli's study, the most common local side effect in our study was pain. We evaluated the short-term side effect results after vaccination. Different from Shengli's study, we questioned the side effects affecting daily life. It was observed that symptoms such as fever, muscle pain, diarrhea, nasal congestion, sore throat, chills-chills, chest pain, cough, headache, blurred vision, and weakness affected daily life significantly.

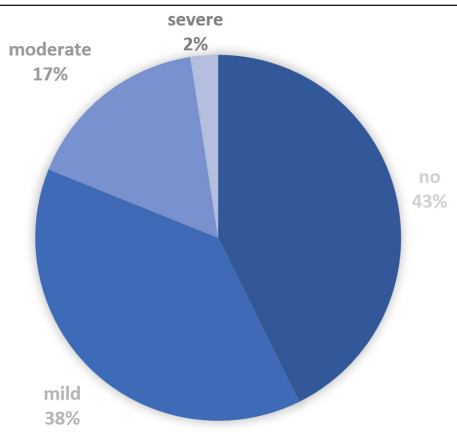

Figure 3. Affecting the daily life of the patients

Table 6: Patients with side effects. going to the hospital, receiving medical treatment and affecting their daily life

		n	%
Going to the hospital	yes	2	1.2
	no	162	98.8
Medical treatment	yes	31	18.9
	no	133	81.1
Effecting daily life	no	70	42.7
	mild	63	38.4
	moderate	27	16.5
	severe	4	2.4

As of December 23rd, 2020, the first dose of the Pfizer-BioNTech COVID-19 vaccine was administered, as reported in the United States, and 4393 (0.2%) side-events were reported after receiving the Pfizer vaccine. Ricardo et al. reported that 25 of 175 people who developed allergic reactions experienced anaphylaxis. In anaphylaxis, symptoms result in rapid onset, usually within minutes, and typically severe general itching, urticaria, angioedema, hypotension or difficulty breathing were seen. Ninety percent of anaphylactic reactions occurred in women (13). In addition to screening contraindications and precautions before administering COVID-19 vaccines, vaccination areas should have the necessary supplies to manage anaphylaxis, implement post-vaccination observation periods, and treat people experiencing signs and symptoms of anaphylaxis promptly with an intramuscular injection of adrenaline. In our hospital, a separate building was designated as a vaccination polyclinic and anesthesiologists and technicians were assigned in the vaccination areas with emergency intervention equipment due to the risk of developing anaphylactic reactions. In our study, we did not see any anaphylactic reactions in any of our patients. However, we found that the side effects were more common in women, as in Ricardo's study. Female sex

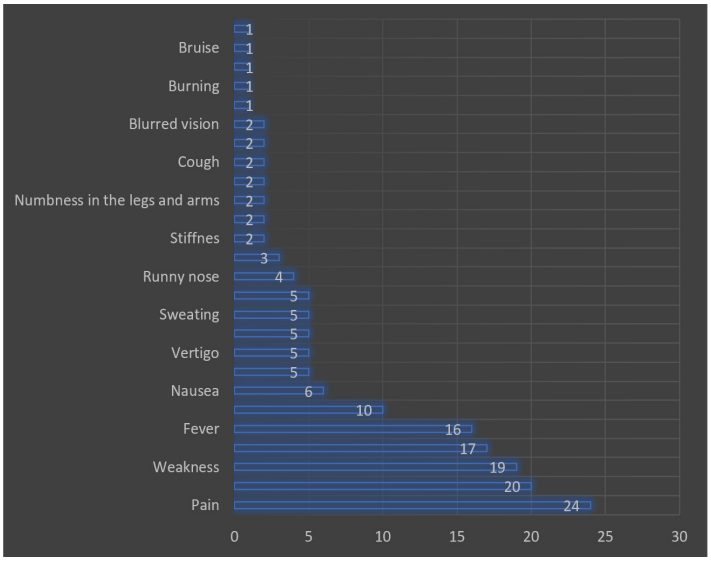

Figure 4. Side effect profiles of patients using medical treatment

significantly increases the incidence of side effects. Few studies have evaluated the effect of sex steroids on immune responses to vaccines. Studies are showing that estrogen mediates more antibody production in women (14). We think that sex hormones effecting the immune response may be important here.

Pfizer/BioNTech and Moderna vaccines are United States Food and Drug Administration (FDA)-approved vaccines that produce an immune response against SARS-COV-2, although some allergic symptoms have been reported with both vaccines. Fever, tiredness, headache, myalgia, nausea, vomiting, itching, chills and joint pain: as well as rarely anaphylactic shock, including pain, redness or swelling may be observed after the second dose (15). In our study, in the inactivated SARS-CoV-2 vaccine produced by Sinovac, similar side effects occurred with these vaccines. However, differently, in our study, we found that 1.2% of the patients with side effects went to the hospital and 18.9% received medical treatment because of these side effects. The symptoms that led the patients to go to the hospital were generally pain, shortness of breath, numbness in the arm and leg, and blurred vision. Patients should be alert to these symptoms, and perhaps medical treatment should be started earlier.

Many factors influence humoral and cellular vaccine responses in humans. These include intrinsic host factors, perinatal, and extrinsic factors. Age is very important in host factors. Many studies have stated that cellular and humoral immune response is higher in young people and decreases with age (16). In our study, we divided the age groups and we found that the side effects were significantly higher in patients aged under 35 years. We could not find a study separating vaccine side effects according to age groups in the literature. Patients aged under 35 years, in particular, should pay more attention in terms of vaccine side effects.

Some studies are reporting rare cases such as supraclavicular reactive lymphadenopathy (LAP), Bell's paralysis after the COVID-19 vaccine. It is important to question the vaccines of patients who present to the head and neck clinic with these symptoms (17,18). In our study, rare side effects such as redness of the eyes, low back pain, and a changed menstrual cycle were observed.

Limitation: We performed our study in a single center with a limited number of volunteers. In the future, multi-center prospective studies with a larger number of volunteers are needed.

CONCLUSION

Inactivated Covid-19 vaccine causes side effects in the majority of patients. In the otorhinolaryngology outpatient clinic, attention should be paid to the side effects of the CoronaVac vaccine in female patients under the age of 35 who have allergies.

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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 Adana City Training and Research Hospital Clinical Research Ethical Committee with date 13012021 and number 1257, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept , AK, SOE, BT, Design , AK, AAÖ OG , Supervision , OG, Materials , AK, SOE, Data collection &/or processing , AK, SOE, Analysis and/or interpretation ,AK, BT, Literature search , AK, AAÖ, Writing , AK, SOE, BT, Critical review , AK, SOE, BT, OG, AAÖ

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Evaluation of family physicians' knowledge level, attitudes and behaviours on Asthma, Chronic obstructive pulmonary disease

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Abstract

Objective: The most common complaints about chest diseases that we encounter in family practice centers are of asthma and Chronic obstructive pulmonary disease (COPD). Thus, it was aimed to evaluate the attitudes, behaviors and knowledge level of family physicians on asthma and COPD.

Methods: Our research is a descriptive cross-sectional study. Our study was conducted between September-November 2019 by including family physicians, family physician research assistants and family physician specialists. 387 physicians participated in the study. The 35-question survey in our study consists of sociodemographic data and consists of questions aiming to evaluate the knowledge level, attitudes and behaviors on asthma-COPD.

Results: A total of 387 family physicians including 251 family physicians, 31 family physician specialists and 105 family physician research assistants were included in this study. When the rates of using the spirometry device in suspected asthma-COPD, were compared, the difference between family medicine research assistants and family physicians was found to be statistically significant ($p<0.001$). When the rates of answer to the "Would you give pneumococcal and influenza vaccines to your patients over 65 years of age?" question were compared, the difference between family medicine specialist and family medicine research assistants and family physicians was found to be statistically significant ($p<0.001$)

Conclusion: According to our study, it was seen that family physicians do not possess sufficient knowledge about asthma-COPD and there are severe shortcomings in diagnosis and treatment stages. Active, applied training seminars should be given importance in primary care, practical guides that physicians can easily reach and communication channels with chest diseases specialists should be increased.

Keywords: Family Practice, Knowledge, Attitude, Asthma, COPD

INTRODUCTION

Chronic diseases are important causes of mortality and morbidity in Türkiye and in the world. According to studies conducted recently, 305.467 (71%) of the 430.459 deaths in Türkiye were caused by chronic diseases. Death from respiratory system diseases is 34,211 (7.9%). Majority of the chronic causes of respiratory system diseases (65%) are chronic airway diseases [asthma, chronic obstructive pulmonary disease (COPD)]. However, it is thought that the level of knowledge of patients, patient relatives and health personnel about the risk factors, findings, diagnosis and treatment of chronic airway diseases is not sufficient (1).

Asthma is a heterogeneous group of diseases in which many cells and cell products in the body play a role, consisting of chronic inflammation and obstruction in the airways. Asthma is estimated to affect a pproximately 300 million people worldwide. This number is approximately 3.5 million people in Türkiye. Chronic airway inflammation and bronchial hyperresponsiveness

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cause wheezing, shortness of breath, chest tightness and/or coughing spells, especially at night or in the morning. Symptoms and airflow limitation often resolve spontaneously or with treatment. Asthma is a chronic disease that poses a high-cost burden for the patient or society. But if the disease is not treated, it causes higher costs to society (2).

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable disease characterized by persistent airflow limitation and respiratory symptoms, often due to airway and/or alveolar damage caused by exposure to harmful particles or gases. The most important cause of COPD formation is being an active cigarette/tobacco product smoker or being passively exposed to cigarette smoke. In some studies, it was reported that the number of patients with COPD was 384 million in 2010, and the global prevalence was found to be 11.7%. Worldwide, approximately 3 million people die each year due to COPD. It is estimated that the prevalence of COPD will increase in the next 30 years, and deaths from COPD and related causes will exceed 4.5 million annually until 2030, due to the increasing use of cigarettes in developing countries and the increase in the elderly population in developed countries (3). Since this disease has a high rate of mortality and morbidity, the knowledge, attitude and behavior of family physicians, who are the first pillar of the health system, in the diagnosis and treatment process is critical. Like many chronic diseases, patients with COPD and asthma also apply to primary health care centers to benefit from health services (4).

There have been significant changes in the health system in Türkiye and the importance of family medicine in primary healthcare services is increasing day by day. Family physicians are the first and most frequently see patients in the provision of health services. Asthma and COPD are the most common diseases we encounter in complaints about chest diseases that come to family medicine. The study will make important contributions to asthma and COPD. It will be useful in closing the lack of education and raising awareness. For this reason, in our study, it was evaluated the level of knowledge, attitudes and behaviors of family physicians in terms of asthma and COPD.

METHODS

This study named the evaluation of knowledge levels, attitudes and behaviors about asthma and COPD in family physicians, was conducted between September and November 2019 by including family physicians, family medicine research assistants and family medicine specialists. The population of our cross-sectional and descriptive study consists of approximately 30000 family physicians working as family physicians in Turkey. When the sample size is calculated based on a 5% margin of error and 95% confidence interval and a frequency value of 0.50 used for cases where the prevalence is unknown, it turns out to be 380. Considering the possibility of data loss, it is reached 390 people. A total of 387 physicians participated in the study. Participants mostly participated in the research from Kahramanmaraş and its surroundings. The interviews were conducted face-to-face by the researcher or questionnaires were applied over the internet via social media. Of the questionnaires, 186 were filled in face to face and 201 were completed online. The physicians who participated in the study were told that the questionnaire was designed for scientific research, it was not an evaluation that had the quality of an examination, and it was a study in which personal information was not obtained.

In the study, a questionnaire consisting of 35 questions was used, which was formed because of the literature review, which evaluated the knowledge levels, attitudes and behaviors of family physicians about asthma-COPD. The 1–8, among questions in the content of the 35-question survey are based on the sociodemographic data of the participants. Questions 9–15, 19, 21–29, 35 are measuring the asthma-COPD knowledge level of family physicians; Questions 17, 18, 30, 31 are attitude questions; 20, 32-34 the questions consist of behavioral questions. Each question questioning the level of asthma and COPD knowledge was accepted as 1 point, and knowledge scores were obtained, with a maximum of 8 points for asthma and a maximum of 9 points for COPD. Ethics committee approval was obtained with the date 04.09.2019 and number 09.

Statistical analysis was performed using the SPSS 19.0 for Windows (SPSS, Inc.; Chicago, USA) package program. Descriptive values are given as number (n), percentage (%), mean (mean), standard deviation (SD), median (median). Pearson chi-square and Fisher tests were used to compare categorical variables. Continuous variables were compared with nonparametric tests (Mann-Whitney U test and Kruskal-Wallis test) since they did not fit the normal distribution according to the normality assessment made by Kolmogorov-Smirnov and Shapiro-Wilk tests. The effects of different predictors determined by pairwise comparisons in predicting asthma and COPD knowledge scores were evaluated with multivariate logistic regression analysis. The Hosmer-Lemeshow test was used to evaluate the model fit. Statistical significance level was set at $p<0.05$.

RESULTS

A total of 387 family physicians, including 251 family physicians, 31 family medicine specialists and 105 family medicine research assistants, were included in our study. The mean age of the physicians participating in our study was 37.06±9.57 years, and their length of service was 11.68±9.36 years. The mean ages were 40.76±9.31 for family physicians, 36.23±7.13 for family medicine specialists, and 28.47±3.04 for family medicine research assistants. The average length of

Table 1. Comparison of descriptive characteristics of study groups

	Working Groups						Total		p*
	Family Physician		Family Medicine Research Assistant		Family Medicine Specialist				
	n	%	n	%	n	%	n	%	
Gender									
Male	154	61.4	32	30.5	13	41.9	199	51.4	<0.001
Female	97	38.6	73	69.5	18	58.1	188	48.6	
Marital status									
Married	207	82.5	66	62.9	26	83.9	299	77.3	<0.001
Single	43	17.1	38	36.2	4	12.9	85	22.0	
Other	1	0.4	1	1.0	1	3.2	3	0.8	
Work Place									
City Center	207	82.5	103	98.0	24	77.4	334	86.3	<0.001
District	33	13.1	1	1.0	7	22.6	41	10.6	
Village-town	11	4.4	1	1.0	0	0.0	12	3.1	
Number of Patients per Day									
<20	32	12.7	66	62.8	11	35.5	109	28.2	0.003
20-49	123	49.0	26	24.8	8	25.8	157	40.5	
>50	96	38.2	12	11.4	12	38.7	121	31.3	
Number of Cigarettes per Day									
Not smoke	169	67.3	93	88.6	22	71.0	284	73.4	0.003
<10	35	13.9	6	5.7	2	6.5	43	11.1	
10-19	34	13.5	4	3.8	7	22.6	45	11.6	
20-29	10	4.0	2	1.9	0	0.0	12	3.1	
>30	3	1.2	0	0.0	0	0.0	3	0.8	

service is 15.00±9.28 years for family physicians, 10.71±7.04 years for family medicine specialists, and 3.97±4.16 years for family medicine research assistants.

The most studied place was the city center with 86.3%. 82.5% of family physicians, 98.1% of family medicine research assistants and 77.4% of family medicine specialists working in the city center. Of the physicians participating in the study, 40.6% mostly care for patients between the ages of 20-49. On the other hand, 49.0% of family physicians care for patients between the ages of 20-49. Family medicine research assistants deal with less than 20 patients a day, 62.9% of them. Family medicine specialists deal with more than 50 patients, 38.7% of them. When the physicians were asked about their smoking status, 73.4% of the physicians stated that they did not smoke (Table 1).

The comparison and statistical comparisons of the answers given by the study groups to the asthma information questions are given in Table 2. When the answers given to the questions 'What is the pathophysiological feature of asthma', 'Which is the most common physical examination finding in asthma', 'It is not a condition that increase the risk of asthma attack', 'Which is wrong about asthma treatment', a statistically significant difference was found according to the study groups. No statistically significant difference was found in the comparison of the answers given to the other information questions according to the study groups.

A comparison of the answers given by the study groups to the COPD information questions is given in Table 3. Because of the comparison of the answers given to each COPD information question according to the study groups, the statistical difference was found to be significant for each question.

Table 2. Comparison of the study groups' responses to asthma information questions

	Working Groups						p*
	Family Physician		Family Medicine Research Assistant		Family Medicine Specialist		
	n	%	n	%	n	%	
Pathophysiological feature of asthma							
Air confinement	27	10.8	5	4.8	1	3.2	0.009
Restriction	25	10.0	3	2.9	1	3.2	
Airway obstruction#	167	66.5	91	86.7	24	77.4	
Alveolar damage	26	10.4	4	3.8	5	16.1	
Interstitial fibrosis	6	2.4	2	1.9	0	0.0	
Asthma prevalence in Türkiye							
%2-6 #	48	19.1	29	27.6	4	12.9	0.076
%7-8	83	33.1	29	27.6	12	38.7	
%9-11	63	25.1	33	31.4	9	29.0	
%12-14	36	14.3	6	5.7	6	19.4	
%15-20	21	8.4	8	7.6	0	0.0	
It is not one of the personal factors in terms of asthma etiology?							
Cigarette #	80	31.9	34	32.4	7	22.6	0.053
Genetic	29	11.6	10	9.5	4	12.9	
Gender	85	33.9	23	21.9	8	25.8	
Obesity	45	17.9	32	30.5	12	38.7	
Atopy	12	4.8	6	5.7	0	0.0	
Which is not a clinical feature of asthma?							
Shortness of breath	10	4.0	0	0.0	0	0.0	0.184
Cough	12	4.8	2	1.9	0	0.0	
Weight loss #	207	82.5	95	90.5	30	96.8	
Wheezing	7	2.8	3	2.9	1	3.2	
Chest tightness	15	6.0	5	4.8	0	0.0	
Most common physical examination finding in asthma							
Wheezing and rhoncus #	203	80.9	102	97.0	30	96.8	0.008
Tachycardia	11	4.4	1	1.0	0	0.0	
İntercostal retraction	23	9.2	0	0.0	1	3.2	
Cyanosis	6	2.4	1	1.0	0	0.0	
Speech difficulties	8	3.2	1	1.0	0	0.0	
The most objective indicator of the presence and severity of asthma attack.							
İncrease in symptoms	68	27.1	28	26.7	5	16.1	0.209
Findings on physical examination	36	14.3	17	16.2	8	25.8	
Radiological findings	17	6.8	2	1.9	0	0.0	
Pulmonary function tests disorders #	122	48.6	56	53.3	18	58.1	
Eosinophil test	8	3.2	2	1.9	0	0.0	

Table 2. Comparison of the study groups' responses to asthma information questions

It is not one of the conditions that increase the risk of attacks in asthma?							
Pregnancy	46	18.3	4	3,8	2	6.5	<0.001
Smoking	15	6.0	0	0,0	1	3.2	
FEV1>70#	102	40.6	78	74,3	18	58.1	
Using high-dose rescue medication (>1 box per month)	50	19.9	17	16,2	9	29.0	
Rhinosinusitis	38	15.1	6	5.7	1	3.2	
Which is wrong about asthma treatment?							
Drugs used in the treatment of asthma are divided into two as controlling and reliever (symptom reliever).	23	9.2	0	0.0	0	0.0	0.001
Long-acting inhaled beta 2 agonists alone are currently the most effective control drugs #	69	27.5	43	41.0	15	48.4	
Inhaled steroids are currently the most effective anti-inflammatory drugs used in the treatment of persistent asthma.	53	21.1	17	16.2	3	9.7	
Rapid-acting inhaled beta 2 agonists are the drugs of choice for the prevention of exercise-induced bronchoconstriction.	22	8.8	4	3.8	4	12.9	
Patients who do not use inhaled steroids are at increased risk for remodeling and loss of lung function.	84	35.5	41	39.0	9	29.0	

n=frequency, %=column percentage, #correct answer, *Pearson chi-square test

Table 4 shows the comparison of the answers given by the physicians to the attitude questions. The rate of using the spirometry device in suspected asthma-COPD was the research assistants with the highest rate of 24.6% among all groups. There was a significant difference between the groups in terms of using the spirometry device ($p<0.001$). Because of the paired comparisons, it was seen that the difference was due to the difference between the family doctor and the research assistant. The group that gave the highest yes answer to the question "Would you give pneumococcal and influenza vaccines to your patients with COPD over 65 years of age" was research assistants with 90.5%. There is a significant difference between the groups ($p<0.001$). Because of the paired comparisons, it was seen that the difference was due to the differences between the family physician and the research assistant, and between the family physician and the specialist.

Table 5 shows the comparison of the answers given by the physicians to the questions measuring behavior. When asked "Can you give a practical explanation about how to use metered dose devices in patients," 44.4% of the physicians said "I sometimes tell." Looking at the working groups; 51.4% of family physicians said I sometimes tell, 37.1% of research assistants said I always tell, 48.4% of specialists said I sometimes tell. There is a significant difference between the groups ($p<0.001$). In the paired comparisons, it was seen that the difference was due to the difference between family physicians and research assistants. All physicians 45.5%, 36.7% of family physicians, 60.0% of research assistants and 67.7% of specialists answered yes to the question "Do you want a consultation from a pulmonologist in the diagnosis-treatment steps of asthma-COPD?" There is a significant difference between the groups ($p<0.001$). In the paired comparisons, it was seen that the difference was due to the differences between family physicians and research assistants, and between family physicians and specialists. To the question "Which resource do you usually use when prescribing medication for a patient with asthma-COPD?" 64.9% of the physicians' answers were asthma-COPD guidelines. Family physicians gave the answer 57.8%, family medicine research assistants 77.1%, and family medicine specialists 80.6% asthma-COPD guidelines. Only in terms of asthma-COPD guidelines there was a significant difference between the groups in terms of the resources used ($p<0.001$). In the paired comparisons, it was seen that the difference was between family physician-research assistant and family physician-specialist.

Each question questioning the level of asthma and COPD knowledge was accepted as 1 point, and knowledge scores were obtained with maximum points of 8 points for asthma and a maximum of 9 points for COPD. The mean asthma knowledge score was 4.32 ± 1.59 for all physicians, 3.98 ± 1.63 for family physicians, 5.03 ± 1.33 for research assistants, and 4.71 ± 1.07 for specialist family physicians. There is a significant difference between the groups ($p<0.001$). Because of the pairwise comparisons, it was seen that the difference was due to the differences between the family physician-research assistant and the family physician-family medicine specialist. The mean COPD knowledge score was 4.64 ± 1.85

for all physicians, 4.18±1.86 for family physicians, 5.44±1.49 for research assistants, and 5.61±1.61 for specialist family physicians. There is a significant difference between the groups ($p<0.001$). Because of the pairwise comparisons, it was seen that the difference was due to the differences between the family physician-family medicine research assistant and the family physician-family medicine specialist.

DISCUSSION

Asthma and COPD are disease groups that cause significant mortality and morbidity and are frequently referred to family medicine in primary care. These patients frequently apply to their family physicians both to have their prescribed medications prescribed and because of their active complaints. For these reasons, family physicians should approach this chronic disease group in a disciplined manner in terms of both diagnosis-treatment and prevention methods. While there are many studies on the approach to asthma and COPD in primary care in the world, we found few studies as a result of our literature review on this subject in Türkiye whereas primary care plays a very important role in the fight against asthma and COPD. In our study, it was aimed to evaluate the knowledge levels, attitudes and behaviors of family physicians about asthma-COPD.

Among the asthma knowledge evaluation questions, the participants gave the correct answer to the question of the pathogenesis of asthma with a rate of 72.9%. Looking at the literature, Ersu R. et al. in his research, similar results were obtained using our study; it was observed that physicians marked the question about the pathogenesis of asthma correctly at a rate of 83%-85% (5). However, it was observed that the pathogenesis information was at lower levels in older studies. In the study by Boyacı et al. on primary care physicians in Kocaeli in 2001, it was determined that the rate of correct answers to the question about the pathogenesis of the participants was 46% (6). Likewise, in the study by Çalıkoğlu et al. with general practitioners in 2001, this rate was found to be 33%, and it was suggested that physicians did not have sufficient knowledge on the definition and pathogenesis of asthma (7). This makes us think that the interest and awareness of physicians about asthma has increased over the years.

In studies conducted in Türkiye, the prevalence of asthma shows differences in adult and childhood age groups. According to a study, it has been shown that the prevalence of asthma varies between 5 and 10% in childhood and 2%-6% in adulthood (8). To the question asked about the prevalence of asthma in adults in Turkey, 32.0% of the physicians answered 7%-8% and 7.5% gave the answer of 15%-20%. When we look at other studies, we see that similar results are obtained (5). The low percentage of correct answers given by physicians to this question, we attribute due to regional differences in the prevalence rate and the possibility that its emphasis in adults may be overlooked. In the question asked family physicians about asthma risk factors, the correct answer rate is 31.3%, and we see that physicians have difficulty in distinguishing between personal and environmental factors in the etiology of asthma. The underlying causes of the development of a disease should be known very well. Because knowing the underlying causes well will guide us in the treatment and prevention of the disease.

When the asthma information questions are evaluated in general, the questions that family physicians give the correct answers are; Physical examination findings of asthma with 86.6%, asthma symptoms with 85.8%, and the pathophysiology of asthma with 72.9%. The other questions are marked correctly with low percentages as stated above. In a study conducted in Canada found that well-trained physicians are more likely to evaluate and manage patients with asthma (9). In a study conducted in Crete, a course was given to family physicians and their knowledge of asthma diagnosis and treatment was evaluated before and after the course. Although the family physicians' awareness of asthma increased after the course, it was determined that their level of knowledge about asthma diagnosis and treatment was insufficient (10). In a study conducted in Canada in 2013, the lack of knowledge of family physicians about asthma control, use of spirometry and theoretical knowledge of asthma was mentioned (11). According to a study conducted in primary care in Kuwait in 2014, doctors' asthma knowledge and treatment scores were found to be low (12). Similar results were obtained in a study on family physicians in Türkiye in 2016 (5). Similar to other studies in the literature, in this study, physicians' general knowledge of asthma diagnosis and treatment were low. Training and courses to be given to physicians are critical in this context and will contribute to public health.

In our study, when the effect of demographic data on the level of asthma knowledge was examined, according to the results of the analysis, family medicine research assistants had 3.06 times more knowledge points than family physicians, and the difference was statistically significant. In addition to it was observed that family medicine specialists had a significantly higher asthma knowledge score than family physicians. A significant effect was not found on the asthma knowledge score of other demographic data. Only one study has been found in the literature on this subject. In the study

Table 3. Comparison of study groups' responses to COPD information questions

	Working Status						p*
	Family Physician		Family Medicine Research Assistant		Family Medicine Specialist		
	n	%	n	%	n	%	
What is the definition of COPD?							
Chronic bronchitis + Asthma	47	18.7	16	15.2	5	16.1	<0.001
Bronchiolitis +Asthma	21	8.4	2	1.9	0	0.0	
Chronic bronchitis+Emphysema#	136	54.2	81	77.1	25	80.6	
Bronchiectasis+Emphysema	47	18.7	6	5.7	1	3.2	
Which is not a COPD risk factor?							
Cigarette	8	3.2	0	0.0	1	3.2	0.017
High socioeconomic status#	176	70.1	94	89.5	22	71.0	
Particles	11	4.4	1	1.0	1	3.2	
Low birth weight	45	17.9	9	8.6	7	22.6	
Biomass exposure	11	4.4	1	1.0	0	0.0	
The first symptom of COPD							
Dyspnea	91	36.3	48	45.7	15	48.4	0.035
Palpitation	11	4.4	3	2.9	0	0.0	
Cough#	107	42.6	48	45.7	16	51.6	
Wheezing	36	14.3	6	5.7	0	0.0	
Speech disorder	6	2.4	0	0.0	0	0.0	
Which sound is heard first in COPD physical examination?							
Ral	34	13.5	7	6.7	3	9.7	0.001
Ronkus#	114	45.4	56	53.3	21	67.7	
Crepitation	20	8.0	0	0.0	0	0.0	
Frotman	16	6.4	2	1.9	0	0.0	
Decreased breath sounds	67	26.7	40	38.1	7	22.6	
What is the definitive diagnosis of COPD?							
CT	39	15.5	16	15.2	3	9.7	0.020
PA Chest X-ray	16	6.4	0	0.0	0	0.0	
Spirometer#	171	68.1	86	81.9	27	87.1	
Sputum sample	9	3.6	1	1.0	0	0.0	
Arterial blood gas	16	6.4	2	1.9	1	3.2	
Which is not a physical examination finding of advanced COPD?							
Keg thorax	23	9.2	3	2.9	1	3.2	0.001
Hyperresonance in percussion	34	13.5	16	15.2	7	22.6	
Decreased breath sounds	45	17.9	6	5.7	3	9.7	
Deep heart sounds	48	19.1	14	13.3	3	9.7	
Expiratory shortening#	101	40.2	66	62.9	17	54.8	
Which is wrong in the treatment of stable COPD?							
Inhaled bronchodilators are the mainstay of symptomatic treatment	11	4.4	3	2.9	3	9.7	0.009
Regular and, when necessary, short-acting beta-agonist-anticholinergic use improves FEV1 and symptoms.	43	17.1	8	7.6	5	16.1	
Regular inhaled corticosteroid therapy reduces the risk of pneumonia#	100	39.8	58	55.3	20	64.5	
Beta agonist + anticholinergic is better than a single drug in improving FEV1	47	18.7	16	15.2	1	3.2	

Table 3. Comparison of study groups' responses to COPD information questions							
Long-term use of oral glucocorticoids has side effects	50	19.9	20	19.0	2	6.5	
Not associated with bad prognosis in COPD exacerbation?							
Old age	38	15.1	14	13.3	6	19.4	0.002
Increased body mass index#	63	25.1	45	42.9	11	35.5	
Heart failure	27	10.8	4	3.8	1	3.2	
History of previous hospitalization for COPD exacerbation	86	34.3	18	17.1	9	29.0	
Lung cancer	37	14.7	24	22.9	4	12.9	
It is not one of the common comorbidities seen in COPD?							
Vitamin D deficiency	95	37.8	50	47.6	13	41.9	0.008
Systemic hypertension	24	9.6	4	3.8	3	9.7	
Metabolic syndrome	27	10.8	13	12.4	0	0.0	
Depression	23	9.2	1	1.0	0	0.0	
Peripheral neuropathy#	82	32.7	37	35.2	15	48.4	
Which is true about the differential diagnosis of asthma-COPD?							
Asthma usually starts in middle age	24	9.6	7	6.7	1	3.2	0.030
COPD is progressive but lung function may return to normal	44	17.5	12	11.4	3	9.7	
The most important etiological factor in asthma is genetics.	80	31.9	28	26.7	4	12.9	
Smoking history in COPD is over 20 pack-years#	91	36.3	51	48.5	19	61.3	
There is no need for spirometry in COPD patient follow-ups	12	4.8	7	6.7	4	12.9	

n=frequency, %=column percentage, *Pearson chi-square test

conducted on family physicians in Sakarya province in 2018, be a family medicine specialist and family medicine research assistant; it was concluded that asthma had a positive effect on attitude and behavior compared (13). As can be seen here, the contribution of education in family medicine is undeniable. Meetings and seminars should be organized for family physicians for proper and regular follow-up of patients with asthma. Family physicians should be encouraged to specialize.

As it is known in COPD, smoking is one of the most important etiological agents. Since smokers attribute their cough and sputum complaints to smoking, patients do not apply to the doctor or apply late; thus, early diagnosis of COPD becomes difficult. Additionally, the lack of knowledge of family physicians on COPD makes an early diagnosis difficult (14). The role of primary care physicians is critical in the fight against COPD, which is an important cause of mortality and morbidity worldwide.

When we look at the COPD knowledge-level questions of the physicians in our study; The first 3 most known questions; 'Which one of the following is not a risk factor for COPD' with 75.5%, 'which one of the following is the definitive diagnosis of COPD' with 73.4% and 'which is the definition of COPD' with 62.5%. In other questions (COPD symptom, COPD physical examination findings, COPD treatment, COPD attack questions), the rate of marking the correct answer was less than half. Generally, when the COPD knowledge questions were evaluated, the knowledge levels of the physicians were found to be low. When we look at the studies in the literature, Başyiğit et al. showed that general practitioners working in primary care have a lack of knowledge about COPD (15). In this study, similar to our study, it was mentioned that the level of knowledge of the physicians in the cause of COPD is good, but the level of success of the physicians in the treatment steps is low. Decramer et al. In a study they conducted on general practitioners, it was suggested that the level of knowledge of physicians in the treatment steps was insufficient and antibiotics were prescribed to patients unnecessarily (16). In a study by Kesten et al. on primary care physicians, physicians were given a virtual case and their approaches were evaluated, according to the results of the study, the obstructive disease thinking index of the physicians was low; although they saw that COPD and asthma are not the same diseases, it was observed that they approached the two diseases with the same treatment (17). When we look at the studies on general practitioners in Türkiye, similar to our study, it was mentioned that the knowledge level of physicians about COPD was weak; it was stated that postgraduate training and seminars should be given to physicians (18,19).

When we examine the factors affecting the answers given to the COPD information questions in general terms, the importance of education has been seen once again. In our study, be a family medicine specialist and a family medicine research assistant; the effect on the COPD knowledge score was statistically significant compared to the family physician.

Table 4. Comparison of physicians' responses to attitude questions

	Working Groups						Total		p*
	Family Physician		Family Medicine Research Assistant		Family Medicine Specialist				
	n	%	n	%	n	%	n	%	
Do you use the spirometry device in suspected asthma-COPD?									
I use	7	5.6	16	24.6	2	12.5	25	12.2	<0.001
I sometimes use	41	33.1	4	6.2	5	31.3	50	24.4	
I start treatment without using	6	4.8	1	1.5	0	0.0	7	3.4	
I will refer you to a pulmonologist	70	56.5	44	67.7	9	56.3	123	60.0	
Do you think your level of knowledge in using spirometry is sufficient?									
Definitely yes	19	7.6	4	3.8	3	9.7	26	6.7	0.550
Partially	111	44.2	50	47.6	11	35.5	172	44.4	
I don't think	121	48.2	51	48.6	17	54.8	189	48.8	
Would you apply pneumococcal and influenza vaccines to your COPD patient over 65 years old?									
Yes	130	51.8	95	90.4	25	80.6	250	64.6	<0.001
I recommend to some patients	109	43.4	9	8.6	6	19.4	124	32.0	
No	12	4.8	1	1.0	0	0.0	13	3.4	

n=frequency, %=column percentage, #correct answer, *Pearson chi-square test

When we look at the literature, there is no study comparing family medicine specialists and general practitioners in this regard. In a study conducted respiratory tract diseases, the rate of diagnosing respiratory tract diseases by primary care physicians were lower than specialists in general (20).

According to our study, the other variable that statistically affected the knowledge level of COPD was working in a county-village-town. Those who work in district-village-town have a 2.44 times higher level of knowledge than those in the city center. No studies were found on this subject. Village-towns do not have health facilities other than family health centers, and patients often apply to family health centers, including their urgent complaints. Physicians in the village-town may have felt the need for more self-development in this regard, as they frequently encounter attack patients with COPD primarily. Generally, the number of physicians participating in this study from districts and villages is very few. Therefore, we believe that the other reason for the high level of COPD knowledge of the physicians working in the village-town may be the low number of participants from the village-town.

According to our study, the demographic data asked the physicians and the level of COPD knowledge; age, gender, the number of patients cared for daily, the smoking behavior of the physician, the years of employment of the physician, and the settlement (province, district) where the physician worked were not affected. In a study conducted on general practitioners in 2006, it was shown that the length of practice did not affect the response rates of information questions about COPD (15). In this study also coincides with the conclusion that the length of service of the physicians in our study has no effect on the level of knowledge of COPD.

Exacerbations seen in COPD are among the leading causes of significant mortality and morbidity. Considering the etiology of COPD exacerbations, approximately 80% of them are caused by bacterial/viral lower respiratory tract diseases. In this context, it is critical to vaccinate patients to combat COPD exacerbations. When physicians were asked about their pneumococcal and influenza vaccinations for patients with COPD over the age of 65, 64.6% answered yes. Studies have shown that vaccination rates in the community are low. According to a study conducted in five different Latin American cities, influenza vaccination percentages; Caracas (Venezuela) was the lowest with 5.1%, and Santiago (Chile) was the highest with 52% (21). In a study by Özsu et al. on 129 people in Türkiye, the rate of getting influenza and pneumococcal vaccines was 11.6% (22). Again, in a study examining the vaccination rates of 85 patients hospitalized for COPD attack in Türkiye in 2018, it was found that only 5 (5.8% of the whole group) of the patients had influenza and pneumococcal vaccines (23). In a study conducted in Germany, it was noted that the most important factor in the vaccination of patients was the doctor's recommendation (24). Another reason for the low vaccination rate in society may be the low socioeconomic level. In a study conducted in Mersin in 2016, it was reported that 52.5% of those with an income level below 1000 Turkish Liras did not get vaccinated (25). The reason for the low vaccination rates in the community; the physicians' inability to spare enough time for the patient due to their workload may be due to the insufficient level of

Table 5. Comparison of physicians' responses to questions measuring behavior

	Working Groups						p*
	Family Physician		Family Medicine Research Assistant		Family Medicine Specialist		
	n	%	n	%	n	%	
Do you give a practical explanation on how to use metered dose devices the patients?							
Yes, I always tell	64	25.5	39	37.1	11	35.5	<0.001
Sometimes I explain	129	51.4	28	26.7	15	48.4	
No, I don't tell	27	10.8	4	3.8	1	3.2	
I do not explain because my level of knowledge is not enough	31	12.4	34	32.4	4	12.9	
When the patient who comes to print his asthma-COPD reports and applies to your clinic							
I do not write a prescription at the request of the patient	45	17.9	19	18.1	8	25.8	
I write a prescription partly at the request of the patient	158	62.9	73	69.5	20	64.5	
I write directly reported drugs without assessment	48	19.2	13	12.4	3	9.7	
Would you like a consultation from a pulmonologist in the diagnosis-treatment steps of asthma-COPD?							
Yes	92	36.7	63	0.0	21	67.7	<0.001
Sometime	79	31.5	26	24.8	5	16.1	
No, I sending directly	80	31.9	16	15.2	5	16.1	
The Resource You Usually Use When Prescribing Medication to a Patient with Asthma-COPD							
Pharmaceutical companies and brochures							
Yes	21	8.4	7	6.7	3	9,7	0.812
No	230	91.6	98	93.3	28	90.3	
Online drug prospectus							
Yes	71	28.3	23	21.9	6	19.4	
No	180	71.7	82	78.1	25	80.6	
Asthma-COPD guidelines							
Yes	145	57.8	81	77.1	25	80.6	<0.001
No	106	42.2	24	22.9	6	19.4	
Main source books (textbook, literature, etc.)							
Yes	54	21.5	25	23.8	9	29.0	0.612
No	197	78.5	80	76.2	22	71.0	
Other							
Yes	33	13.1	14	13.3	1	3.2	0.271
No	218	86.9	91	86.7	30	96.8	

n=frequency, %=column percentage, *Pearson chi-square test

knowledge of the patients about the possible effects of the vaccine. Brochures and posters can be useful to increase the awareness of patients in this regard. The key factor here is family physicians in primary care, who encounters patients frequently. According to a survey conducted by evaluating 61 patients in the chest diseases outpatient clinic in Düzce, none of the family physicians recommended pneumococcal vaccine to patients in primary care, whereas influenza vaccine was recommended to 16% of patients (26). This rate was found to be lower than in our study. In our study, influenza and pneumococcal vaccination recommendations by family medicine specialists and family medicine research assistants to patients were higher among compared to family physicians. When we look at the literature, no study has been found on this subject that compares family medicine specialists and family physicians.

In this section, which evaluates the behavioral status of family physicians on asthma-COPD, 29.5% of the physicians answered yes to the question "Can you inform the patient

about how to use inhaler drugs?" Especially, when using inhaler drugs in elderly patients, misuse techniques often arise due to the decline of cognitive functions with age. Misuse makes it difficult to control the disease. In an external-centered study, misuse technique was found in 71% of 4078 asthma patients who were treated with metered dose inhalers and steroids. It has been concluded that asthma control in patients who receive asthma inhaler medication with the correct technique is better than those who use their medication with the wrong technique (27). In a study by Chopra et al. in which they investigated the skills of using inhaler techniques on healthcare workers, correct inhaler technique was found that they used it in 81.6% of respiratory therapists, 77.7% of primary care physicians, 57.7% of pharmacists, 54.4% of nurses and 53.8% of assistants (28). In a study conducted in Türkiye in 2014 in which the skills of healthcare professionals on inhaler techniques were investigated, it was found that specialist physicians had a significant level of inhaler use skills compared to other healthcare professionals (family physician, nurse, pharmacist). There was no significant difference between other healthcare professionals groups. It was mentioned that they had moderate and bad use skills (29). When these studies were examined, results similar to our study emerged. In this section, the role of health professionals, especially physicians, as a guide is critical. Patients should be questioned about their use of drugs at each visit, and how they should be used in practice should be explained with visual techniques if necessary. Of course, physicians should also be aware of this issue. In this question, 17.8% of the physicians stated that they did not know about this issue, and 8.3% of them answered 'no,' probably because they did not have knowledge or because of the density of patients. It would not be right to expect family physicians to show the patient these technical methods that they do not know. The deficiencies of family physicians and nurses can be eliminated by including in-service trainings and seminars. Additionally, it was concluded that family medicine research assistants were significantly more sensitive than family physicians in informing the patient about inhaler preparations.

"Would you like a consultation with a thoracic specialist?" 45.5% of the physicians answered yes to the question on asthma-COPD. In this section, it is questioned how relevant and sensitive the physicians are to the patient in the diagnosis and treatment steps, and how active they are about adherence to treatment and clinical course. In a study conducted in primary care in Türkiye in 2014, when family physicians were asked the question "Do you call the specialist you common follow your patient with information?" 27% of them answered yes (30). When we look at the family physicians in our study, 36.7% stated that they wanted a consultation, and similar results emerged. Physicians may need to refer the patient to a pulmonologist because of the lack of additional necessary materials for diagnosis in the family health center and limited opportunities to start asthma-COPD preparations in the treatment. In this section, in the chronic follow-ups of the patient, the chest diseases consultation results and medications should be checked without losing contact with the patient and should be in contact with the chest diseases specialist if necessary. The feedback of information about patients consulted with chest diseases is critical for both the follow-up of patients and for the professional development of family physicians. In our study, it is surprising that family medicine specialists and family medicine research assistants requested consultation at a higher rate than family physicians. This situation contradicts the fact that despite their low scores, family physicians in asthma-COPD information questions ask for consultation less than specialists and research assistants. Here, this contrast suggests that family medicine specialists and research assistants better know the possible comorbidities and complications about asthma-COPD, and their more cautious approach to patients may lead to higher referrals to pulmonologists in these groups.

Physicians stated that the most common sources they use when prescribing drugs to patients are asthma-COPD guides, and they use prospectuses on the internet as the second most frequent source. In a primary care study in Kuwait, it was emphasized that education level, knowledge about asthma, and clinical practice were important determinants of adherence to asthma guidelines (12). In our study, it was observed that family medicine specialists and research assistants benefited from asthma-COPD guidelines statistically significantly more than family physicians. Accordingly, it was concluded that as the level of education increases, the rate of resource use increases and the treatment is more scientifically approached.

CONCLUSION

In this study, which evaluated the knowledge levels, attitudes and behaviors of family physicians about asthma-COPD diseases, it was observed that family physicians did not have sufficient knowledge levels and there were great deficiencies in diagnosis and treatment steps. There is an obligation to have a spirometry or peak flowmetry device in family health centers in Türkiye. Despite this, the inadequacy of diagnosis and treatment in primary care is thought-provoking. The fact that family medicine specialists and family medicine research assistants have higher levels of knowledge and positive attitudes in our research reveals the necessity of education in family medicine. Therefore, family physicians should be encouraged to specialize in family medicine.

Active, applied training seminars should be given importance in primary care. Practical guidelines that physicians can easily reach in primary care should be increased. The focus should be on system models that will create active communication channels with the pulmonologist and/or other specialties, if necessary, to improve the family physicians, both in terms of improving themselves and to provide excellent disease control. Additionally, informative brochures and posters about asthma-COPD should be disseminated in society and supported with trainings for prevention of the development of the disease, its early diagnosis, the prevention of the progression of the disease and its effective treatment, in order to reduce mortality and morbidity. The limitations of the study are that the study was conducted in a certain region and that it was carried out with a standard scale. Conducting studies with a country-wide population and a standard scale may strengthen the results to be obtained.

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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 fromthe Kahramanmaraş Sütçü İmam University Faculty of Medicine Non-Pharmaceutical Clinical Research Ethics Committee with the date 04.09.2019 and number 09 and Helsinki Declaration rules were followed to conduct this study.

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Authorship Contribution

Concept: AY, CK, Design: AY, CK, MEE, Supervising: CK, RŞG, FFinancing and equipment: AY, CK, Data collection and entry: AY, MEE, Analysis and interpretation: CK, RŞG, Literature search: AY, RŞG, Writing: AY,CK, MEE, Critical review: CK, RŞG

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The prognostic role of neutrophil/lymphocyte ratio and monocyte/lymphocyte ratio in advanced stage gastric cancer patients receiving chemotherapy: a single center experience

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Abstract

Objective: Several studies revealed that peripheral blood Neutrophil/Lymphocyte ratio (NLR) and Monocyte/Lymphocyte Ratio (MLR) were prognostic in various cancer types. However, there are no excessive information about the prognostic significance of NLR and MLR in patients with advanced gastric cancer. As a result, we examined whether NLR and/or MLR could be used as a prognostic marker to predict survival outcomes in patients with advanced gastric cancer receiving palliative chemotherapy.

Methods: We retrospectively analyzed 119 patients with gastric cancer receiving chemotherapy. We evaluated the relationship between potential prognostic factors and overall survival (OS) times using the Kaplan-Meier method and Cox regression survival modelling.

Results: The median overall survival of the patients was 6.9 (2.1-41.6) months. In univariate analysis, NLR ($p< 0.001$), ECOG performance status ($p< 0.001$), presence of liver metastases ($p< 0.001$) and presence of peritoneal metastases ($p< 0.001$) were found to be associated with survival. The multivariate survival model showed the high NLR (HR=1.59, 95% CI 1.6-2.40, $p= 0.026$), the patients with ECOG performance score 2-3 (HR=2.91, 95% CI 1.60-5.27, $p<0.001$), the presence of liver metastasis (HR=2.10, 95% CI 1.35-3.21, $p=0.001$) and the presence of peritoneal metastases (HR=2.68, 95% CI 1.72-4.17, $p<0.001$) as independent predictors of survival.

Conclusion: Pretreatment high NLR, ECOG performance status, and presence of liver or peritoneal metastases are powerful prognostic factors in advanced gastric cancer patients. These prognostic factors, which are easily accessible in clinical practice, can be used as helpful tools for clinicians in the management of the disease.

Keywords: Gastric Cancer, Chemotherapy, Survival, Neutrophil-Lymphocyte Ratio, Monocyte-Lymphocyte Ratio

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide (1). Although the incidence of gastric cancer has decreased with the recognition of risk factors such as Helicobacter pylori, environmental factors or dietary influences, the annual absolute number of new cases are increasing due to the aging of the world population (2,3). Mortality has been declining in recent years, thanks to advances in gastric cancer management, including improved surgical techniques, early detection tools, and perioperative chemotherapy; however, it is still an important cause of cancer-related deaths (4). Currently, the prognosis of the gastric cancer is primarily based on the TNM staging classification (6). It is thus essential to identify readily available biomarkers that predict the prognosis and help clinicians to implement better treatment strategies. Recently, emerging data has revealed that systemic inflammatory response markers could be used as independent prognostic biomarkers in various tumor types (7,8). Of these markers, the neutrophil/lymphocyte ratio and the monocytic/lymphocyte ratio have been

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identified as promising prognostic markers (9). Studies have shown that inflammatory markers such as NLR and/or MLO are highly reproducible, cost-effective, and widely available (10). In literature, there are studies showing that survival can be predicted by NLR and MLR in early stage or operable, locally advanced gastric cancer patients (11,12,13). In this study, we aimed to investigate the relationship between NLR and MLR before chemotherapy and survival in patients with advanced gastric cancer.

METHODS

In this study, patients who were treated with the diagnosis of pathologically proven gastric cancer between January 2016 and December 2019; were retrospectively analyzed. Patients aged 18 years and older who received at least 2 months of chemotherapy (platinum, taxane, fluorouracil) as for the first-line therapy and who were radiologically considered metastatic were included in the study. Patients with active infection, using immunosuppressive drugs, under nutritional support or those with missing data were excluded from the study.

Data

Patients' demographic data, clinicopathological characteristics and peripheral blood hemogram neutrophil, lymphocyte and monocyte values before chemotherapy were recorded from the hospital electronic record system. NLR was calculated by the neutrophil count divided by the lymphocyte count; MLR was calculated by dividing the number of monocytes by the number of lymphocytes.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences version 26.0; SPSS Inc.Chicago, Illinois, USA) package program was used for statistics. Overall survival (OS) was defined as the time from diagnosis of the disease to the date of death, while for survivors, the time from diagnosis to last follow-up was considered. Optimal cut-off value for NLR was determined by Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC). The median value was used as the cut-off for MLO. With these cut-off values, patients were divided into two groups as "low NLR/ high NLR" and "low MLR/ high MLR" separately for NLR and MLR (Figure 1). Survival analysis was performed using the Kaplan-Meier method and Log-Rank test was used for group comparison. Multivariate analysis of factors affecting survival was created with the Cox proportional-hazards model. "Forward: LR" method was used for multivariate analysis. Statistical significance was accepted as $p < 0.05$.

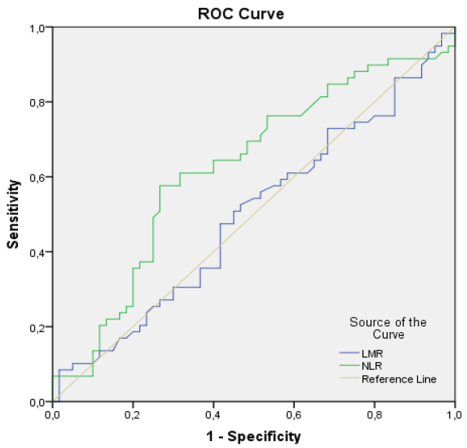

Figure 1. Roc-Curve analysis of NLR for survival

RESULTS

A total of 119 patients were included in our study. The median age of the patients was 68 (37-91). 116 (97.5%) patients died due to cancer-related reasons. The median overall survival of the patients was 6.9 (2.1-41.6) months. General characteristics and laboratory data of the patient population are summarized in Table 1.

Table 1. Demographic, clinical and biochemical characteristics of the patients

Clinicopathologic Characteristics	n	%
Age		
≤60	32	26.9
>60	87	73.1
BMI		
< 25	86	72.3
≥ 25	33	27.7
Sex		
Male	82	69.9
Female	37	30.1
ECOG PS		
0-1	101	84.9
≥2	18	15.1
Peritoneal Metastasis		
Yes	39	32.78
No	80	67.22
Liver Metastasis		
Yes	73	61.34
No	46	38.66
NLR		
<3.22	69	57.98
≥3.22	50	42.02
MLR		
≤2.79	60	50.42
>2.79	59	49.58

BMI, Body Mass Index; ECOG PS, Eastern Cooperative Oncology Group Performance Score; MLR, Monocyte-Lymphocyte Ratio;, NLR, Neutrophil-Lymphocyte Ratio

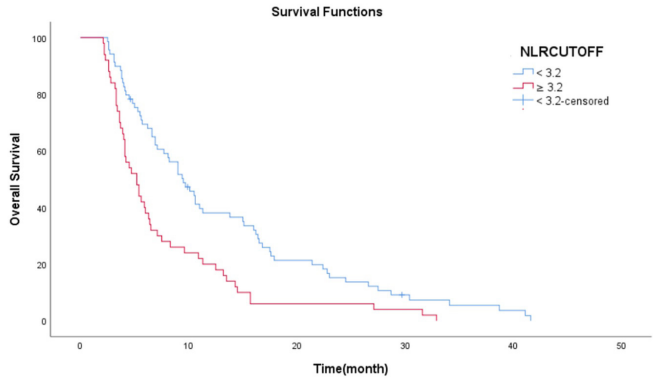

Figure 2. Survival analysis of high NLR versus low NLR

Cut-off values for NLR and MLR

According to the relationship between neutrophil-lymphocyte ratio and survival time, the ideal threshold value that divides patients into two groupes was calculated as 3.22 with Roc-Curve (n=119 AUC: 0.625, 0.52-0.73 at 95% confidence interval, P=0.019) (Figure 2). The specificity (specificity) of this value was 73.3% and the sensitivity (sensitivity) was 69.9%. The ideal cut-off for MLR could not be determined. The median value was accepted for cut-off.

Table 2. Kaplan-Meier analysis of patients' clinical and laboratory parameters

	n	OS(months)	p value
Age			
≤60	32	6.4	0.452
>60	87	7.1	
BMI			
< 25	86	6.9	0.787
≥ 25	33	6.6	
Sex			
Male	82	7.1	0.266
Female	37	5.6	
ECOG PS			
0-1	101	0.266	<0.001
≥2	18	0.266	
Peritoneal Metastasis			
Yes	39	4.8	<0.001
No	80	8.3	
Liver Metastasis			
Yes	73	9.7	<0.001
No	46	6.0	
NLR			
<3.22	69	9.5	<0.001
≥3.22	50	5.2	
MLR			
≤2.79	60	6.9	0.469
>2.79	59	6.6	

*Since the age variable provides the assumption of normality, the p value was determined according to the independent sample student's t-test, and the p value of the other variables was defined by the chi-square test.

NLR: Neutrophil/lymphocyte ratio, MLR, Monocyte-lymphocyte ratio, OS: Overall survival time, BMI: Body-Mass Index

Univariate and Multivariate Survival Analysis

In univariate analysis, high NLR (p<0.001) as well as ECOG performance score (p<0.001), presence of liver metastases (p<0.001), and presence of peritoneal metastases (p<0.001) were significantly associated with overall survival. There was no relationship between age, gender, body mass index, MLR and survival (Table 2).

A multivariate survival model was created with the parameters found to be significant in the univariate analysis (Table 3). According to this model, high NLR (HR=1.59, 95% CI 1.6-2.40, p= 0.026), ECOG performance score (HR=2.91, 95% CI 1.60-5.27, p<0.001), presence of liver metastases (HR=2.10) 95% CI 1.35-3.21, p=0.001) and presence of peritoneal metastases (HR=2.68, 95% CI 1.72-4.17, p<0.001) were determined as independent predictors of survival.

Table 3. Multivariate cox regression model predicting overall survival

Variable	HR	(95% CI)	p value
High NLR (vs. Low NLR)	1.592	1.057-2.398	0.026
ECOG PS. 2-3 (vs ECOG PS 0-1)	2.906	1.603-5.267	<0.001
Presence of liver metastases	2.080	1.346-3.212	0.001
Presence of peritoneal metastases	2.679	1.722-4.169	<0.001

HR: Hazard Ratio, NLR: Neutrophil/Lymphocyte Ratio, ECOG PS: ECOG Performance Score

DISCUSSION

In this study, we investigated the prognostic significance of NLR and MLR along with the clinical and laboratory data of 119 patients with advanced gastric cancer. Patients with the high peripheral blood sample NLR before chemotherapy had worse overall survival compared to those with low NLR, whereas high or low MLR did not affect overall survival. Both univariate analysis and multivariate analysis showed that NLR, ECOG performance score, presence of liver metastases or peritoneal metastases can be used as a prognostic marker. In recent years, knowledge of the inflammatory microenvironment of cancer has grown rapidly, and there is increasing interest in the relationship between inflammation and cancer (14). Various indicators investigating this relationship between cancer and inflammation have been researched and developed (15). Albumin-bilirubin index, Nutritional risk score (NRS-2002), NLR, Platelet-Lymphocyte Ratio (PLO), monocyte-lymphocyte ratio (MLR), Gamma-

interferon/Interleukin-4 ratio are among the reported and investigated markers (16-18). There are many studies shows a relationship between NLR and gastric cancer prognosis, however, these studies focused on postoperative survival in patients with early or operable gastric cancer rather than metastatic gastric cancer patients (19-21). In addition, the relationship between NLR and therapeutic response in gastric cancer is important for predicting chemotherapeutic response and prognosis in gastric cancer patients (22). In a study that included advanced gastric cancer patients divided into two groups as high/low by median NLR pre-chemotherapy, Cho, In Rae et al. showed that patients with higher NLR before chemotherapy had shorter survival and disease-free survival (23). In a study of 537 patients with advanced gastric cancer receiving chemotherapy, Zhou, Danyang et al. reported that high NLR and MLR were associated with poor PFS and OS (24). In our study, in accordance with the literature, patients with high NLR before treatment were found to be disadvantaged in terms of survival, but no significant relationship was found between LMO and overall survival.

In a study by Zhao, Guanghui et al. in metastatic gastric cancer patients, high baseline NLR, high platelet-lymphocyte ratio, being older, and having liver or peritoneal metastases were shown to be predictors of overall survival (25). In another study by Chau, Ian et al., investigating the overall survival of 1080 patients with locally advanced or advanced gastric cancer, the presence of peritoneal metastases, the presence of liver metastases before treatment, and worse ECOG performance scores were reported as independent predictors of shorter overall survival (26,27). In the present study, the presence of liver or peritoneal metastases before treatment was associated with shorter survival. In addition, patients with worse performance status were found to be poor prognostic factors consistent with the literature.

The main limitation of this study is that it was a single center and retrospective design. Furthermore, current findings need to be validated in a larger patient population and by performing subgroup analysis with different treatment settings and regimens.

CONCLUSION

As a result, the treatment method in patients with advanced gastric cancer is planned by considering multiple clinical and biochemical factors, including prognosis estimation. Pretreatment high NLR is associated with worse survival in this group of patients; and it is suggested that these biomarkers, with their simplicity and usability, are useful in predicting the prognosis of advanced gastric cancer.

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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 Tekirdağ Namık Kemal University Clinical Research Ethical Committee with date 31.05.2022 and number 2022.91.05.18, and Helsinki Declaration rules were followed to conduct this study.

Authorial Contributions

Concept: KK, Design: KK, ESŞ, Supervising: KK, ESŞ, Financing and equipment: KK, ESŞ, Data collection and entry: ESŞ, Analysis and interpretation: KK, ESŞ, Literature search: KK

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ORIGINAL RESEARCH

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The frequency and associated factors of infusion-related reactions to rituximab for patients with rheumatoid arthritis

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Abstract

Objectives: Rituximab is an effective biological agent for treating patients with rheumatoid arthritis (RA). Rheumatologists can avoid rituximab therapy because of infusion-related reactions (IRR). There is a lack of data about rituximab-related IRR, especially in rituximab-naïve patients with RA; therefore, we aimed to determine the frequency and associated factors of rituximab-related IRR in these patients.

Methods: Baseline demographic, laboratory, and treatment data were noted. One course of rituximab was used in two infusions to 95 rituximab-naïve patients with RA. Standardized premedication was administered before infusions. Rates, severity, and management of IRR were recorded. Efficacy and infections were also noted if there were.

Results: Ninety-four of 95 patients completed the rituximab course successfully. We observed a total of 23 IRRs in 20 patients. The frequency of IRR was 12.1%, and serious IRR was 0.52%. Grade 1-2-3 IRRs had a rate of 52.2%, 30.4%, and 17.4%, respectively; grade 4 or 5 IRR wasn't detected. Age <60 years, anti-CCP <200U/ml and absence of biologic agent use before rituximab was significantly higher in patients with IRR than without IRR (p=0.01, p=0.002, p=0.01 respectively). We found out that if only the disease age is above 60 months, it is protective against IRR as per the results of multivariate model analysis.

Conclusion: Results supported that rituximab is a safe biological agent option for patients with RA at secondary central hospitals. Identified risk factors of IRR need to be corroborated in larger studies for safer rituximab therapy.

Keywords: Rituximab, Infusion-Related Reactions, Rheumatoid Arthritis, Risk Factors

INTRODUCTION

Rituximab is an IgG1 kappa chimeric monoclonal anti-CD20 antibody, which consists of a variable region of mouse origin (against human CD20) and a constant region of human origin (including the Fc portion). CD20 is a probable calcium ion channel and plays an essential role in B-cell differentiation. Rituximab binds with high affinity to cells expressing the CD20 antigen on the surface of malignant and normal pre-B/mature B lymphocytes, so these immune cells are targeted for lysis with different mechanisms. Rituximab was approved by the US Food and Drug Administration (FDA) for the indication of relapsed or refractory, CD20 positive B-cell, low-grade or follicular non-Hodgkin's lymphoma in November 1997; thus, rituximab was the firstly approved monoclonal antibody (Mab) for cancer therapy (1).

Recently, the role of B lymphocytes in the pathogenesis of rheumatic diseases is better understood (2), and rituximab was approved by FDA for rheumatoid arthritis (RA) in 2006 (3), for microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA; also known as Wegener's granulomatosis) in 2011 (4). Currently, rituximab is not licensed for autoimmune connective tissue diseases such as systemic lupus erythematosus (SLE), Sjogren's syndrome, systemic sclerosis, and idiopathic

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inflammatory myopathies, but uncontrolled studies and case reports described the efficacy of rituximab for these diseases (5). Therefore, rituximab is used worldwide as labeled and off-labeled for the treatment of many rheumatic diseases by rheumatologists.

Biological drugs (Mabs, fusion proteins, and cytokines) are produced using biotechnological techniques; act on the immune system and inflammation. In contrast to chemical drugs, biological drugs are highly immunogenic proteins, administered parenterally, and are not metabolized (6). Distinctive side effects of Mabs are non-allergic infusion reactions caused mainly by cytokine release, and they are not mediated by immunoglobulin E (IgE). Allergic infusion reactions like anaphylactic type 1 hypersensitivity, mediated by IgE, are rarely seen in Mab therapy. The cytokine release syndrome (CRS) is clinically similar to hypersensitivity and may be indistinguishable during Mab infusion therapy. Releasing cytokines from targeted and immune effector cells is the mechanism of CRS, which usually occurs in the first infusion within 30 minutes to two hours. Symptoms are generally mild to moderate, resolved by slowing or short-term cessation of infusion and restarting the infusion at a slower rate (7).

Despite the efficacy and safety of rituximab in RA treatment (3,8), rheumatologists can avoid rituximab therapy (especially in secondary central hospitals) because of infusion-related reactions (IRRs). What are the risk factors or the clinical features of rituximab-related IRR in rituximab-naïve patients with RA? The answers to these questions are still uncertain; current data is insufficient about risk factors and clinical courses of IRR in rituximab-naïve patients with RA. The primary aim of this study was to answer the above questions. We hope that our research will be helpful for rituximab therapy in daily rheumatologic practice.

METHODS

Patient selection

A retrospective analysis of rituximab-naïve patients with RA, diagnosed according to The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria (9) and aged ≥18 years, was performed in a secondary central state hospital in the East of Turkey. Patients who received rituximab therapy between October 2018 and June 2020 during the follow-up period as a rheumatologist were included in the study. Patients who have a malign disorder or immune-mediated inflammatory diseases (such as Crohn's disease, multiple sclerosis) history or immunosuppressive drug use (such as cyclosporine, azathioprine, or mycophenolate mofetil) were excluded from the study. Patients' electronic files were evaluated for clinical features, demographic data, and laboratory findings, which also included baseline complete hematologic and biochemical profile, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), autoantibodies including rheumatoid factor: RF (determined by nephelometric assay, samples with results ≥14 IU/ml were defined as positive), anti-cyclic citrullinated peptide: anti-CCP (determined by enzyme-linked immunosorbent assay: ELISA, samples with results ≥20 U/ml were defined as positive) and anti-nuclear antibody: ANA (determined by ELISA), serologic tests for hepatitis B virus and hepatitis C virus. Regarding treatment, daily steroid doses, concomitantly conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) use, and biological agent use before rituximab were noted.

Treatment Protocol

Rituximab was administered in the outpatient clinic of the hospital. Premedication with paracetamol 1g orally, methylprednisolone 80-120 mg I.V., and an anti-histamine agent I.V. were administered to every patient before infusion; premedication protocol was applied according to van Vollenhoven RF et al.'s study (8). Patients received infusions in two steps. The first infusion was 1000 mg on day 1(D1), and the second infusion was 1000 mg on day 15 (D15); a total of 2000 mg rituximab was administered. Only six patients received therapy with half doses (two 500 mg infusions; a total of 1000 mg), preventing infections because of advanced age. The initial infusion rate was 50 mg/hour according to the administration protocol. If IRR wasn't observed and the vital findings were normal, the infusion rate would increase by 50 mg/hour every 30 minutes to a maximum 400 mg/hour rate. If any IRR were detected, the infusion rate would decrease or stop; treatment was resumed with half of the initial rate after resolving IRR.

Assessments

The infusion-related reaction occurred during or within 24 hours after an infusion (10). A serious infusion-related reaction (SIRR) was defined as discontinuing treatment, requiring hospitalization, persistent disability, or death. Signs, symptoms, duration, management (either reducing or stopping the rate), and additional premedications were recorded. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used to grade IRR severity (11). Rheumatoid arthritis disease activity was classified according to DAS-28 categories (12). The clinical efficacy of rituximab was evaluated within 4.5 to 8 months after the first course. In addition to disease activity, serum globulin level was assessed after the rituximab course. Hypogammaglobulinemia was defined if the serum globulin level was <2.5g/dl. In case of infection, this was noted.

Statistical analysis

SPSS 21.0 software package was used for data analysis. The results were described as a number, frequency, and

percentage. The chi-square test was used to assess differences between qualitative variables. A p-value smaller than 0.05 and a 95% confidence interval were considered statistically significant. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of patient outcome. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A 5% type-1 error level was used to infer statistical significance. Results were expressed as odds ratios and 95% confidence intervals for logistic regression. The study was approved by the Ethics Committee of the University where the study was conducted.

RESULTS

Of the 95 patients included, 77 (81%) were female, and the mean age was 58 years. The female-to-male ratio was 4.3/1, and the mean disease duration was 108 months. Concomitantly used csDMARDs included leflunomide (LEF), hydroxychloroquine (HQ), methotrexate (MTX), and sulphasalazine (SSZ); MTX use had a low rate because of drug incompatibility, gastrointestinal problems, and insufficient effectiveness. The rarest used csDMARD was sulphasalazine because most patients were seropositive, and sulphasalazine had insufficient effectivity. Glucocorticoid (prednisolone: P or methylprednisolone: MP) use was 88.4%, and the mean MP dose was 3.6 mg/day orally. A total of 23 biological agents were used in 18 patients before rituximab therapy. Table 1 shows demographic, laboratory, and treatment characteristics.

At the baseline, the DAS-28 scores of all patients were greater than 5.1. The mean evaluation time of rituximab efficacy on disease activity was at the sixth month. Rituximab treatment was effective in all patients who completed the cycle (n=94); 86% had remission, 12% had low disease activity, and 2% had moderate disease activity.

Ninety-four of 95 patients completed the first course successfully. Only one (40-year-old male) patient experienced grade 3 IRR in D1 infusion, and rituximab was discontinued; symptoms were fully resolved in two hours, and prolonged hospitalization wasn't required. 188 of 189 infusions were completed; the total number of IRR was 23 (12%), and the SIRR number was only one (0.5%). Rates of grade 1,2 and 3 IRR were 52% (n=12), 31% (n=7), and 17% (n=4), respectively; grade 4 or 5 IRR didn't occur. Generally, IRR developed in D1 infusion; only; only three patients developed IRR during both D1 and D15 infusions. All IRRs that occurred in the D15 infusion were grade 3. Still, we didn't consider a type 1 hypersensitivity reaction because IRRs occurred 30 minutes after starting the infusion, and infusion was completed successfully by short-term cessation of infusion and restarting the infusion at a slower rate.

Table 1. Demographic, laboratory, and treatment characteristics

Age, mean (range), years	58 (21-86)	
Female sex, n, %	77	81
Male sex, n,%	18	19
Disease duration, mean (range), months	108 (12-482)	
RF positivity, n, %	78	82
RF mean titer, IU/ml	217	
Anti-CCP positivity, n, %	70	74
Anti-CCP mean titer, U/ml	2 53 (available data from 62 /70 patients)	
RF or anti-CCP or both positive, n, %	81	85
ANA positivity, n, %	4	4
Serum globulin levels at baseline, mean (range), g/dl	2.9 (2.1-4.2)	
Serum globulin levels after RTX course, mean (range), g/dl	2.7 (1.8-3.5)	
Globulin decline after RTX therapy, n, %	52	57
Hypogammaglobulinemia after RTX course, n, %	14	15
Concomitantly used drugs, n, (%)		
-Hydroxychloroquine (HQ)	49	52
-Sulphasalazine (SSZ)	9	10
-Methotrexate (MTX)	32	34
-Leflunomide (LEF)	71	75
-Glucocorticoids (GC) (prednisolone: P or methylprednisolone: MP), n, %	84	89
Daily methylprednisolone dose, mean (range), mg	3.6 (2-16)	
Patients who received biological agent before the RTX course, n (%)	18	19
Number of biological agents before the RTX course	23	
Biological agents before RTX, n		
-Adalimumab	8	
-Etanercept	6	
-Tocilizumab	3	
-Certolizumab pegol	2	
-Abatacept	2	
-Infliximab	1	
-Tofacitinib	1	

Table 2. Adverse events of rituximab therapy

Patient with IRR, n, %	20	21
Number of total IRR	23	
Number of total SIRR	1	
The severity of IRR, n, %		
-Grade 1	12	52
-Grade 2	7	31
-Grade 3	4	17
-Grade 4 or 5	0	0
Infections, n (%)	3	3.1

Abbreviations: IRR, infusion-related reaction; SIRR, serious infusion-related reaction

Twenty-one of 23 IRR (91%) developed during infusion; two developed within 24 hours after infusion. We decreased the infusion rate in 18 IRRs and stopped in five IRRs. Thirteen of 23 IRR were persistent and not tolerated by patients; therefore, additional methylprednisolone (40 mg I.V.) was used to resolve IRR. We managed all of the stopped IRRs with additional steroid doses and restarted the infusion at a slower rate when symptoms resolved and infusions completed successfully. Signs/symptoms of IRRs were pruritus (n=13), erythema (n=12), sore throat (n=6), dyspnea (n=4), nausea/vomiting (n=2), hypotension (n=2), tinnitus (n=1), and headache (n=1). Infections developed in three (3%) patients after rituximab therapy; one patient had pneumonia and needed hospitalization, and intravenous antibiotic therapy, one had cellulitis, and one had cutaneous herpes zoster infection.

In univariate analysis, we found that age <60 years (p=0.01), anti-CCP titer <200 U/ml (p=0.002), and absence of biological agent used before rituximab therapy (p=0.01) were significantly higher in patients with IRR than without IRR (table 3). Age, sex, disease duration time, RF, anti-CCP, and biologic agent history were included in the multivariate model; increasing disease age was the only independent predictor of IRR and being protective against IRR.

Table 3. Univariate analysis of variables

Variable	IRR(+) group	IRR (-) group	p-value
Age <60 years	16/20	36/75	**0.01**
Female sex	18/20	59/75	0.25
Disease duration time ≥60 months	11/20	56/75	0.08
Serum baseline globuline ≥3g/dl	11/20	34/75	0.4
RF positivity	17/20	61/75	0.70
RF titer ≥100 IU/ml	11/17	35/61	0.58
Anti-CCP positivity	13/20	57/75	0.32
Anti-CCP titer <200 U/ml	12/23	26/57	**0.002**
Hydroxychloroquine use, n	11/20	38/75	0.73
Methotrexate use, n	10/20	24/75	0.13
Leflunomide use, n	14/20	59/75	0.41
Biologic naïve history, n	20/20	57/75	**0.01**

Abbreviations: IRR, infusion-related reaction; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; RTX, rituximab

DISCUSSION

The primary aim of this study was to identify the frequency and associated factors of rituximab-related IRR in rituximab-naïve patients with RA, and we found that age <60 years, anti-CCP titer <200 U/ml, and having biologic-naïve history were the associated with IRR. In medical literature, we defined that increasing disease age was the only independent predictor of IRR and protective against IRR. Totally, 21% of patients experienced IRR, and the rate of IRR was 12% in 189 infusions; 83% of patients had grade 1 and 2 IRRs, prolonged hospitalization or death was absent; 98% of patients completed the first rituximab course successfully.

Data from a global RA clinical trial with 2578 patients with RA, the first infusion was the most IRR occurring infusion with a rate of 25%, and the IRR rate decreased with subsequent infusions. Overall, 36% of patients experienced IRR, and <1% withdrew because of IRR; IRR rate, severity, and drug discontinuation were similar to our study (8). The most common adverse event of rituximab treatment in patients with RA is IRR, which has a lower incidence if the intravenous steroid is given as a part of premedication (13). Faster rituximab administration in patients with RA at the second and subsequent infusions doesn't cause an increasing rate or severity of IRR (14); nevertheless, our patients received therapy with the same protocol in D1 and D15 infusions.

There are many biological agent options for the treatment of RA which act with different mechanisms on disease pathogenesis, and IRR can be a reason for biological agent choice by rheumatologists. In a prospective study (n=4145), rituximab had a higher SIRR incidence than abatacept and tocilizumab in patients with RA; absence of concomitantly csDMARDs use, and anti-CCP positivity were the risk factors for SIRR, and patients with SIRR had more often previous anti-tumor necrosis factor (anti-TNF) use (15). Previous biological agent history could be a risk factor for IRR because anti-TNF agents lead to B-cell hyperactivity, as an immunologic side effect. Still, our results were controversial regarding this phenomenon (16).

Rituximab-related IRR rates are lower in patients with SLE than in those with RA, which may result from higher glucocorticoid doses in SLE. Indeed our patients had a low dose of glucocorticoid treatment (17). In patients with SLE, the first infusion is the most frequently rituximab-related IRR occurring infusion, and decreasing rates in subsequent infusions are similar to the RA studies. Still, risk factors are unknown (18). Rituximab-related IRR rates for lymphoproliferative disorders are higher than for autoimmune diseases (19), probably due to tumor burden. Rituximab-related IRR occurs in 84% of patients who have relapsed low-grade or follicular lymphoma, and the majority of IRRs are grade 1 or 2 and occur during the first infusion; fever and chills which were not observed in our patients are the most common symptoms (20). On the other hand, patients with multiple sclerosis (MS) treated with rituximab have similar IRR rates and severity to RA (21). If steroid treatment is not given before rituximab infusion in patients with MS, IRR increases dramatically (22). Regardless of the disease type (RA, SLE, MS, or lymphoproliferative diseases), steroid use decreases rituximab-related IRR.

Usually, Mabs are better tolerated and have lower toxicity than conventional cytotoxic drugs. However, IRR is a problem for all the Mabs (it is not specific to rituximab). Although the IRR varies among Mabs, it is most common in rituximab and generally occurs at the first infusion (23). Levels of inflammatory cytokines increase significantly during rituximab infusion compared with baseline measurements (24). IRR generally depends on CRS, which was caused by massive B cell lysis, and levels of inflammatory cytokines (TNF-a and IL-6) are correlated with IRR severity (25). The negative effects of aging on B-cells may explain the protective feature of increasing age against IRR (26).

Retrospective design, small sample size, absence of analysis for comorbidities such as diabetes mellitus or hypertension, and lack of allergy-immunology department consultation in IRR-developing patients (especially in D15 infusions) were the study's limitations.

CONCLUSION

In conclusion, 98% of rituximab-naive patients with RA successfully completed the first rituximab course in a secondary central hospital; IRR occurred in 21% of patients and 12% of total infusions. Drug discontinuation was very rare. Age <60 years, anti-CCP titers <200 U/ml and bio-naïve history were significantly higher in IRR developing group. Only the independent predictor of IRR was disease age; increasing disease age was protective against it. The unique results of our study will contribute to the safety of rituximab therapy in daily rheumatologic practice if patient-based risk factors are evaluated before infusion. Current knowledge about identified risk factors, rates, and severity of rituximab-related IRRs was generally obtained from non-RA patients. The identified factors of our study need to be corroborated in larger studies for safer rituximab treatment. Safety data of Mab infusion therapy is needed for other rheumatic diseases and drugs so that further studies can be focused on this subject.

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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 Mus Alparslan University Clinical Research Ethical Committee with date 29.10.202 and number E-79236777-605.99-2541, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

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

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Surveillance of urine cultures and evaluation gram negative uropathogens; five year data from Erbil

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Abstract

Objective: Urinary tract infections (UTIs) are most common infectious disease and a public health problem that imposes a large economic burden. Determining the distribution and resistance profiles of uropathogens in a region is important for planning empirical treatments, preventing antimicrobial drug resistance and establishing rational antibiotic use policies. The aim of this study is to gather surveillance data of urine cultures and determine the prevalence of uropathogens in urine samples of patients referred to outpatient clinics in Erbil region and to evaluate the antimicrobial susceptibility of the gram negative uropathogens.

Methods: All urine cultures result of patients referred to Erbil hospitals in the last 5 years (2015-2020) are retrospectively examined in this study. Microorganisms are identified by standard bacterial methods and their susceptibilities are assessed by VITEK 2 (bioMérieux, Marcy l'Etoile, France) automated system.

Results: The results of urine culture of 3380 suspected UTI cases are examined and out of 3097 positive cultures observed, a total of 1961 (63.3%) isolates are gram-negative and 1136 (36.7%) are gram-positive pathogens.

Conclusion: The most common urinary pathogen determined in this study is Escherichia coli. The highest resistances of gram-negative urinary pathogens are against the ampicillin, trimethoprim/sulfamethoxazole and ceftriaxone. It is thought that the data obtained from this study will be useful in the planning of empirical treatment of urinary tract infections and in the development of rational antibiotic use policies.

Keywords: Urine Culture, Urinary Tract Infections, Antimicrobial Resistance

INTRODUCTION

Urinary tract infections (UTIs) with a significant burden of economic are considered as common human's diseases of infectious and are a general health issue. UTIs, in the United States, are the most common urinary tract disease and are responsible for annual physician visits of more than 7 million and 15% of all antibiotics of community prescribed. Many European countries have similar incidence rates as well. (1) UTI-related health care costs are more than 3 billion $ per year globally (2). A systematic review by Beyer et al., reports the prevalence of UTIs in eight different countries to be between 17% and 82% (3). Gram-negative bacteria are the most common cause of UTI. The primary pathogens which lead to pyelonephritis and inflammation of uncomplicated bladder are *E. coli,* and other *Enterobacteriaceae* strains including *K. pneumoniae* and *P. mirabilis,* and gram-positive pathogens including *S. saprophyticus* and *E. faecalis* (4, 5). Urinary tract infections are common in women. A reason for this variation between the genders is due to anatomical differences such as a urethra of shorter and the fair urethra proximity to anus. Many other elements are involved, such as intercourse practices of sexual and utilizing spermicides that alter the natural flora of the vagina (6, 7).

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Several medications including fluoroquinolones, fosfomycin, trimethoprim-sulfamethoxazole, nitrofurantoin and beta-lactams are recommended in international recommendations for the treatment of pyelonephritis and tract infections of uncomplicated urinary tract infections (1, 5). Nevertheless, there is a worrying amount of resistance of antimicrobial in urinary pathogens because of the widespread and indiscriminate applying antibiotics. Broad-spectrum beta-lactamase-producing bacteria show resistance to several antibiotics regardless of carbapenem and are constantly enhancing within people (1, 8). Evaluation of pathogens and their sensitivity to different antibiotics has a high effect on the empirical treatment of patients with UTI, and if the appropriate antibiotic is selected by the physician, further costs and complications will be avoided. Health policies and rational antibiotic use protocols will be both more reliable and more applicable when created based on surveillance data.

The aim of this study is to provide surveillance data for the Erbil region and to evaluate the urine culture results according to gender and age groups and to reveal the contamination rates. Also, the prevalence of gram-negative pathogens and their antimicrobial susceptibilities in urine samples of patients referred to outpatient clinics in Erbil region.

METHODS

This cross-sectional-analytical retrospective study was performed to evaluate the results of urine culture of outpatients of Rzgary Teaching Hospital, Hawler Teaching Hospital, General Health Laboratory, and CMC Private Hospital which are all serving Erbil region during the years from 2015 to 2020. A total of 3380 samples were examined. Standard bacterial methods and biochemical tests together with VITEK 2 (bioMérieux, Marcy l'Etoile, France) automated identification system were used to identify uropathogens. VITEK 2 automated system was also used to evaluate antimicrobial susceptibilities of the causative bacteria according to Clinical & Laboratory Standards Institute: (CLSI Guidelines-M100). Outpatients over 18 years of age with positive urine culture reports were included in this study. Hospitalized patients and the patients who were younger then 18 years were excluded.

The results were evaluated based on the sex and age groups of 18-48 years, 46-60 years and more than 60 years. The antibiotic susceptibility panels including ampicillin, cefepime, aztreonam, cefixime, ceftriaxone, ertapenem, amoxicillin/clavulanate, piperacillin/tazobactam, amikacin, cefotaxime, imipenem, meropenem, ceftazidime, nitrofurantoin, levofloxacin, trimethoprim/sulfamethoxazole, ciprofloxacin and gentamicin were tested for the Gram-negative uropathogens.

As a limitation, since this study is retrospective, it was not possible to gather information such as previous or ongoing use of antibiotics which are not routinely questioned or recorded from outpatients.

Statistical Analyses

The data were analyzed using SPSS version 26.0 software (IBM Corp). The results of descriptive analysis were reported by tables and graphs. Chi-square test was used to examine the relationship between variables and a p value less then 0.005 is considered as significant.

RESULTS

Total number of 3380 urine cultures were evaluated retrospectively. Out 3380 cultures, 3097 (91.6%) were reported as positive. The contamination was determined in 95 (2.8%) of the cultures (Table 1). When evaluated according to age groups, there was not any significant difference in terms of "no growth", contamination or positive cultures ($p > 0.005$).

When all urine cultures were evaluated according to gender, 69.1% (n= 1045) of the urine cultures were requested from female outpatients where 30.9% (n= 2335) were from males. For the positive urine cultures, the ratios were similar and causative bacteria were more isolated from female patients. Moreover, significant difference was determined when positive urine cultures were evaluated according to age groups and sex. Urine culture positivity was higher in 18 to 45 years female age group compared to the male age group and in total (Table 2).

Table 1. Urine culture results according to age groups.

	18 to 45 years		46 to 60 years		>60 years		Total		
No growth	79	5.3%	56	5.8%	53	5.6%	188	5.6%	p > 0.005
Contamination	41	2.8%	22	2.4%	32	3.4%	95	2.8%	
Positive	1369	91.9%	877	91.8%	851	91%	3097	91.6%	
Total	1489	100%	955	100%	936	100%	3380	100%	

Among the positive urine cultures 1961 (63.3 %) of the isolates were gram-negative and 1136 (36.7%) were gram-positive pathogens. No significant difference was detected but gram-negative dominance was clearly observed between age groups and in total (Table 3).

The most common gram-negative pathogen identified was *E. coli*, which accounted for 70% of gram-negative isolates. *K. pneumoniae* (17%), *Proteus mirabilis* (3.9%) and *P. aeruginosa*

Table 2. Positive urine culture results according to age and sex groups.

	18-45 years		46-60 years		>60 years		Total		
Male	104	3.4%	326	10.5%	429	13.9 %	859	27.7%	
Female	11265	40.8%	551	17.8%	422	13.6 %	2238	72.3%	$p < 0.005$*
Total	1369	44.2%	877	28.3%	851	27.5%	3097	100%	

*For the 18 to 45 years group and when all age groups in total evaluated.

Table 3. Distribution of gram-negative and gram-positive pathogens according to age groups.

	18-45 years		46-60 years		>60 years		Total		
Gram-negative	867	28%	553	17.9%	541	17.5%	1961	63.3%	
Gram-positive	502	16.2%	324	10.5%	310	10%	1136	36.7%	$p > 0.005$
Total	1369	44.2%	877	28.3%	851	27.5%	3097	100%	

(3.4%) were the following most common pathogens, respectively (Table 4). Among gram-positive pathogens, coagulase negative *staphylococcus spp.* followed by *S. aureus* were most commonly isolated microorganisms.

Of the *Escherichia coli* isolates, 67.7% are resistant to ampicillin, 52% to TMP / SMX, 32.7% to ceftriaxone and 31.4% to cefixime. The lowest antibiotic resistance was reported to *Escherichia coli* for the antibiotics amikacin (0.2%), meropenem (0.3%), imipenem (0.4%) and ertapenem (0.4%). These four antibiotics also showed the highest sensitivity in other isolates. The pattern of resistance of antibiotics to *K. pneumoniae* was largely similar to that of *E. coli*. In *Enterobacter cloacae* complex isolate, the highest resistance was related to amoxicillin/clavulanate. Resistance to ertapenem and levofloxacin was reported in only three types of gram-negative urinary pathogens and the rest of the strains were quite sensitive. Only *S. marcescens* and *Salmonella* strains showed no resistance to Ciprofloxacin, and resistance to this antibiotic was observed in other strains (Table 5).

Table 4. Distribution of gram-negative uropathogens

Group	*Bacteria*	n	%
Fermentative (n=1868)	*E. coli*	1373	70.0
	K. pneumoniae	334	17.0
	P. mirabilis	77	3.9
	E. cloacae complex	27	1.4
	E. aerogenes	25	1.3
	K. oxytoca	12	0.6
	M. morganii	9	0.5
	S. marcescens	5	0.3
	Salmonella group	3	0.2
	Shigella group	3	0.2
Non-fermentative (n=93)	*P. aeruginosa*	67	3.4
	S. paucimobilis	4	0.2
	A. baumannii cplx	13	0.7
	A. haemolyticus	4	0.2
	A. lwoffii	5	0.3
Total		1961	100.0

Of the *E. coli* isolates, 38.6% were broad-spectrum beta-lactamase (ESBL) producing strains. However, the strains with the highest ESBL production were *Shigella group* (66.7%; 2 out of 3), *K. oxytoca* (41.7%; 5 out of 12) and *K. pneumonia*. (40.1%; 134 out of 334 cases). Overall, 35.5% (696 cases) of gram-negative isolates produced ESBL.

DISCUSSION

The problem of antimicrobial resistance in bacterial pathogens is described as a growing global crisis. The reported resistance to common pathogens in many parts of the world has reached a level where the experimental use of many of the strongest and most reliable antimicrobial agents available has been ineffective (9). The present study is unique because no research has been conducted with this large sample size in Erbil. The contamination rate is low as 2.8 % and there is no difference between age groups. This is compatible with literature. The urinary tract pathogens were determined higher in females in all age groups which is also as expected (4, 10). In general, the level of antimicrobial resistance among gram-negative uropathogens in Erbil is relatively high, which is a warning to prevent unnecessary use of antibiotics. Also in the present study, compared to others, the ratio of *E. coli* to other pathogens was higher. Therefore, the prevalence of *E. coli* is increasing compared to previous studies in Erbil.

Findings from previous studies have shown that resistance to antibiotics varies in different parts of the world. Developing countries such as India and Libya have reported very high resistance to conventional antibiotics (5). However, in the present study, antibiotic resistance was relatively high and it

Table 5: Antimicrobial resistance of gram-negative isolates.

Antibiotics	Gram negative uropathogens (percentage)														
	E coli	*K. pneumoniae*	*P. mirabilis*	*P. aeruginosa*	*S. paucimobilis*	*E. cloacae complex*	*A. baumannii*	*S. marcescens*	*Salmonella group*	*E. aerogenes*	*K. oxytoca*	*A. haemolyticus*	*A. lwoffii*	*M. morganii*	*Shigella group*
Ampicillin	67.7	74.9	59.7	29.9	25	0	0	0	0	0	58.3	0	0	55.6	33.3
Amoxicillin/Clavulanate	13.8	13.8	9.1	31.3	0	70.4	0	40	0	72	8.3	0	0	55.6	33.3
Amikacin	0.2	2.7	2.6	3	0	3.7	0	0	0	0	0	25	0	0	0
Aztreonam	5.9	6.9	1.3	0	0	3.7	0	0	0	8	16.7	0	0	0	33.3
Ceftazidime	25	33.2	3.9	10.4	0	48.1	30.8	0	0	44	16.7	0	0	11.1	66.7
Cefixime	31.4	31.4	7.8	31.3	25	48.1	0	20	0	52	0	0	0	11.1	0
Ciprofloxacin	26.5	9.3	10.4	6	25	3.7	30.8	0	0	4	16.7	25	20	11.1	33.3
Ceftriaxone	32.7	33.5	2.6	17.9	0	37	15.4	20	0	60	33.3	25	0	11.1	33.3
Cefotaxime	8.1	10.8	1.3	6	0	11.1	15.4	0	0	8	16.7	0	0	0	0
Ertapenem	0.4	0.9	1.3	0	0	0	0	0	0	0	0	0	0	0	0
Cefepime	4	4.5	2.6	3	0	3.7	7.7	0	0	8	0	0	0	0	33.3
Nitrofurantoin	2.1	7.8	62.3	25.4	0	0	7.7	40	33.3	12	0	0	0	33.3	0
Gentamicin	14.1	23.7	18.2	4.5	0	33.3	30.8	0	0	28	8.3	25	0	22.2	0
Imipenem	0.4	0.6	9.1	3	0	3.7	7.7	0	0	0	0	0	0	22.2	0
Levofloxacin	3.4	1.5	0	3	0	0	0	0	0	0	0	0	0	0	0
Meropenem	0.3	0.6	0	1.5	0	0	7.7	0	0	0	0	0	0	0	0
TMP/SXT	52	46.7	55.8	29.9	25	51.9	15.4	0	0	36	33.3	25	0	66.7	33.3
Piperacillin/tazobactam	4.9	3.3	0	9	0	7.4	30.8	0	0	24	16.7	25	0	0	33.3

*TMP/SXT: Trimethoprim/Sulfamethoxazole

seems that widespread and irrational use of antibiotics has caused this resistance. If available, planning of treatments depending on antimicrobial susceptibility testing results is a logical approach to prevent increased antimicrobial resistance. If antimicrobial susceptibility testing is not available, empirical treatment schemes should be designed with local data such as in this study to avoid the treatment failures with uneffective antibiotics.

In the present study, the most common uropathogen is *E. coli*, which accounted for 70% of gram-negative isolates, followed by *K. pneumonia* (17%), *Proteus mirabilis* (3.9%) and *P. aeruginosa* (3.4%). Previous studies have reported similar results. In the study of Ahmed et al. (2019), the most common uropathogens were *E. coli* (27%), *K. pneumoniae* (12.4%), *Proteus mirabilis* (4.5%) and *P. aeruginosa* (4.5%) (11). Aktaş and Denktaş (2017) identified *E. coli* as the most common strain (48%) among gram-negative pathogens, followed by *Klebsiella* (12). Abujnah et al. (2015) reported similar results in Libya. Osman (2019) Gupta et al. (2007) and Giwa et al. (2018) identified the most common gram-negative uropathogens as *E. coli*, *K. pneumoniae*, *P. mirabilis* and *P. aeruginosa* (13-16). The present study evaluated a larger sample than others, which increases the validity of the results.

In the present study, imipenem, meropenem, ertapenem and amikacin were the most effective antibiotics against gram-negative uropathogens (especially *Escherichia coli*). In the study of Aktaş and Denktaş (2020), *E. coli* strains showed the lowest resistance to these four antibiotics (12). A study by Ali et al. (2017) in Erbil showed the lowest resistance of *Escherichia coli* to imipenem (1.25%), meropenem and amikacin (1.9%) and Ertapenem (3.8%). These findings were consistent with our results. On the other hand, in the present study, *E. coli* strains showed the highest resistance to Ampicillin (67.7%), TMP / SXT (52%), Ceftriaxone (32.7%) and Cefixime (31.4%). Consistent with these findings, Edlin et al. Showed that *E. coli* strains in UTI patients were most resistant to ampicillin and trimethoprim / sulfamethoxazole (18). A study by Abujnah et al. (2015) in Libya showed that

the resistance to ampicillin in *Escherichia coli* and *Klebsiella* species was 69.2% and 100%, respectively (16). Similarly, the study of Osman (2019) and Mohammed et al. (2016) reported the highest antimicrobial resistance to ampicillin (15,16,19) Gupta et al. (2007) reported resistance of co-trimoxazole, ampicillin and ciprofloxacin to the three uropathogens of *E. coli*, *K. pneumoniae* and *Pseudomonas* between 90% to 96%, 92% to 98% and 55% to 65%, respectively (14).

ESBL-producing bacteria are resistant to many common antibiotics, and the increasing prevalence of these bacteria is an indicator of increased antimicrobial resistance. In the present study, 38.6% of *E. coli* strains were ESBL positive. Aktaş and Denktaş (2020) reported 27.8% of *E. coli* samples as extended-spectrum beta-lactamase-producing strains (12). Given the novelty of the above study, it can be concluded that the prevalence of EBSL-producing strains of *E. coli* in Erbil, Iraq is higher than in Turkey. It appears to be because of the unscrupulous use of antibiotics in Erbil. According to previous studies, the treatment of ESBL-producing *E. coli*, which is commonly observed in community-acquired UTIs, is a challenge (20). In the study of Giwa et al. (2018), ESBL-producing strains generally accounted for 34.3% of cases (13). These findings were consistent with the results of present study with a 35.5% prevalence of ESBL-positive bacteria.

CONCLUSION

The most common gram-negative urinary pathogen determined in this study was *E. coli*. The highest resistances of gram-negative urinary pathogens were against the antibiotic ampicillin, trimethoprim/sulfamethoxazole and ceftriaxone, and the lowest resistances were for amikacin, meropenem, ertapenem and imipenem. The results of this study also show that Gram-negative uropathogens show significant resistance to trimethoprim/Sulfamethoxazole and ciprofloxacin, which are uncomplicated first-line therapies for UTI, and are unlikely to be ineffective. One of the best options for antibiotic treatment is fluoroquinolones, that show significantly low resistance levels. The data presented in this study, which was collected over a long period of time and had a large sample size, can be useful for planning empirical treatment schemes and setting appropriate and rational antibiotic use policies.

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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 permission was obtained from the Sakarya University, Medical Faculty Clinical Research Ethics Committee for this study with date 30/06/2021and number E-40035, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: MSS, TD, MA; Design: TD, MA; Supervising: TD, MA; Financing and equipment: MSS, TD; Data collection and entry: MSS, HSG; Analysis and interpretation: MSS, HSG, TD, MA; Literature search: MSS, HSG; Writing: MSS, HSG, TD; Critical review: TD, MA.

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ORIGINAL RESEARCH

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The approach of society regarding the violence against healthcare providers

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Abstract

Objective: The aim of this study is to investigate the society's approach to violence and to offer solutions to prevent violence in health.

Methods: This study was conducted in Kahramanmaraş province in February and March 2020. The questionnaire of 50 questions was applied to 1306 people face-to-face.

Results: 53.8% of our participants were female. Among the people who had an argument with healthcare providers, 53.0% of them were male. 40.2% of the people who had an argument were aged 25-40. 78.1% have a high school or less education. 86.6% of the ones who considered violence as a tool of demanding justice had high school. Only 19.2% of the people who consider violence as demanding justice had information about code white. 82.9% of the people who state that the most significant reason for the violence is the attitude of healthcare providers had a high school or lower level of education. Participants were asked about the reasons for violence, and 44.0% of them answered that it was the presence of angry and aggressive people.

Conclusion: Violence in the health sector has many complicated and intertwined aspects. Its solution is for the people in charge to do their part.

Keywords: Violence, Health, Healthcare providers

INTRODUCTION

Violence is a very complex concept that has existed since the beginning of human history and has sociological, cultural, psychological, philosophical, political aspects, and takes away the right to live humanely. According to the definition of the World Health Organization (WHO), violence is the threat of intentional use of force resulting in injury, death, psychological harm, developmental delay or negligence against oneself, another person or a group (1).

With the development of societies, the value given to people has also increased, and the concept of violence and the reactions to the consequences of violence have also changed day by day (2). The definition, purpose, and orientation of violence vary from culture to culture, in different periods of the same culture (3). In a study, it was stated that the rate of exposure to violence in health sector workers in Türkiye is 50.8% and that the most frequent victims are general practitioners (67.6%) and nurses (58.4%) (4). In a study conducted in 2019, 90.5% of the participants stated that they experienced violence at least once during their work-life, and 50.8% stated that they experienced violence at least once in their workplace in the last

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year (5). In a multicenter study conducted in western Turkey, the frequency of being exposed to violence at least once in the last year was determined as 49.5% and it was reported that 48.3% of the cases were exposed to violence between 1-5 times (6).

This problem, which can increase the incidence of stress and depression, causes a decrease in the satisfaction of the job, thus causing serious disruptions and obstacles in the current functioning is one of the primary problems of health systems in developed and developing countries (7,8). In the study conducted by İlhan et al. on patients who applied to health institutions, 55.5% of the participants stated that violence in health is mostly seen in public hospitals, 56.3% of health institutions mostly experienced violence in emergency departments, 79.4% stated that their personnel was exposed to verbal violence the most (9).

The socio-economic effects of violence in health institutions, which are very important, can be seen in healthcare organizations and healthcare professionals, healthcare delivery and community (10). In the study conducted by Ayrancı et al., it was stated that 43.5% of the healthcare professionals who were subjected to violence did not report any mental problems, while 56.2% had mental trauma findings such as anxiety (6). In another study, it was stated that 55.0% of physicians who were subjected to violence were diagnosed with post-traumatic stress disorder and some mental trauma findings such as insomnia, stress, depression and agoraphobia were present (11).

Violence in healthcare institutions is defined as a form of situation consisting of threatening behavior, verbal assault, physical assault, and sexual assault that pose a risk to the healthcare worker from the patient, patient relatives or any other individual. (12). In the study of İlhan et al., it was stated that healthcare workers are 16 times more at risk of being exposed to violence than other workplaces (9). It is estimated that violence in health institutions is higher than detected. The reason for the lower rate of reporting of violence in health institutions is only because serious situations such as injuries are perceived as violence (4). The one-year prevalence of physical violence was reported in the review, which was published in 2020 and obtained from 65 different studies from 30 countries and aimed to measure the extent of physical violence against healthcare workers. The prevalence values ranged from 2.7% to 88.3%, the lowest one-year prevalence was found among nurses in Thailand, and the highest rate was observed among psychiatric nurses in the UK (13).

In Turkan's study, the causes of violence are low education level, as well as ignorance, intolerance and impatience, negative attitudes and behaviors of healthcare professionals, not going as expected in the treatment process, negative statements of politicians and health administrators, alcohol and drug use, psychiatric patient group, provocative publications in the media, the patients or their relatives' reflecting their own flaws to healthcare professionals, transfer of the health system problems of the past to the present, the attitude of the physicians in the centers where the patient is referred (14). According to a study conducted by ILO (International Labor Office), WHO, ICN (International Council of Nurses), PSI (Public Services International) in Bulgaria in 2002, the causes of violence in health institutions are stated as the current social and economic situation in the country, health reform, stress, and social tension, personality of patients, managerial skills of healthcare managers, patients with special conditions such as mental patients, security weaknesses, lack of legal procedures. (15).

This study is aimed at investigating the perceptions of individuals aged 18 and over on violence against healthcare professionals. Our aim is to investigate these violent incidents in the health sector from the eyes of society and to determine the reasons and raise awareness about the violence against healthcare workers in society.

METHODS

Our research is a descriptive and cross-sectional study. Our 50-question questionnaire was applied face-to-face between 01.02.2020-31.03.2020 for people who live in Kahramanmaraş province, who are 18 years of age and over, but are not health workers or who do not receive education in health departments.

Table 1. Distribution of demographic characteristics of the participants

	n	%
Age groups		
18-24	468	35.8
25-40	439	33.6
41 and over	399	30.6
Sex		
Male	603	46.2
Female	703	53.8
Marital Status		
Married	690	52,8
Single	616	47,2
Job		
Officer	146	11,2
Worker	167	12,8
Student	441	33,8
Housewife	260	19.9
Artisan	70	5.4
Retired	74	5.7
Self-employment	68	5.2
Unemployed	69	5.3
Other	11th	0.8
Education		
High school and below	1047	80.2
University and above	259	19.8
Economic status of the family		
Very bad	20	1.5
Bad	118	9.0
Middle	764	58.5
Good	367	28.1
Very good	37	2.8

Table 2. Characteristics of those stating negative statements -1

		Those who have an argument (n = 415)		I argue with the person victimizing me (n = 71)		The most important cause of violence is the attitude of healthcare providers (n = 310)		Those who say that being a doctor is not sacred (n = 208)		Those who see violence as seeking justice (n = 276)	
	n	n	%	n	%	n	%	n	%	n	%
Age Groups											
18-24	468	123	29.6	33	46.5	114	36.8	73	35.1	91	33.0
25-40	439	167	40.2	18	25.4	103	33.2	87	41.8	96	34.8
> 41	399	125	30.1	20	28.2	93	30.0	48	23.1	89	32.2
		χ^{2*} = 14.501 p = 0.001		χ^2 = 44.949 p <0.001		χ^2 = 2.490 p = 0.646		χ^2 = 9.526 p = 0.009		χ^2 = 1.272 p = 0.529	
Sex											
Male	603	220	53,0	44	62.0	154	49.7	126	60.6	166	60.1
Female	703	195	47,0	27	38.0	156	50.3	82	39.4	110	39.9
		χ^2 = 11.453 p = 0.001		χ^2 = 20.677 p <0.001		χ^2 = 2.416 p = 0.299		χ^2 = 20.657 p <0.001		χ^2 = 27.494 p <0.001	
Education status											
High school and below	1047	324	78.1	59	83.1	257	82,9	163	78.4	239	86.6
University and above	259	91	21.9	12	16.9	53	17.1	45	21.6	37	13.4
		χ^2 = 1.681 p = 0.195		χ^2 = 8.022 p = 0.091		χ^2 = 7.650 p = 0.022		χ^2 =, 506 p = 0.477		χ^2 = 9.089 p = 0.003	
Marital Status											
Married	690	234	56.4	30	42.3	163	52.6	88	42.3	150	54.3
Single	616	181	43.6	41	57.7	147	47.4	120	57.7	126	45.7
		χ^2 = 3.081 p = 0.079		χ^2 = 20.356 p <0.001		χ^2 = .020 p = 0.990		χ^2 = 10.999 p = 0.001		χ^2 = 0,322 p = 0,570	
Economic Status											
Bad	138	59	14.2	12	16.9	39	12.6	38	18.3	49	17.8
Middle	764	242	58.3	41	57.7	190	61.3	105	50.5	156	56.5
Good	404	114	27.5	18	25.4	81	26.1	65	31.3	71	25.7
		χ^2 = 10.034 p = 0.007		χ^2 = 23.372 p = 0.003		χ^2 = 6.933 p = 0.139		χ^2 = 16.619 p <0.001		χ^2 = 20.411 p <0.001	
Habit											
No habit	845	217	52,3	41	57,7	194	62.6	100	48.1	147	53.3
Cigarette + Wild tobacco	403	172	41.4	21	29.6	100	32.3	82	39.4	105	38.0
Alcohol + Other	58	26	6.3	9	12.7	16	5.2	26	12.5	24	8.7
		χ^2 = 41.142 p <0.001		χ^2 = 23.917 p = 0.002		χ^2 = 6.832 p = 0.145		χ^2 = 52.631 p <0.001		χ^2 = 27.200 p <0.001	
Knowing the white code											
I have no idea	648	207	49.9	46	64.8	163	52.6	101	48.6	148	53.6
I heard but I don't know what it is	313	100	24.1	7	9.9	73	23.5	57	27.4	75	27.2
I know	345	108	26.0	18	25.4	74	23.9	50	24.0	53	19.2
		χ^2 = .048 p = 0.976		χ^2 = 27.218 p = 0.001		χ^2 = 5.912 p = 0.206		χ^2 = 1.805 p = 0.405		χ^2 = 9.528 p = 0.009	
Relative from health sector											
There is	780	245	59.0	34	47.9	171	55.2	94	45.2	130	47.1
No	526	170	41.0	37	52.1	139	44.8	114	54.8	146	52.9
		χ^2 =, 120 p = 0.729		χ^2 = 7.041 p = 0.134		χ^2 = 3.710 p = 0.156		χ^2 = 21.720 p <0.001		χ^2 = 23.181 p <0.001	

* Chi-square or Fisher test was used.

Questionnaire questions include sociodemographic data, the place of health workers in society, view of violence against health workers, and evaluation questions about the thoughts about the violence experienced. The population of this study consists of voluntary participants who reside in … city and do not work in a health institution. Participants were informed and consent was obtained. According to TUIK 2019 data, the population of Kahramanmaraş is 1,154,102. The number of people aged 18 and over that constitute the population of the study was 768,577. The sample size was calculated as 1306 when 50% unknown frequency was calculated with a 3% margin of error and 97% confidence interval. This study has been applied to 1306 people from different age groups who are living in the houses, apartments and sites, student dormitories, workplaces in Kahramanmaraş city center, and accepted the survey.

Statistical Analysis

Mean and standard deviation are given in the descriptive statistics of continuous variables, and frequency (n) and percentage (%) values are given in the definition of categorical variables. Relationships between categorical variables were examined using Chi-square/Fisher's exact analysis. In cases where a significant difference was detected in chi-square analyzes with 2x3 and more groups, follow-up tests (post-hoc) were conducted to determine the groups from which the difference originated from. The data were transferred to IBM SPSS.23 program and evaluated with statistical analysis and $p < 0.05$ was accepted as the significance level in all analysis.

RESULTS

The demographic characteristics of the participants are shown in detail in Table 1. The proportions of men and women married and single in the study are close to each other, and it is seen that individuals from various professions and with different economic levels are included in the study.

As approximately two-third of the 891 participants stated that they had never had any discussions with a healthcare worker in any health institution, and 27 (2.1%) of them stated that they had more than five. Of those who had an argument, 152 (11.6%) stated that they had an argument with the doctor, 128 (9.8%) with the nurse, and 118 (9.0%) with the secretary. It is seen that the controversial behavior is mostly in the form of verbal discussion (31.2%) and assault (0.5%) at the least.

As shown in Table 2, 40.2% of the 415 participants who are "having a dispute" are from the 25-40 age group, 53% are men, 58.3% have a moderate economic situation, and 52.3% did not have a habit. A significant relationship was found between the participants who had an argument and age groups ($p = 0.001$), sex ($p = 0.001$), economic status ($p = 0.007$) and habits ($p < 0.001$).

Of the 71 participants who said that they would argue with the person who victimized themselves, 46.5% were in the 18-24 age group, 62% were male, 57.7% were single, 57.7% had middle economic status, and 57.7% did not have any habits while 64.8% of them did not know the white code. There is a significant relationship between the statement I would discuss with the person victimizing me and age group ($p < 0.001$), sex ($p < 0.001$), marital status ($p < 0.001$), economic status ($p = 0.003$), habit ($p = 0.002$) and knowing the white code ($p = 0.001$) (Table 2). 82.9% of 310 participants who think that "the most important cause of violence is the attitude of healthcare providers" have high school or lower education level and this situation is statistically significant ($p=0.022$) (Table 2).

Of the 208 participants who think that being a doctor is not sacred, 41.8% are from the 25-40 age group, 60.6% are male, 57.7% are single, 50.5% are from middle economic status, 48.1% do not have any habit and lastly 54.8% were people without relatives from health sector. A significant relationship is found between the age group ($p=0.009$), sex ($p<0.001$), marital status ($p=0.001$), economic status ($p<0.001$), habits ($p<0.001$) and not having a relative from health sector ($p<0.001$) among participants who think that being a doctor is not sacred (Table 2).

Of the 276 participants who define violence as seeking justice, 60.1% are male, 86.6% have a high school or below education level, 56.5% are from middle economic status, 53.3% have no habit, 53.6% of them do not know white code and 52.9% do not have relatives from health sector. A significant relationship was found between considering violence as seeking justice and sex ($p<0.001$), educational status ($p=0.003$), economic status ($p<0.001$), habituation ($p<0.001$), knowing white code ($p=0.009$) and having a relative from health sector (Table 2).

As shown in Table 3, 70% of 70 respondents who stated that nothing can stop them when they try to use violence are male, 87.1% have a high school or less education, 57.1% from middle economic status and 50% do not have any habit. A significant relationship was found between those who stated that nothing could stop them when they wanted to use violence and sex ($p<0.001$), educational status ($p = 0.008$), economic status ($p = 0.014$), and habits ($p<0.001$) (Table 3).

Of the 420 participants who think they are against violence but sometimes it is deserved, 37.6% are in the 25-40 age group, 52.1% are male, 80.7% have a high school or below education level, 55% are married, 61.9% of them have a moderate economic situation, 61% of them do not have a habit, 52.4% of them have no knowledge of white code and 55% of them have relatives from health sector. Those who think they are against violence but sometimes it is deserved were found to be related with age group ($p = 0.017$), sex ($p < 0.001$), educational status ($p = 0.032$), marital status ($p =$

Table 3. Characteristics of those stating negative statements -2

		Nothing stops me when I want to do violence (n = 70)		Those who say I am against violence, some deserve it (n = 420)		Those who say that violence can be applied if my child deserves it (n = 135)		Those who say that more than 50% of the violence is caused by healthcare workers (n = 250)		Those who say that violence does not impair their mental health (n = 201)	
	n	n	%	n	%	n	%	n	%	n	%
Age Groups											
18-24	468	30	42.9	144	34.3	44	32.6	79	31.6	61	30.3
25-40	439	22	31.4	158	37.6	55	40.7	83	33.2	81	40.3
> 41	399	18	25.7	118	28.1	36	26.7	88	35.2	59	29.4
		$\chi 2$ * = 15.800 p = 0.326		$\chi 2$ = 15.526 p = 0.017		$\chi 2$ = 13.274 p = 0.039		$\chi 2$ = 3.750 p = 0.153		$\chi 2$ = 5.265 p = 0.072	
Sex											
Male	603	49	70.0	219	52.1	84	62.2	124	49.6	93	46.3
Female	703	21	30.0	201	47.9	51	37.8	126	50.4	108	53.7
		$\chi 2$ = 29.315 p <0.001		$\chi 2$ = 27.820 p <0.001		$\chi 2$ = 17, 132 p = 0.001		$\chi 2$ = 1.462 p = 0.227		$\chi 2$ = 0.001 p = 0.976	
Education status											
High school and below	1047	61	87.1	339	80,7	118	87,4	213	85,2	175	87.1
University and above	259	9	12.9	81	19,3	17	12,6	37	14,8	26	12.9
		$\chi 2$ = 19.001 p = 0.008		$\chi 2$ = 8.833 p = 0.032		$\chi 2$ = 17.274 p = 0.001		$\chi 2$ = 4.923 p = 0.026		$\chi 2$ = 7.106 p = 0.008	
Marital Status											
The married	690	33	47.1	231	55.0	71	52.6	143	57.2	113	56.2
Single	616	37	52.9	189	45.0	64	47.4	107	42.8	88	43.8
		$\chi 2$ = 7.934 p = 0.338		$\chi 2$ = 9, 061 p = 0.028		$\chi 2$ = 1.666 p = 0.645		$\chi 2$ = 2.366 p = 0.124		$\chi 2$ = 1.093 p = 0.296	
Economical situation											
Bad	138	13	18,6	53	12.6	30	22.2	41	16.4	26	12.9
Middle	764	40	57.1	260	61.9	79	58.5	147	58.8	109	54.2
Good	404	17	24.3	107	25.5	26	19.3	62	24.8	66	32.8
		$\chi 2$ = 27.971 p = 0.014		$\chi 2$ = 22.541 p = 0.001		$\chi 2$ = 26.384 p <0.001		$\chi 2$ = 13.723 p = 0.001		$\chi 2$ = 2, 280 p = 0.320	
Habit											
No habit	845	35	50	256	61.0	69	51.1	133	53.2	107	53.2
Smoking + Wild tabacco	403	24	34.3	147	35.0	55	40.7	104	41.6	76	37.8
Alcohol + Other	58	11th	15.7	17	4.0	11th	8.1	13	5.2	18	9.0
		$\chi 2$ = 87.107 p <0.001		$\chi 2$ = 78.728 p <0.001		$\chi 2$ = 23.124 p = 0.001		$\chi 2$ = 18.285 p <0.001		$\chi 2$ = 19.451 p <0.001	
Knowing the white code											
I have no idea	648	43	61.4	220	52.4	77	57.0	138	55.2	99	49.3
I heard but I don't know what it is	313	12	17.1	104	24.8	21	15.6	53	21.2	48	23.9
I know	345	15	21.4	96	22.9	37	27.4	59	23.6	54	26.9
		$\chi 2$ = 19.633 p = 0.142		$\chi 2$ = 24.302 p <0.001		$\chi 2$ = 24.726 p <0.001		$\chi 2$ = 3.858 p = 0.145		$\chi 2$ = .025 p = 0.987	
Relative from health sector											
There is	780	35	50	231	55.0	65	48.1	138	55.2	98	48.8
No	526	35	50	189	45.0	70	51.9	112	44.8	103	51.2
		$\chi 2$ = 14.840 p = 0.380		$\chi 2$ = 23.943 p <0.001		$\chi 2$ = 10.721 p = 0.013		$\chi 2$ = 2,631 p = 0.105		$\chi 2$ = 11.881 p = 0.001	

* Chi-square or Fisher test was used.

0.028), economic status (p = 0.001), habit (p <0.001), knowing the white code (p <0.001) and having a relative from health sector (p <0.001) (Table 3).

Of the 135 people who think that violence can be used when they deserve it, 40.7% are in the 25-40 age group, 62.2% are male, 87.4% have a high school or less education, and 58.5% have a middle economic status, 51.1% have no habit, 57% do not know the white code, and 51.9% do not have a relative from health sector. A significant correlation was found between educational status (p = 0.001), economic status (p <0.001), habituation (p = 0.001), knowing the white code (p <0.001) and having a relative from health sector (p = 0.013) (Table 3).

A significant relationship was found between those who think that more than half of the violence in health is caused by the behaviors of healthcare workers and their educational status (p = 0.026), economic status (p = 0.001), and habituation (p <0.001) (Table 3).

Of the 201 participants who think that the psychology of healthcare workers who are exposed to violence will not be impaired, 87.1% of them have a high school or less education level, 53.2% have no smoking or alcohol habits, and 51.2% have no relatives from health sector. A significant relationship was found between those who think that the psychology of healthcare workers exposed to violence will not deteriorate and their educational status (p = 0.008), habituation (p <0.001) and having a relative from health sector (p = 0.001) (Table 3).

DISCUSSION

Since the violence experienced in health institutions creates a serious social problem, many studies are conducted on this issue. Studies mostly show the perspective of healthcare professionals. This study, unlike most studies, is aimed at determining the public's perspective on violence in health. Health services are a whole consisting of patients and healthcare professionals, it is not possible to perform this service in an environment of violence. Violence must end in order to provide this service.

As approximately one-third of the 415 participants stated that they discussioned with a healthcare worker in a health institution so far. Most of the discussions were with the doctor (11.6%) in a state hospital (18.8%), and in the emergency department (10.2%). It has been reported that most of the discussions in Sarcan's study in the field of health services were experienced with doctors, in the state hospital, and the emergency department of the hospital (16). In the study conducted by İlhan et al., the participants stated that healthcare workers were exposed to violence mostly in emergency services and it occurred mostly in public hospitals (9). In the study of Ayrancı et al., it was determined that 63.1% of the violence occurred in emergency services and 63.1% in state hospitals (6).

In this study, only 9 (0.7%) of the 415 (31.8%) participants who experienced controversy stated that they used physical violence and 13 (1.0%) stated that they used psychological violence. Almost all of those who experienced an argument stated that their discussion was verbal violence. In Gündüz's study in 2019, 93% of the patients stated that they did not have any discussions with healthcare workers before, and 94.3% stated that they had never used violence against healthcare workers before (17). In a study conducted by Kuruöz in 2016 with 394 participants of patients and their relatives in the emergency service, 83 (21%) people stated that they had an argument with healthcare professionals, 6 (1.5%) people used physical violence, and the remaining 79 people stated verbal violence (18). In Sarcan's study on healthcare services, it was observed that 49.1% of the participants used verbal violence and 3.1% used physical violence (16). Winstanley et al. (19) stated that verbal violence rate was 68% in their study regarding healthcare providers, İlhan et al. reported as 80% and this rate was identified to be changing between 53.7% and 60% in other studies (20, 21) conducted with healthcare providers in Turkey. In a study conducted in the United States of America, it was observed that 74.9% of emergency doctors were subjected to verbal violence (22). If we look at other violence against healthcare professionals, in a study conducted in 10 European countries (Belgium, Finland, France, Netherlands, Germany, Norway, Slovakia, England, Italy, and Poland), 77,681 nurses received a questionnaire between 2002 and 2003, 39,894 people answered it, 22.0% of nurses (8,778) were reported to have been exposed to violence (23). It has been stated that 68.0% of the healthcare workers in the UK have been subjected to verbal violence and 27.0% to physical violence in the last year (24). In the study conducted with 1973 healthcare workers from 39 different institutions in Germany, it was found that 56.0% were subjected to physical violence, 78.0% to verbal violence, and 10.5% to sexual harassment (25). In the study conducted in Finland, it was reported that one out of every ten healthcare workers experienced violence in the workplace where they worked in the last year (26). It is seen that mostly oral discussions take place in the studies. The reason why verbal violence is experienced more may be that those who perpetrate this violence think that they will not be punished for verbal violence or that the punishment will not be severe. The fact that the rates of responses to questions of violence are far from each other because of the participants' not being healthcare workers or being healthcare workers originates from the participant population's being completely different in this study.

If we look at the results regarding the questions that reflect the perspective of the society toward healthcare professionals, 38.6% states the main reason of violence against healthcare providers is the people receiving the health service, 37.4% states as the healthcare system, and 23.7% considers it as the people providing the health care service. In the study conducted by Bıçkıcı with healthcare workers, the reason for the violence was determined as the health system (43.6%), the attitudes of the healthcare providers (25.6%), the attitudes of the healthcare providers (2.6%), and all of the above (28.2%) (27). Although we did not ask the healthcare professionals in this study, the fact that most participants (76.3%) indicated the health system and health service as the reason is an important guide for focusing on this area.

If we look at the information about society's perspective on violence; 78.9% of the participants do not consider using violence as a method of seeking justice, 16.2% partially support this idea and 4.9% definitely support it. In Sarcan's study, 79.7% of the participants stated that violence is not a way of seeking justice, 20.3% stated that violence is a way of seeking justice (16). In Gündüz's study with patients, 93.7% of the participants stated that violence is not a method of seeking remedies, 2.7% stated that it is a method of seeking remedies (17). The fact that twenty percent of those who perceive violence as a method of seeking justice is a terrifying issue that needs to be dwelled on.

95.0% of the participants think that violence against healthcare workers will not be a solution. In a study published in 2019, in line with this study, the participants thought that violence against healthcare workers would not be a solution (28).

In this study, the majority of those who had an argument with healthcare workers were between the ages of 25-40, and those who said that they would argue with those victimizing them were mostly in the 18-24 age group, and this situation was found to be statistically significant. Those who thought they were against violence, but some doctors deserved it, were significantly in the 25-40 age group. In Sarcan's study on non-healthcare professionals, the age range of those who resort to violence is between 24 and 30 years old (16). In a study conducted in Türkiye by Çevik et al. In 2020, in which 948 physicians participated, it was stated that physicians among those between the ages of 25-50 (78.7%) were exposed to violence the most. (29). Similarly, in this study, the age range of 25-40 years was the majority, and in some, 18-24 years were the majority.

In this study, those who had discussions with healthcare professionals, who said that they would argue with those victimizing them, who saw violence as seeking justice, and those who thought that they were against violence but some doctors deserved it were significantly included in the male sex group. In the study of Al et al., the characteristics of those prone to violence are male and having a low socioeconomic level (30). In Öztürk and Babacan's study with patients and healthcare professionals, both patients and healthcare professionals stated that most perpetrators of violence were men (31). In Sarcan's study, it is seen that those who resort to violence are mostly men (16). The prominence of the male sex in relation to the female sex may be due to our patriarchal society and cultural lifestyle.

Those who regarded violence as seeking justice and who thought that they were against violence but some doctors who deserved it were mostly and statistically significantly consisted of those with high school or lower education levels. In the study of Annagür et al., it was stated that the education level of those who were violent was low. (32). We believe that increasing the level of education will significantly reduce violence.

CONCLUSION

This study provides clues to the solution of violence in the health sector, which tends to increase gradually, by asking questions about the solution of this problem, as well as determining the perspective of the society on violence in the health sector.

In this study, it was determined that as approximately one-third of the participants had discussions in health institutions, they lived this discussion mostly in state hospitals, mostly with doctors, then with nurses and secretaries, they mostly experienced in emergency services as a department, and the violence they used was generally verbal violence. Healthcare workers generally do not complain about verbal violence. The fact that the legal sanctions and punishments to be taken because of acts of violence against healthcare workers is effective and deterrent and raising awareness about these deterrent penalties in the society can reduce the incidents of violence.

The rate of those who think they are against violence but sometimes it is deserved is as approximately one-third of the participants. This answer is an effective result showing the level of violence. 40.2% of those experiencing a dispute are between the ages of 25-40, 53.0% are male, 78.1% have a high school or less education, 56.4% are married, 26.0% know the white code. Struggling with the problem of education, which is one of the most fundamental problems of the society, training on violence and the health system from the beginning of the education period can change the way of seeking justice.

Employing personnel according to the intensity of the emergency services and the fact that the personnel working

there are qualified to manage crises and communicate well with patients, and the increase in security measures in proportion to this density may reduce the occurrence of violence. Also, the fact that the news and publications that blame and defame healthcare professionals for malfunctions in the health system are not judgmental can be beneficial for both physicians and patients.

As the limitations of our study were that the questionnaires were conducted face-to-face, the participants may have hesitated while answering the questions about violence and may have hidden their true thoughts or negative events.

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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 the Kahramanmaraş Sütçü İmam University Faculty of Medicine Non-Pharmaceutical Clinical Research Ethics Committee with the date 19.02.2020 and number 12, and Helsinki Declaration rules were followed to conduct this study.

Authorship contribution

Concept: YGU, CK, Design: YGU, CK, MEE, Supervising: CK, RŞG, Financing and equipment: YGU, CK, Data collection and entry: YGU, MEE, Analysis and interpretation: CK, RŞG, Literature search: YGU, RŞG, Writing: YGU, CK, MEE, Critical review: CK, RŞG.

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Comparison of efficacy of Ketorolac %0.4 and Dexamethasone %0.1 in inflamed Pterygium and Pinguecula

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Abstract

Objective: This study investigated the effect of the ketorolac %0.4 and dexamethasone %0.1 on suppressing symptoms in inflamed pterygium and pinguecula.

Methods: 50 patients were included in the study. The patients were divided into two groups, each consisting of 25 patients. Ketorolac %0.4 eye drops were dropped in group 1, and dexamethasone %0.1 eye drops were started in group 2. Groups were compared 3,7,14,30,45. days in terms of total signs and symptoms.

Results: After 14 days of drug administration group 1, scores were reduced %85 for total signs (2.52+1.16, p=0.001), %86 for total symptoms (4.10+2.61, p=0.001) and total scores showed a significant reduction of %86 (6.62+2.91, p=0.001) for the score. After 14 days of drug administration in group 2, scores were reduced %85 for total signs (2.70+1.46, p=0.001), %86 for total symptoms (4.25+2.36, p=0.001), and total scores showed a significant reduction of %86 (7.10+2.99, p=0.001) for the score. The scores for each sign and symptom decreased during the study. However, the statistical evaluation of each sign and symptom was similar in groups 1 and 2. There was no difference between groups 1 and 2 for total signs, total symptoms, and total score on days 3,7 and 14. No significant difference was found between groups 1 and 2 for total signs, total symptoms, and total score on days 14,30 and 45 (p>0.05).

Conclusion: Current study revealed that topical ketorolac %0.4 solutions are as effective as dexamethasone in treating inflammatory pterygium and pinguecula. We suggest that it can be used alone to treat this disease. We need more studies to support our work.

Keywords: Pterygium, Pinguecula, Ketorolac, Dexamethasone

INTRODUCTION

Repetitive microtrauma, solar radiation, chronic irritation, and many other factors are thought to be effective in developing pterygium and pinguecula. (1-3). They consist of newly synthesized elastic fibers, presumably synthesized by actinically damaged fibroblasts of the substantial propria. (4). Some researchers have suggested that the inflammatory mechanism (5,6) may be responsible for the development of pterygium and pinguecula while others have suggested that the immune (7) and angiogenic mechanism (8) may be responsible.

Pterygium and Pinguecula may develop due to dry eye, mechanical irritation, and other tear film anomalies (9). Pinguecula is a yellowish lesion derived from the nasal conjunctiva and located close to the limbus (10). The incidence increases in the presence of male gender, age, UV rays and Diabetes Mellitus (11). Histological studies reported abnormal differentiation and squamous metaplasia of the conjunctival epithelium, exaggeration and distortion in the production of elastic fiber s, and abnormality of their organization in the subepithelial connective tissue (12). The incidence in the population varies between 22.5% and 70.1% (13). This change in prevalence may vary depending on age, ethnicity, geographical location.

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Inflamed pterygium and pinguecula are primarily seen in chronic eye discomfort, itching, foreign body sensation in the eye, pain, watering, and redness. Topical lubricants and steroid-containing drops are used for highly symptomatic patients. However, the patient's complaints may recur after the treatment is stopped. In addition, continued use of steroids in mildly inflammatory patients may be undesirable due to associated complications (cataracts and increased intraocular pressure) (14).

Topical non-steroidal anti-inflammatory drugs have limited use in ophthalmology (15-18) and have fewer side effects than topical steroids (19). In addition, topical 0.4% ketorolac for two weeks can control the inflamed pterygium and pinguecula (20). Therefore, topical non-steroidal anti-inflammatory drugs may be preferred instead of topical steroids in inflamed pterygium and pinguecula. Consequently, we conducted a study comparing the efficacy of topical ketorolac 0.4% and topical dexamethasone 0.1% in patients with symptomatic pterygium and pinguecula.

METHODS

The study was conducted in Düzce Atatürk State Hospital in a prospective, double-masked and controlled manner with ketorolac 0.4% and dexamethasone 0.1% topical eye drops between January 2021 and April 2021 on the signs and symptoms of patients with inflammatory pterygium and pinguecula. 50 (25 male, 25 female) patients were included in the study. The age range of the patients ranged from 25 to 78. Sixteen of the patients had pterygium, and 34 of them had pinguecula. Photophobia, eye pain, watering, eye discomfort, and foreign body sensation in the eye were accompanied by sudden eye redness in all patients. All patients had inflammation in one eye. Exclusion criteria from the study were those with a Schirmer test less than 10 mm, who took systemic analgesic or immunosuppressive agents, who had previous keratitis, those who used contact lenses, and those with a last inflammatory conjunctival disease.

All patients underwent a complete ophthalmologic examination, including visual acuity, slit-lamp examination, intraocular pressure measurement, fundoscopic examination, and Schirmer test. Objective symptoms included corneal or conjunctival staining, conjunctival congestion or edema, and flushing. All these objective findings were evaluated on a scale (0=no findings, 1=mild, 2=moderate, 3=severe), and each patient was given a score. The sum of this scoring was called the total objective finding score. Subjective symptoms were Photophobia, eye pain, burning, foreign body sensation, discomfort in the eye, and watering. Each patient scored all subjective symptoms on a scale (0=no symptoms, 1=mild, 2=moderate, 3=severe), and this total was subjective and constituted the symptom score. The sum of total objective symptom scores and total subjective symptom scores were called the total score.

All patients were numbered from 1 to 50. Odd numbers constituted group 1. There were 16 female and nine male patients in group 1, and the mean age was 47. Topical ketorolac 0.4% eye drops were dropped. Ketorolac 0.4% eye drops were instilled six times daily for the first four days. Between 5-14 days, it was applied as a drop four times a day, the drug was discontinued on the 14th day, and the follow-up of the patients continued until the 45th day.

The even numbered patient group constituted group 2. Group 2 included nine female and 16 male patients. In Group 2, the mean age was 43 years. Dexamethasone 0.1% topical eye drops were started in group 2. Dexamethasone eye drops were instilled six times daily for the first four days. Then, between 5-14 days, it was applied as one drop four times a day, the drug was discontinued on the 14th day, and the follow-up of the patients continued until the 45th day.

Statistical analysis

SPSS 11.5 program was used in the analysis of the data. Mean ± standard deviation and median (minimum-maximum) were used as descriptors for quantitative variables, and the number of patients (percentage) for the qualitative variable. The Mann-Whitney U test was used to determine whether there was a difference between the qualitative variable and the two categories of quantitative variables since the assumptions of normal distribution were not met. When the relationship between two quantitative dependent variables was wanted to be examined, the Wilcoxon Signed Rank test was used since the assumptions of normal distribution were not met. The statistical significance level was taken as 0.05.

RESULTS

One patient from each group of 50 patients left the follow-up on the 14th and 30th days of the treatment.

At enrollment, 46 of 50 patients had conjunctival congestion, 46 had redness, and 6 had punctate staining. In addition, photophobia was present in 9 patients, pain in 17 patients, foreign body sensation in 30 patients, eye discomfort and burning sensation in 41 patients, and watering in 9 patients.

Before treatment, none of the signs and symptoms studied differed in the two groups (p=0.809, p=0.990, and p=0.927, respectively). In Group 1, mean prior to treatment scores were 5.57±1.57 for total signs, 9.90±4.35 for total symptoms, and 15.62±5.07 for total scores. İn Group 2, mean scores before treatment were 5.52±1.59 for total signs, 9.85±4.25 for total symptoms, and 15.55±5.24 for total scores (Table 1).

Table 1. Scores before medical treatment in inflammatory pterygium and pinguecula group 1 (ketorolac 0.4%) and group 2 (dexamethasone 0.1%)

Variables	Group 1		Group 2		
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	p-value
Total Signs	5.57±1.57	5.00 (2.00-9.00)	5.52±1.59	5.00 (2.00-9.00)	0.809
Total Symptoms	9,90±4,35	9,00 (5.00-18.00)	9.85±4.25	8.50 (4.00-18.00)	0.990
Total Score	15.62±5.07	15.00 (9.00-27.00)	15.55±5.24	14.00 (9.00-27.00)	0.927

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

After 14 days of drug administration in group 2, scores were reduced 85% for total signs (2.70+1.46, p=0.001), 86% for total symptoms (4.25±2.36, p= 0.001) and total scores showed a significant reduction of 86% (7.10+2.99, p= 0.001) for the score. (Table 2).

The scores for each sign and symptom decreased during the study. However, the statistical evaluation of each sign and symptom was similar in groups 1 and 2. There was no difference between groups 1 and 2 for total signs, total symptoms, and total scores on days 3, 7, and 14 (p>0.05) (Table 2).

On the 14th, 30th, and 45th days, it was checked whether each of the signs and symptoms differed between groups 1 and 2. No significant difference was found between groups 1 and 2 for total signs, total symptoms, and total score on the 14th, 30th, and 45th days (p>0.05) (Table 3). Each sign on the 14th, 30th, and 45th days and whether the symptom differed between groups 1 and 2. No significant difference was found between groups 1 and 2 for total signs, total symptoms, and total score on days 14, 30, and 45 (p>0.05) (Table 3)

All-time descriptors for the total score in groups 1 and 2 are given in Figure 1.

In the study, one patient had a headache (group 1), and one patient had eyelid swelling that disappeared despite the continuous use of drops. No other complication related to drug use occurred.

Table 2. Post-medical treatment scores, 3-, 7-, and 14-days group 1 and group 2

Variables		Group 1		Group 2		
		Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	p-value
Total Signs	Day 3	4.65±1.72	4.00 (1.00-9.00)	4.57±1.53	5.00 (1.00-7.00)	0.750
	Day 7	3.48±1.56	3.00 (1.00-8.00)	3.70±1.36	4.00 (1.00-8.00)	0.246
	Day 14	3.04±1.07	3.00 (1.00-5.00)	2.83±1.15	3,00 (1.00-5.00)	0.524
Total Symptoms	Day 3	8.10±3.81	7.00 (3.00-17.00)	7.75±3.46	7.00 (2.00-15.00)	0.864
	Day 7	6.62±3.09	6.00 (2.00-14.00)	6.45±3.19	6.00 (2.00-14.00)	0.864
	Day 14	5.81±2.84	5.00 (2.00-13.00)	5.60±2.54	5.00 (2.00-11.00)	0.958
Total Score	Day 3	12.90±4.81	11.00 (7.00-26.00)	12.50±4.22	12.00 (7.00-22.00)	0.948
	Day 7	10.24±4.07	9.00 (5,00-21.00)	10.30±3.83	10.00 (5.00-19.00)	0.792
	Day 14	9.00±3.21	8.00 (6.00-17.00)	8.45±2.96	7.50 (4.00-15.00)	0.680

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

DISCUSSION

Inflammation is joint among advanced pterygium and pinguecula ocular surface diseases. Although this inflammatory process is self-limiting mainly (20), most patients require medical treatment to alleviate symptoms and signs. Most patients with provocative eyes use vasoconstrictors or topical steroids intermittently or continuously. Inflamed pterygium and pinguecula, we determined the efficacy of topical ketorolac 0.4% solution and the natural history of this disease. Since we examined the same patient population living in the same environment and treated by the same ophthalmologists, the use of topical ketorolac 0.4% with 0.1% topical dexamethasone was not included in patients treated with placebo patients we compared.

Table 3. Posttreatment Scores, Days 14, 30, and 45, in Patients in Group 1 and Group 2

Variables		Group 1		Group 2		
		Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	p value
Total Signs	Day 14	3.04±1.07	3.00 (1.00-5.00)	2.83±1.15	3.00 (1.00-5.00)	0.524
	Day 30	0.70±0.77	1.00 (0.00-2.00)	0.83±0.98	0.00 (0.00-3.00)	0.802
	Day 45	0.04±0.21	0.00 (0.00-1.00)	0.22±0.52	0.00 (0.00-2.00)	0.154
Total Symptoms	Day 14	5.81±2.84	5.00 (2.00-13.00)	5.60±2.54	5.00 (2.00-11.00)	0.958
	Day 30	0.90±1.22	1.00 (0.00-4.00)	1.15±1.09	1.00 (0.00-3.00)	0.324
	Day 45	0.20±051	0,00 (0.00-2.00)	0.25±0.72	0.00 (0.00-3.00)	0.932
Total Score	Day 14	9.00±3.21	8.00 (6.00-17.00)	8.45±2.96	7.50 (4.00-15.00)	0.680
	Day 30	1.67±1.68	1.00 (0.00-6.00)	2.10±1,68	2.00 (0,00-5,00)	0.365
	Day 45	0.24±0,54	0.00 (0.00-2.00)	0.50±1.00	0.00 (0.00-4.00)	0.394

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

Application of topical ketorolac 0.4% solution (group 1) in patients with inflammatory pterygium and pinguecula reduction is 85% for total signs (2.52+1.16, p=0.001) and 86% for total symptoms (4.10±2.61, p= 0.001) and 86% (6.62+2.91, p= 0.001) for the total score. A 14-day application of topical dexamethasone 0.1% similarly resulted in a similar reduction in total signs, total symptoms, and total score. In addition, the efficacy of topical dexamethasone was not different from the

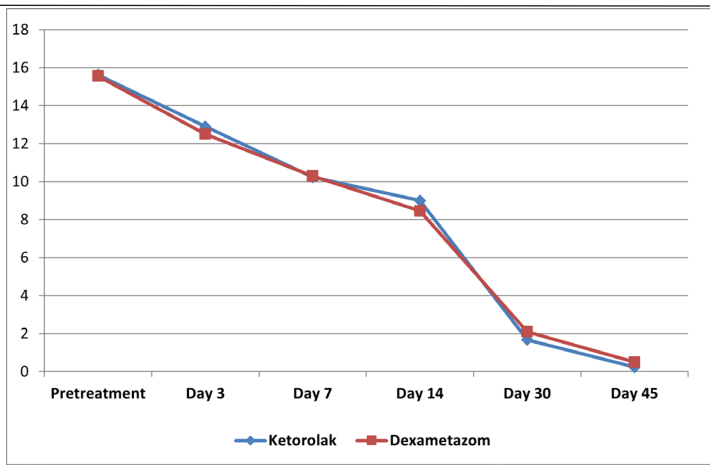

Figure 1. Identifiers oftwo groups for total score

efficacy of topical ketorolac. Patients in both groups stated that they were satisfied with the treatment. In addition, the lubricant (3) properties of instillation of the drops may have had some beneficial effects on our patients.

In a study conducted by Frucht-Pery J et al., as a result of using indomethacin 0.1% for 14 days, they found an 85% decrease in total sings, an 86% decrease in total symptoms, and an 86% decrease in total score. İn the same study, after 14 days of dexamethasone 0.1% use, they found a 91% decrease in total sings, a 95% decrease in total symptoms, and a 93% decrease in total score (30).

Another study conducted by Karlok bh et al., found that the length of the pterygium decreased from 1.5 mm to 1.00 mm as a result of 12-month use of dipyridamole in patients with inflamed pterygium.it was found that the height of the pterygium decreased to 0.3 mm per 1.00 mm. It was observed that hyperemia and vascularization in the conjunctiva completely regressed.

In a study conducted by J Frucht-Pery et al., in inflamed pterygium, a significant decrease in total symptoms, total score and total signs was observed after 14 days of topical indomethacin 0.1% use (19).

Although inflammation is suppressed in treated patients, the ocular surface lesion and primary pathology remain, and signs and symptoms may recur. The analgesic effects of topical indomethacin (18) and diclofenac (21,22) have been reported. Anti-inflammatory (17,24-29) activities are used in cataract surgery and trabeculoplasty operations. These reports show that topical non-steroidal anti-inflammatory drugs are at least as effective as topical steroids in treating ocular surface inflammation (17,28,29).

Most importantly, although topical non-steroidal anti-inflammatory drugs are safer than the uncontrolled use of topical steroids, which can cause many complications, non-steroidal anti-inflammatory drugs have some side effects.

Our findings showed that topical dexamethasone 0.1% had no superiority over topical 0.4% ketorolac solution in treating inflamed pterygium and pinguecula. Our study revealed that a topical 0.4% ketorolac solution is as effective as 0.1% dexamethasone in treating inflammatory pterygium and pinguecula.

CONCLUSION

Inflamed pterygium and pinguecula are frequently encountered in the clinic. Our studies showed us that the efficacy of ketorolac %0.4 and dexamethasone %0.1 in reducing total symptoms and total signs in inflammatory pterygium and pinguecula is not superior to each other. This study showed that ketorolac %0.4 alone can be used in this disease. More comprehensive and prospective studies are needed to support current study.

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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 permission was obtained from the Duzce University, Medical Faculty Clinical Research Ethics Committee for this study with date 25-07-2022 and number 2022/139, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept:K.Ç Design: K.Ç, Ş.K, Supervising: K.Ç,Ş.K Financing and equipment: K.Ç,Ş.K Data collection and entry:Ş.K Analysis and interpretation: K.Ç,Ş.K, Literature search:Ş.K, Writing: K.Ç, Critical review: Ş.K

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The relationship between prognostic nutritional index and mortality in patients hospitalized with COVID-19 Pneumonia

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Abstract

Objective: We aimed to investigate the ability of the Prognostic Nutritional Index (PNI) score to predict the prognosis and mortality of patients hospitalized for COVID-19 Pneumonia.

Methods: One hundred seventy-three patients were included in the study. The patients were grouped as patients with or without pneumonia, those who were hospitalized in the ward or intensive care unit, who were discharged, or who died. The ability of the PNI score, which was calculated according to the results at the time of admission, to predict hospitalization and mortality in the intensive care unit was evaluated.

Results: The mean age of the patients was found to be 53.9 years. Pneumonia was detected in 72.3% of the patients. The need for intensive care developed in 26% of them. The PNI score was found to be significantly lower ($p<0.05$) in patients with pneumonia compared to patients without pneumonia. The PNI score of the patients hospitalized in the intensive care unit was found to be significantly ($p<0.05$) lower than the patients hospitalized in the ward. The PNI score of the patients who died was found to be significantly lower ($p<0.05$) than the patients who were discharged. The cut-off value of the PNI score was found to be 46.

Conclusion: The PNI score which are among routine blood tests, was found to be effective in predicting intensive care unit admission and mortality. We believe that using the PNI score together with other biomarkers will be beneficial for clinicians in the prediction of the prognosis of patients.

Keywords: Albumin, COVID-19, Lymphopenia, Prognostic Nutritional Index, Prognosis

INTRODUCTION

COVID-19 is defined as an epidemic of viral pneumonia that begins with cold symptoms, progresses to severe pneumonia, and can result in multiple organ failure and ARDS (1). Although COVID-19 can be seen at any age, its frequency increases in advanced age, and critical illness and death are more common. Advanced age, male gender were associated with poor prognosis and mortality (2). Mortality and morbidity were also found to be high in patients who presented with fever, shortness of breath and were found to have pneumonia. It has been reported that the prognosis is poor in those with comorbid diseases. Due to the excessive inflammation seen in the pathogenesis of COVID-19, clinical pictures suggesting cytokine storm or macrophage activation syndrome are seen in the follow-up of these patients after the 7th day (3-7). When biochemical tests are examined, C-Reactive protein (CRP), Procalcitonin (PCT), Ferritin, D-Dimer, Lactate Dehydrogenase (LDH) elevation, hypoalbuminemia are used in clinical practice as a poor prognostic indicator in the diagnosis and follow-up of the disease in the course of COVID-19. Lympopenia has been reported frequently in COVID-19. An excessive immune response is thought to cause lymphopenia (8). Neutrophil/lymphocyte ratio (NLR) is a parameter that has been used for many years to predict prognosis in the course of bacterial and viral infections, and this ratio has been used in many studies. NLR has also been used

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to predict the prognosis of patients in the course of COVID-19 (9). Prognostic nutritional index (PNI) is considered as a parameter that reflects the immunological and nutritional status of patients. Albumin is low in blood levels in cases of inflammation and malnutrition. In the case of malnutrition, the immune system is affected and this situation appears as lymphopenia. This parameter, which predicts the evaluation of immunity, inflammation and malnutrition together, has been used to determine the prognosis and mortality of many diseases (10-16). In this study, it was aimed to investigate the ability of the PNI score to predict the prognosis and mortality of patients hospitalized for COVID-19.

METHODS

Study Design

Our study was planned as a single-centered, retrospective observational cohort study, and patients between March 2020 and March 2021 were screened from the hospital electronic data system. The study protocol was approved by the Turkish Ministry of Health and Sutcu Imam University, Medical Faculty Clinical Ethics Committee. (Decision no: 31.08.2021-277). Declaration of Helsinki criteria was taken into account throughout the study.

Study Population

Patients over the age of 18 who applied to the emergency department or the COVID-19 outpatient clinic and were hospitalized with positive reverse transcription polymerase chain reaction (RT-PCR) were included in the study. Pregnant patients, patients with chronic liver disease, nephrotic syndrome, hematological disease, immunosuppressive patient and malignancy were excluded from the study. According to thorax computed tomography (CT) findings, the patients were divided into groups such as those with or without pneumonia; admitted to the ward or intensive care unit; discharged, and exitus.

Study Protocol

During hospitalization, the patients were admitted to the ward or intensive care unit according to the case definitions in the Ministry of Health General Directorate of Public Health COVID-19 (SARS-CoV-2) Infection Adult Patient Treatment Guidelines, and the severity of pneumonia was determined according to the same guideline (17).

Cough, shortness of breath, fever and other symptoms, vital signs at the time of admission, saturation values, demographic data and accompanying comorbidities were examined.

The first complete blood count, complete biochemistry, D-Dimer, arterial blood gas (ABG), CRP, Ferritin, Procalcitonin, and coagulation tests during hospitalization were obtained from the hospital data system. PNI scores (PNI = 10 × serum albumin (g/dL) + 0.005 × peripheral lymphocyte count (/mm3)) were calculated from laboratory results (18). Thorax CT images were evaluated from the hospital system or ministry of health personal health record system. Patients with COVID-19 were grouped with and without pneumonia, and prognosis and mortality were compared. In the follow-up of the patients who were admitted to the ward, their admission to the intensive care unit, mortality and whether they were discharged were evaluated. Mortality and discharge of patients hospitalized in the intensive care unit were followed up. The contribution of the laboratory findings obtained at the time of admission to the hospital to the prognosis and mortality in the course of the disease was evaluated.

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency and ratio values were used. The distribution of variables was measured with the Kolmogorov-Smirnov test. ANOVA (Tukey test), Independent Sample T-test, Kruskal-Wallis, and Mann-Whitney u test were used in the analysis of quantitative independent data. The Chi-square test was used in the analysis of qualitative independent data, and the Fisher test was used when the Chi-square test conditions were not met. The effect level was investigated with the ROC curve. SPSS 28.0 program was used for the analyses.

RESULTS

One hundred seventy-three patients were included in the study. The mean age of the patients was 53.9 (19-95) years. The sex distribution of the patients was as follows: 118 males (68.2%) and 55 females (31.8%). Fever was detected during the admission in 45.7% of patients. The three most common symptoms of the patients were cough, shortness of breath and myalgia. Cough was the most prominent symptom with 42.2%. Pneumonia was not detected on thorax CT in 48 patients (27.7%) at the time of admission. The need for intensive care developed in 45 patients (26%). 27 (15.6%) of these patients died. 146 patients (84.4%) were discharged (Table 1). In the group with pneumonia, the rate of comorbid disease was found to be significantly higher ($p<0.05$) when compared to the group without pneumonia. The rate of admission to the intensive care unit in the group with pneumonia (35.2%) was significantly higher than the group without pneumonia, 2.1% ($p<0.05$). Mortality in the group with pneumonia was 21.6%, while mortality was not observed in the group without pneumonia. When we evaluated the laboratory parameters of both groups, oxygen saturations (SpO_2) in the group with pneumonia (mean SpO_2: 94%) were found to be significantly ($p<0.05$) lower than in the group without pneumonia (mean SpO_2: 97%), lymphocyte, hemoglobin and thrombocyte counts in the group with pneumonia were significantly lower

(p<0.05) when compared to the group without pneumonia, and there was no significant difference in leukocyte count (p>0.05). When the biochemical parameters were evaluated CRP, Ferritin, D-Dimer, Procalcitonin and lactate dehydrogenase (LDH) were found to be significantly higher (p<0.05) in the pneumonia group. When the PNI score was evaluated between the groups with and without pneumonia, the average PNI score was significantly lower (p<0.05) in the group with pneumonia, with 44.6. The mean PNI score was found to be significantly lower (p<0.05). The PNI score of the patients admitted to the ward or intensive care unit at the time of admission was found to be significantly lower (p<0.05) in the patients admitted to the intensive care unit. NLR was found to be significantly higher (p<0.05) in patients admitted to intensive care. (Table 2). When the groups of patients who were discharged and those who died were compared, when the PNI score was evaluated, the PNI score (mean 34.9) in the group who died were found to be significantly (p<0.05) lower than the group who were discharged (mean 55.1). When NLR was evaluated, NLR (median 9) was found to be significantly higher in the group who died than in the group who were discharged (median 2.4) (Table 3). The sensitivity of 46 cut-off values of the PNI score was 88.9%, the positive predictive value was 58.8%, the specificity was 77.3%, and the negative predictive value was 95.2% in differentiating patients admitted to the ward or intensive care unit (Table 4). The sensitivity of the 46-cut-off value of the PNI score was 92.6%, the positive predictive value was 36.2%, the specificity was 69.9%, and the negative predictive value was 97.1% in separating the discharged patients from the dead. It was found that 92.5% of patients who died had a PNI score below 46. The PNI score of 88.9% of the patients hospitalized in the intensive care unit was below 46.

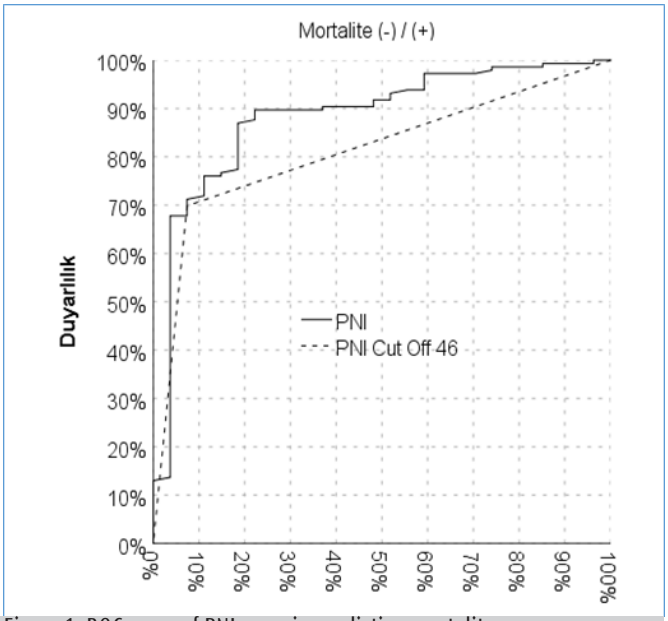

Figure 1. ROC curve of PNI score in predicting mortality

Table-1 Clinical findings of the patients included in the study

		Min-Max			Median	Mean±sd/n-%		
Age		19.0	-	95.0	55.0	53.9	±	19.4
Sex	Female					55		31.8%
	Male					118		68.2%
Comorbidities	No					79		45.7%
	Yes					94		54.3%
HT						59		34.1%
Asthma-COPD						21		12.1%
DM						33		19.1%
Pneumonia	No					48		27.7%
	Yes					125		72.3%
Fever	No					94		54.3%
	Yes					79		45.7%
Symptom	No					24		13.9%
	Yes					149		86.1%
Cough						73		42.2%
Dyspnea						56		32.4%
Myalgia						28		16.2%
Disease severity	Light					112		64.7%
	Moderate					36		20.8%
	Severe					25		14.5%
Need for Intensive Care	No					128		74.0%
	Yes					45		26.0%
Result	Discharged					146		84.4%
	Exitus					27		15.6%

HT: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus

DISCUSSION

It has been reported in studies that a large number of factors play a role in mortality in COVID-19 (19-21). In this study, the effect of the PNI score on mortality was evaluated. The PNI score was found to be significantly lower in the group with pneumonia, who are admitted to the intensive care unit and died, when compared to the group without pneumonia, admitted to the ward and discharged. Again, cut-off values of the PNI score were determined to evaluate prognosis and mortality.

There have been studies evaluating the prognostic value of CRP, ferritin, procalcitonin, LDH, D-Dimer and albumin levels, neutrophil, lymphocyte and platelet counts in the diagnosis and follow-up of patients in the course of COVID-19 (22-24). Among these studies, 32 studies were reviewed in a compilation by Malik et al., the data of a total of 10491 COVID-19 patients

Table 2. Laboratory findings of the ward and intensive care patients

	Intensive Care (-)		Intensive care (+)		p	
	Mean+sd	Median I.Q-3.Q	Mean+sd	Median I.Q-3.Q		
Sp O_2 %	95.8±2.1	96.0 95.0-97.0	83.5±11.9	88.0 82.0-91.0	<0.001	m
Hemoglobin (g/dl)	14.2±1.8	14.5 13.2-15.5	13.4±2.2	13.7 11.9-14.8	0.008	m
WBC (x10^9/l)	6.0±2.2	5.6 4.5-7.3	9.3±5.0	8.2 5.9-11.9	<0.001	m
Neutrophil (x10^9/l)	3.9±1.9	3.3 2.6-4.9	7.6±4.6	6.1 4.4-9.7	<0.001	m
Lymphocytes (x10^9/l)	1.7±1.8	1.5 1.1-1.9	1.0±0.7	0.8 0.5-1.3	<0.001	m
Platelets (x10^9/l)	206.4±62.5	195.0 167.0-237.8	202.4±80.8	182.0 148.5-245.0	0.434	m
NLR	3.1±2.9	2.3 1.6-3.3	11.9±12.5	6.24 4.0-15.5	<0.001	m
CRP (mg/l)	17.5±23.2	8.1 3.1-19.3	123.0±92.6	109.0 38.7-184.5	<0.001	m
Ferritin (ug/l)	190.2±167.8	129.0 69.5-249.3	728.7±767.3	502.0 294.5-1017.5	<0.001	m
D-Dimer (mg/l)	0.6±0.9	0.4 0.2-0.7	4.7±12.6	1.2 0.6-3.1	<0.001	m
Prokalcitonin (ug/l)	0.1±0.2	0.1 0.0-0.1	3.2±14.9	0.3 0.1-0.9	<0.001	m
PNI Score	57.1±50.6	50.7 46.2-55.7	37.3±9.3	38.1 33.0-43.3	<0.001	m

[m] Mann-whitney U test WBC:White Blood Cell, NLR:Neutrophil-Lymphocytes Ratio, CRP: C-Reactive Protein PNI:Prognostıc Nutrituonal Index

Table 3. Laboratory findings of patients who were discharged and are exitus

	Discharged			Exitus		p	
	mean±sd	Median		mean±sd	Median		
SpO_2 %	95.1 ± 2.7	96.0		78.9 ± 13.5	84.0	<0.001	m
Hemoglobin (g/dl)	14.1 ± 1.8	14.3		13.5 ± 2.5	13.7	0.112	m
WBC (x10^9/l)	6.2 ± 2.3	5.7		10.5 ± 5.6	9.3	<0.001	m
Neutrophil (x10^9/l)	4.1 ± 2.2	3.5		8.6 ± 5.1	7.9	<0.001	m
Lymphocytes (x10^9/l)	1.6 ± 1.7	1.4		1.0 ± 0.8	0.8	<0.001	m
Platelets (x10^9/l)	202.9 ± 64.1	192.0		218.5 ± 84.0	201.0	0.567	m
NLR	3.9 ± 4.9	2.4		13.6 ± 13.8	9.0	<0.001	m
CRP (mg/l)	25.7 ± 38.4	10.0		149.1 ± 99.0	147.0	<0.001	m
Ferritin (ug/l)	245.1 ± 259.0	161.0		790.9 ± 932.7	550.0	<0.001	m
D-Dimer (mg/l)	0.7 ± 0.9	0.4		7.3 ± 15.9	1.9	<0.001	m
Prokalcitonin (ug/l)	0.2 ± 1.4	0.1		4.4 ± 19.0	0.4	<0.001	m
PNI Score	55.1 ± 47.7	49.5		34.9 ± 10.5	36.8	<0.001	m

[m] Mann-Whitney U test WBC: White Blood Cell, NLR: Neutrophil-Lymphocytes Ratio, CRP: C-Reactive Protein PNI: Prognostic Nutritional Index

Table- 4 Analysis of the distribution of the cut-off value of the PNI score by patient groups

		PNI ≤ 46		PNI > 46		Sensitivity	Positive Estimation	Specificity	Negative Estimation
		n	%	n	%				
Disease severity	Light	19	27.5%	93	89.4%	82.0%	72.5%	83.0%	89.4%
	Moderate-severe	50	72.5%	11	10.6%				
Pneumonia	(-)	5	7.2%	43	41.3%	51.2%	92.8%	89.6%	41.3%
	(+)	64	92.8%	61	58.7%				
Need for Intensive Care	(-)	29	42.0%	99	95.2%	88.9%	58.8%	77.3%	95.2%
	(+)	40	58.0%	5	4.8%				
Result	Discharged	44	63.8%	102	98.1%	92.6%	36.2%	69.9%	97.1%
	Ex	25	36.2%	2	1.9%				

were evaluated, and lymphopenia, thrombocytopenia, high CRP, procalcitonin, LDH, and D-Dimer levels were reported to be associated with critical illness in COVID-19 patients (22). In a study conducted in Iran, the data of 233 patients were examined. Lymphopenia was observed in 79% of the patients in the mortal group. It has been reported that a high neutrophil/lymphocyte (NLR) ratio and platelet/lymphocyte ratio (PLR) are independent risk factors for mortality (23). In the meta-analysis of Huang et al. (24), it was reported that high CRP, procalcitonin, ferritin and D-Dimer levels are associated with poor prognosis in COVID-19 patients . In another meta-analysis, in which 30 studies were compiled, the risk factors for severe COVID-19 disease were examined. It has been reported that lymphopenia, high CRP, LDH levels, and hypoalbuminemia have prognostic significance for severe disease (25). In our study, similar to the other studies, when CRP, procalcitonin, ferritin, D-Dimer, and LDH levels are evaluated; in patients with pneumonia, who were admitted to the intensive care unit and who died; it was found to be significantly higher than the patient groups without pneumonia, hospitalized and discharged. The albumin levels and lymphocyte counts were found to be statistically significantly lower in the patient groups with pneumonia and those who were hospitalized in the intensive care unit, and those who died. The neutrophil count was found to be significantly higher in the patient group hospitalized in the intensive care unit and in the group who died, and when the platelet count was evaluated for all patient groups, no significant difference was observed. Elevated levels of CRP, procalcitonin, LDH, ferritin, D-Dimer, lymphopenia, and hypoalbuminemia were associated with being taken to the intensive care and mortality. We think that the results of our study were similar to the literature due to the fact that the studies were conducted in the first year of the pandemic, the vaccination had not started, and the treatment regimens were similar.

PNI score is a parameter obtained from albumin and lymphocyte counts and it reflects the nutritional and inflammatory status of the patients and has been used to show prognosis in many diseases (9-10). In a study conducted by Song et al. (26), the ability of parameters reflecting the malnutrition at the time of admission to indicate in-hospital mortality was evaluated. In this study, PNI, Controlled Nutrition Index (CONUT) and Geriatric Nutritional Risk Index (GNRI) scores were used. All three scores were found to be independent risk factors for mortality. The elevation of D-Dimer and CRP were found to be associated with poor prognosis. Albumin levels were found to be significantly lower in severe patients. No significant difference was observed between the body mass index and lipid panel of severe patients. In this study, it was reported that a PNI score below 44 was associated with in-hospital mortality. Similar to our study, it was stated that a low PNI score may be a risk factor for in-hospital mortality.

In a study conducted with 295 COVID-19 patients in China, risk factors for mortality were retrospectively investigated according to the findings at the time of admission. It was observed that the mortality of patients with advanced age (>74), male sex and hypertension was high. In our study, we also found that advanced age and co-morbid hypertension are risk factors for mortality. In this study, it was also reported that platelet count, LDH and PNI score were independent risk factors for mortality (25). The authors stated that a PNI score below

33.4 may be an important risk factor for mortality. In our study, we also determined that a PNI below 46 is a risk factor for mortality.

In the study conducted by Doğancı et al. (27) with 397 patients, the prognostic factors in COVID-19 patients were investigated. It has been reported that having a PNI score below 44.7 is associated with a poor prognosis. In another study by Nalbant et al. (28) with 118 patients, the importance of PNI and systemic inflammatory index were investigated in showing the prognosis of patients with COVID-19. Elevated CRP, procalcitonin, ferritin, D-Dimer and LDH levels were found to be significantly higher in intensive care patients. Albumin and lymphocyte counts were also found to be significantly lower. In addition, it was reported that the PNI score was lower in intensive care patients with a mean value of 34.1, compared to the other group. Again, in the same study, when the cut-off value of the PNI score was ≤36.7%, it was reported that the PNI score had a sensitivity of 73.4% and a specificity of 70.8% in predicting the severity of the disease. In this study, results similar to our study were reported in many aspects. The fact that both studies were conducted in Turkey on the same dates, included a similar number of patients, and the absence of race and sex differences support the similar results. In both studies, it was observed that a low PNI score was associated with increased intensive care hospitalization. In another Turkey-based study with the number of 1579 patients (29), PNI scores were found to be significantly lower in patients who had to be hospitalized in the intensive care unit and died, similar to our study.

Limitations of the Study

The limitations of the study can be stated as that our study was single-center, retrospective, did not include patients with negative COVID-19 RT-PCR test but with typical involvement of Thorax CT, not being the optimum treatment method, and being administered before vaccination.

CONCLUSION

As a result, albumin and lymphocyte counts are used as parameters that reflect the inflammation and malnutrition status of the patients. In our study, the PNI score of the patients hospitalized with the diagnosis of COVID-19 was calculated; It was found that the prognosis of the patients was poor and the morbidity and mortality were high in case of PNI <46. It is thought that this situation occurs secondary to a decrease in albumin and lymphocyte counts in cases of excessive inflammation in COVID-19 patients. It is known that the prognosis of patients is poor, morbidity and mortality are high in case of excessive inflammation. As a result, we think that PNI score calculated using albumin and lymphocyte count can be used together with other biomarkers to predict the prognosis of patients, but new studies are needed.

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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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Previously presented

Some part of this study was presented as oral presentation at the 25th annual congress of the Turkish Thoracic Society in Antalya.

This study was prepared by rearrangement of the specialty thesis by Muhammed Şahin, entitled as “Covid-19 Pnömonisi ile Yatan Hastalarda Prognostik Nutrisyonel İndeks- Mortalite İlişkisi”.

Ethical Declaration

Ethical permission was obtained from the Sutcu Imam University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 31.08.2021.and number 277, and Helsinki Declaration rules were followed to conduct this study.

This study is a rearranged version of the thesis named “Covid-19 Pnömonisi ile Yatan Hastalarda Prognostik Nutrisyonel İndeks- Mortalite İlişkisi

Authorship Contributions

Concept: MŞ, BA, Design: BA, MŞ, Supervising: BA, MŞ, Financing and equipment: NA, FB, HK, BK, MŞ, BA, Data collection and entry: MŞ, Analysis and interpretation: BA, MŞ, Literature search: BA, MŞ, FB, Writing: MŞ, BA, Critical review: BA, HK.

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ORIGINAL RESEARCH

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Determination of 25 hydroxyvitamin D reference ranges in Hatay region by indirect method

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Abstract

Objective: The aim of this study is to determine the reference ranges of 25 hydroxyvitamin D (25(OH)D) levels from the serum 25(OH)D results of the patients and to investigate variations across age and gender groups.

Methods: The patients (n=26829) who applied to Hatay Mustafa Kemal University Hospital between January 2018 and December 2019 and whose 25(OH)D levels were studied were included in this retrospective study. Serum 25(OH)D levels were studied by the chemiluminescence immunoassay method. The hospital information management system was used to obtain the test results and patient data. The indirect method was used to determine the reference ranges.

Results: The prevalence of 25(OH)D deficiency in the patients participating in this study was 60.9% in the general population, 54.9% in men, and 67.5% in women. It has been observed that 25(OH)D deficiency is more common in women than in men. The reference ranges determined in this study were lower than the reference ranges provided by the manufacturer.

Conclusion: In this study, 25(OH)D levels and reference ranges of Hatay Region were determined in a very large population. It can be said that the results of our region will contribute to the studies to be carried out on the determination of 25(OH)D levels and reference ranges throughout the country.

Keywords: Vitamin D, Vitamin D Deficiency, Laboratory Tests

INTRODUCTION

Vitamin D is a vitamin in steroid-structured, belonging to the group of fat-soluble vitamins (1). This vitamin is taken with food at a rate of 10-20%, and 80-90% is synthesized in the skin under the influence of UVB rays. Vitamin D plays a very crucial role in maintaining calcium and phosphorus balance and bone mineralization (2). Furthermore, studies have shown that vitamin D is associated with chronic diseases such as diabetes and cardiovascular diseases, psychiatric and sleep disorders, some malignancies, osteoporosis, infectious diseases, autoimmune diseases, and hypertension (3). The best indicator of the status of vitamin D synthesized in the human body is serum 25 hydroxyvitamin D (25(OH)D) level, but there is no consensus in the literature regarding the optimal level of 25(OH) D. In most of the published guidelines, serum 25(OH)D levels above 20 ng/mL are considered sufficient, between 10-20 ng/mL as insufficient and below 10 ng/mL as deficiency (4).

The reference range is the interval wherein the reference values, determined through statistical methods for a given test determined in the population of reference individuals are defined (5). In determining the reference range, direct or indirect methods are used in the selection of the reference individual from the reference population.

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The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommends the use of the direct method for reference range determination. However, there are various studies in the literature in which the indirect method was used as a reference (6-9). There are reference ranges determined by the relevant manufacturer for each test studied in clinical laboratories, but it is recommended that each clinical laboratory determine its own reference range due to differences between populations and clinical laboratories (5,10). The objective of this study is to ascertain the reference ranges for serum 25(OH)D levels based on patient data and to investigate variations among age and gender groups.

METHODS

Patients who applied to Hatay Mustafa Kemal University Hospital between January 2018 and December 2019 and whose 25(OH)D levels were studied were included in this retrospective study. Serum 25(OH)D levels were analyzed by the chemiluminescence immunoassay method using a Siemens kit and calibrators on the ADVIA Centaur XP (Siemens, Germany) autoanalyzer in Hatay Mustafa Kemal University Hospital Central Laboratory, Department of Biochemistry. Demographic data of the patients and 25(OH)D vitamin results were obtained from the Hospital Information Management System (HIS). The 25(OH)D results of the patients followed up with the diagnosis of hyperparathyroidism, cancer, celiac disease, chronic liver disease, and stage III, IV, and V chronic kidney disease was excluded from the study. Furthermore, patients who had more than one 25(OH)D test result had their initial result accepted for the research, and the remaining findings were excluded. To obtain serum, blood samples were centrifuged at 1500*g for 10 minutes using gel-coated biochemistry tubes. During the period of the study, two different levels of internal quality control samples and an external quality control program were used in the laboratory, and quality control follow-up was carried out. In addition, during the study, all tests were studied on serum samples taken into the same brand biochemistry tubes, using autoanalyzers, kits, and calibrators from the same manufacturer.

Statistical analysis

Analyzes were performed after removing outliers with the SPSS software program version 23.0 (IBM Corporation, Armonk, NY, USA). Patient data were defined as a number, percentage, and mean±SD. Kolmogorov-Smirnov test, Shapiro-Wilk test, and histograms were used to evaluate the normal distribution of test results. Student-t test was used for comparisons between groups. Comparisons between age groups were made with the ANOVA test, and post-hoc with the Tukey test.

The non-parametric (percentage estimation method) method was used to determine the lower and upper limits of the reference ranges. In the distribution of the test results of the reference population, the results within the 95% section in the center were accepted as the reference range, and the results between 2.5% and 97.5% for men and women were determined according to the formula below.

Lower limit value=0.025 x (n+1)

Upper limit value= 0.975 x (n+1)

n represents the number of data. $p<0.05$ was considered statistically significant.

RESULTS

At first stage, 25(OH)D results of 28240 patients were evaluated. In these results, extreme values were removed by using the statistical program. Afterward 25(OH)D reference ranges were determined as a result of the test of 26829 patients. The 25(OH)D data for the general population and by gender are shown in Table 1 before and after the exclusion of extreme values, respectively. The 25(OH)D reference ranges for which 2.5 percentile and 97.5 percentile values were determined

Table 1. General and sex based vitamin D statistics before and after exclusion of extreme values

VITD (ng/mL)	n	Mean	SD	Median	CI (%95)		Var	Range	Min	Max	IQR
					Lower Limit	Upper Limit					
Before extreme are removed	28240	15.44	9.56	13.79	15.33	15.55	91.55	143.89	4.2	148.09	10.53
After extreme are removed	26829	14.77	7.02	13.79	14.69	14.69	49.31	33.33	4.2	37.53	9.94
Females	19006	14.45	7.03	13.42	14.35	14.35	49.47	33.33	4.2	37.53	10.04
Males	7823	15.53	6.93	14.63	15.38	15.38	48.11	33.32	4.2	37.52	9.67

VITD: 25(OH) Vitamin D, SD: Standard Deviation, CI: Confidence Interval, Var: Variance, Min: Minimum, Max: Maximum, IQR: Interquartile Range

by the indirect method are given in Table 2. The mean age of 19006 female patients participating in the study was 43.99±8.17 years, and the mean age of 7823 male patients was 44.39±21.41 years. There was no statistical difference in the mean age of men and women (p>0.05).

After eliminating the extreme values, the 25(OH)D level was found to be 14.77±7.02 ng/mL in the general population, 14.45±7.03 ng/mL in female patients, and 15.53±6.93 ng/mL in male patients (Table 1). The 25(OH)D reference range was found to be 4.50-31.25 ng/mL in the general population, 4.35-30.95 ng/mL in women, and 4.97-31.63 ng/mL in men (Table 2).

Table 2. Reference ranges determined according to 25(OH) Vitamin D values observed in the 2.5th and 97.5th percentiles.

VITD (ng/mL)	n	Age (Mean±SD)	Percentile	
			2.5.	97.5.
General	26829	44.11±19.17	4.5	31.25
Females	19006	43.99±18.17	4.35	30.95
Males	7823	44.39±21.41	4.97	31.63

VITD: 25(OH) Vitamin D

Figure 1 shows that 25(OH)D data according to age groups are given. Serum 25(OH)D level is 13.72±6.68 ng/mL in the 18-30 age group, 14.4±6.88 in the 31-40 age group, 14.74±6.95 ng/mL in the 41-50 age group mL is 14.93±6.94 ng/mL in the 51-60 age group, 14.89 ±6.96 ng/mL in the 61-70 age group, and 15.38±7.41 ng/mL in those over 70 years of age.

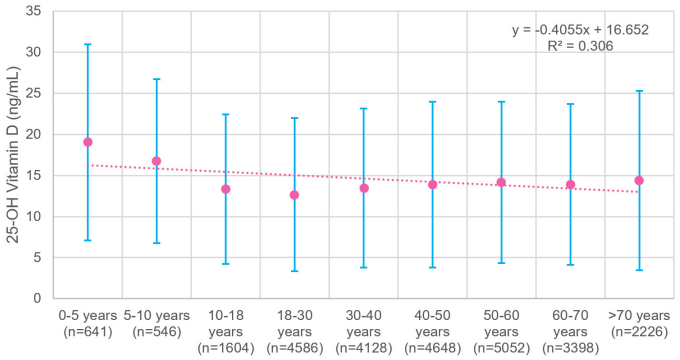

Figure 1. 25(OH) Vitamin D values according to age groups after removing extreme values.

In this study, the prevalence of 25(OH)D insufficiency (<20 ng/mL considered as insufficiency) was 76.8% in the general population, 73.7% in men, and 78.3% in women. 25(OH)D deficiency (<10 ng/mL was considered as the deficiency) was found in 60.9% of the general population, 54.9% in men, and 67.5% of women.

DISCUSSION

In the present study, the reference ranges of 25(OH) D levels in different age and gender groups were determined and the differences between the groups were showed. It has been found that the reference ranges for both men and women in the Hatay Region are lower than the current reference ranges proposed by the manufacturer.

Reference ranges play an important role in the evaluation of test results studied by clinical biochemistry laboratories by clinicians. It is essential to determine the reference population correctly in determining the reference range. Among the methods used here, the direct method is a laborious and costly method. For this reason, the indirect method, which is an easy-to-apply and inexpensive method, can be preferred in determining the reference population. In this method, patient results are obtained via HIS to determine the reference range with percentile distribution. Results are ordered from smallest to largest, and then 2.5% of the lower and upper limits are eliminated. Thus, the 95% part in the center is determined as the reference range. The high number of results in determining the reference range is an important factor that increases the reliability of the results. In this method, the results of at least 120 patients are required to obtain a healthy result (5-7). In the current study, a reference range study was performed on the test results of 26829 patients using the method mentioned above. This number of patients is sufficient for reference range studies.

The manufacturer has reported the reference values for 25(OH)D levels as 7.4-44.0 ng/mL for adult individuals. However, the reference ranges for 25(OH)D in the central laboratory of our hospital are given as 15.7-60.3 ng/mL for summer and 8.8-46.3 ng/mL for winter in patient results. In this study, the 25(OH)D reference range was found to be 4.50-31.25 ng/mL in the general population, 4.35-30.95 ng/mL in women, and 4.97-31.63 ng/mL in men. These values are lower than the values of the manufacturer. With the present study, 25(OH)D reference ranges of Hatay Region were evaluated for the first time in a very large population by using the HIS data using the indirect method. These results obtained from Hatay Region may contribute to the studies to be carried out on the determination of 25(OH)D levels and reference ranges throughout the country. In addition, it was aimed that the reference ranges determined in this study can

be used by clinical laboratories in our region, so that the 25(OH)D results of the patients will be evaluated more accurately.

There was no significant difference in mean age between male and female patients included in the study. The mean ages of female and male patients were found to be similar to previous vitamin D reference range studies in our country (8,9,11).

In studies conducted in Turkey, the prevalence of 25(OH)D deficiency was reported to be 63% (the lowest 34%, the highest 91%) in adult patients (12-14), 39.5% in male patients, and 64.7% in female patients (14). In a study conducted in Adana, which is a neighbor of Hatay Region, the rate of 25(OH)D deficiency was found to be 60.6% (15). In this study, the prevalence of 25(OH) D deficiency was found to be 60.9% in the general population, 54.9% in men, and 67.5% in women. In this study, deficiency rates were found similar to previous studies in our country. In addition, the results of studies conducted in our country and around the world have shown that the prevalence of 25(OH)D deficiency is higher in women (14). The reasons why vitamin D deficiency is more common in women than in men are biological differences, behavioral differences, and clothing style. In the current study, vitamin D deficiency was found to be higher in women, which is consistent with the literature.

Many studies have shown that 25(OH)D levels are affected by various factors such as geography, seasons, race, chronic kidney and liver diseases, obesity, gender, insufficient exposure to sunlight, and age (14, 16). However, in various studies examining 25(OH)D levels according to age groups, it was seen that there was no significant difference between the groups ($p>0.05$). There was no statistically significant difference in terms of age groups in the studies conducted by Durmaz et al. in the Amasya region (17), by Hekimsoy et al. in the Manisa region (18), by Alpdemir and Alpdemir in the Bilecik region (9), and by Uçar et al. in the Ankara region (19). Similar to the previous studies no difference was found between age groups in terms of 25(OH)D levels.

CONCLUSION

In conclusion, in this study, serum 25(OH)D levels and reference ranges of Hatay Region were determined in a very large population. It can be said that the results will contribute to the studies to be carried out on the determination of 25(OH)D levels and reference ranges throughout the country and that the reference ranges determined in this study can be used by our institution and the clinical laboratories of Hatay Region, so that the serum 25(OH)D results of the patients will be evaluated more accurately.

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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 permission was obtained from the Hatay Mustafa Kemal University, Medical Faculty Clinical Research Ethics Committee for this study with date 23/05/2019 and number 22, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

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

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CASE REPORT
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Intestinal-type adenocarcinoma of the sinonasal mucosa: a rare case report

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Abstract

Intestinal-type adenocarcinoma is the most commonly seen adenocarcinoma of the sinonasal region following adenoid cystic carcinoma. They are aggressive tumors that are generally diagnosed in the advanced stage. Histopathological subtype is an important prognostic indicator. In this report, we have presented a case we diagnosed as intestinal-type adenocarcinoma with right nasal cavity localization.

Keywords: Sinonasal, Adenocarcinoma, Intestinal-type

INTRODUCTION

Intestinal type adenocarcinoma (ITAC) is the most commonly seen adenocarcinoma of the sinonasal region following adenoid cystic carcinoma (1). They are classified as papillary, colonic, solid, mucinous and mixed type according to histological features (1, 2). It is more frequently found in males due to occupational exposure and between ages 50-64 years (1, 3). They are most commonly detected in the ethmoid sinuses followed by nasal cavity and maxillary antrum (1). They are generally diagnosed in the advanced stage, they are clinically aggressive tumors and its histopathological subtype is an important prognostic indicator (1, 4, 5). They may have a morphological appearance of normal intestinal mucosa, villous adenoma, colorectal adenocarcinoma, mucinous adenocarcinoma and signet-ring cell carcinoma (4, 6).

In this report, we have presented a case we diagnosed as intestinal-type sadenocarcinoma with right nasal cavity localization.

CASE

The 74-year-old male patient admitted to the policlinic of Otolaryngology Department due to the complaint of difficulty in breathing. Rhinoscopy revealed polypoid tissue that fills the right nasal cavity in the septal midline. No pathological finding was detected in the examination of other systems. The computed tomography encountered a soft tissue density lesion that extended from right maxillary sinus to right nasal passage through secondary ostium and to nasal pharyngeal region. The patient was operated with prediagnosis of antrochoanal polyp? inflammatory polyp? and inverted papilloma? The pathology material consisted of gray-white colored tissue fragments with a volume of 9cc. Microscopic examination showed a tumor with sparse papillary and remarkable tubuloglandular architecture (Figure 1). Tumor cells included hyperchromatic nuclei and sparse goblet cells (Figure 2). No lymphovascular and perineural invasion was present. Tumor cells demonstrated CDX2-positive and CK20-positive immunoreactivity (Figure 3). No staining was observed for CEA and CK7. No lesion detected in the colon by colonoscopy. The patient was diagnosed with intestinal-type adenocarcinoma according to these findings.

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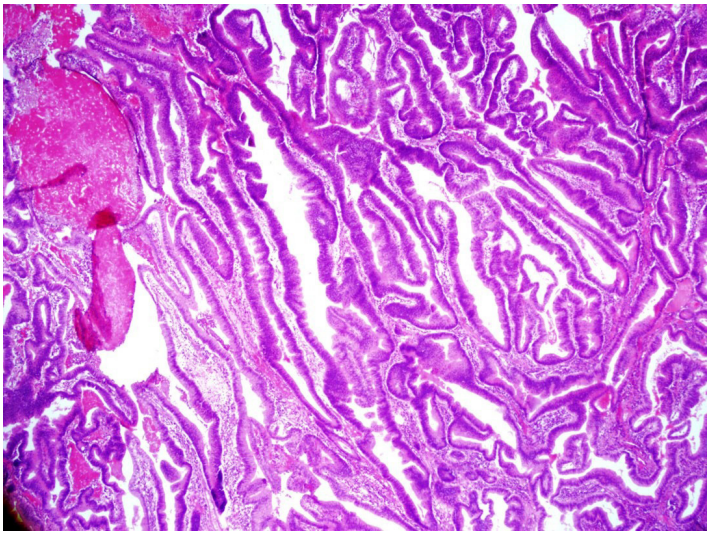

Figure 1. Tubuloglandular architecture (H+E, x100)

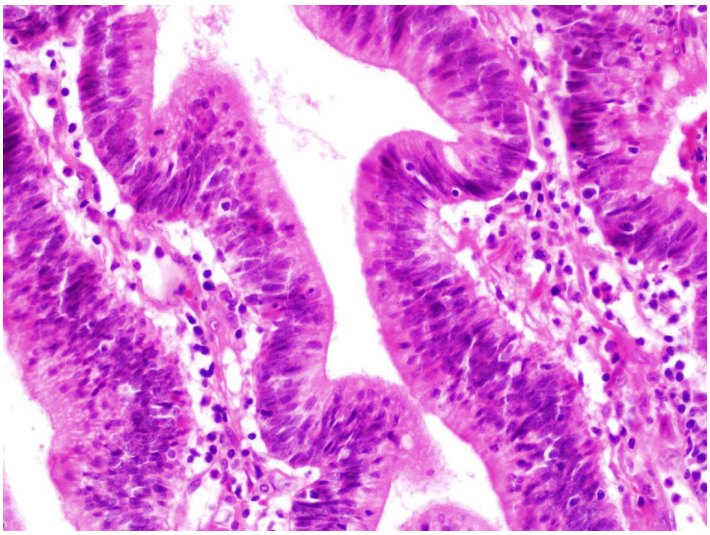

Figure 2. Tumor cells included hyperchromatic nuclei (H+E, x400)

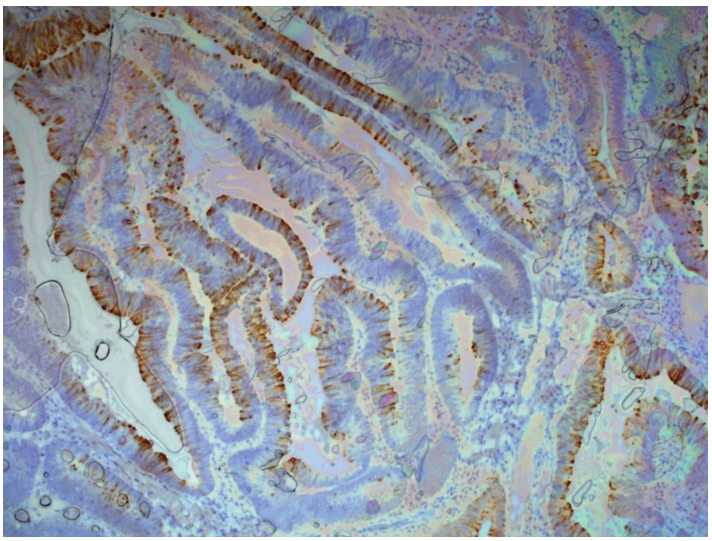

Figure 3. Cytoplasmic immunostaining with CK20 (CK20, x200)

DISCUSSION

The adenocarcinomas of the nasal cavity and paranasal sinuses (SNAC) are very rarely seen tumors and they constitute 10-20% of the primary sinonasal carcinomas and 3-5% of all head and neck malignancies (2). They are divided into two as salivary and non-salivary types based on the originating cell while non-salivary type is classified as intestinal type and non-intestinal type adenocarcinoma according to histopathological features (2, 6). ITAC is the second most common type of sinonasal adenocarcinoma after adenoid cystic carcinoma (1). Occupational exposure (leather dust, nicel, wood dust) is blamed etiologically, however, sporadic cases also have been reported (2, 4, 6). The time elapsed from exposure to tumor development is 18-50 years, however, there is no sufficient data on the relationship between inhaled dust amount and tumor development period. The other factors considered to be etiologically responsible are Epstein-Barr viral infection and cigarette smoking (7). The studies carried out in Europe have determined a strong relationship between occupational exposure and development of these tumors (2, 3, 8) whereas a weaker relationship has been detected in the USA-based studies (2, 9). Occupational exposure has been reported more frequently in males as an etiological factor in the Europe-based studies whereas it has been reported in 2014 Survival, Epidemiology and End Results (SEER) study that these tumors were found with frequency in both genders (2, 10). Our case was also a male patient with advanced age and no risk factor was present.

ITACs of the nasal cavity are the destructive lesions that generally emerge in the nasal midline. These tumors present better prognosis compared with squamous cell carcinomas (7). They constitute 8-25% of all malignant sinonasal tumors. It is supposed to develop from intestinal metaplasia of the ciliated respiratory epithelium and inferior and middle turbinates are the preferred sites in nasal cavities. Epistaxis, unilateral nasal obstruction and rhinorrhea are the most commonly seen complaints (11). Pain, neurological deficits, exophthalmos and visual impairments may be seen in the advanced stage tumors. They have grossly papillary or polypoid features and fungating appearance, and they may have gelatinous viscosity resembling mucocele (12). Our case was found to have a polypoid tissue that filled the nasal cavity.

There are two major classifications for ITACs as Barnes Classification and the Classification of Kleinasser and Schroeder. There are five subtypes as papillary, colonic, solid, mucinous and mixed ITACs according to Barnes Classification while Kleinasser and Schroeder have defined four subtypes as papillary tubular cylinder cell ITACs (grade 1, 2, 3), alveolar goblet type, signet-ring type and transitional type (6, 13). There are differences between histological classes and clinical behaviors (1, 5, 6, 13). The colonic ITAC is the

most frequently seen subtype (1). Goblet cell, paneth cell and argentaffin cell may be observed in all subtypes and well-differentiated ITAC may resemble normal intestinal mucosa. Immunohistochemical staining indicates that ITACs are positive for CK20, CDX-2, villin and MUC2, and variably positive for CK7 (1, 4, 5).

The differential diagnosis of ITAC involves colonic adenocarcinoma metastasis and sinonasal low-grade non-intestinal adenocarcinoma (1, 6). Morphological and immunohistochemical differentiation of primary ITAC from colonic adenocarcinoma metastasis is difficult. The clinical features and colonoscopic findings of the patient will be helpful in differential diagnosis. Thus, if an intestinal-type tumor has been detected in the sinonasal tract, colonoscopy or colorectal radiographic studies should be performed to rule out primary colorectal adenocarcinoma. Colonoscopy revealed no lesion in our case. The differential diagnosis of ITAC from sinonasal non intestinal adenocarcinomas is supported by immunohistochemistry for CK20, CDX-2, villin and SATB-2 that only stain ITACs.

The treatment for ITACs is surgical and type of surgery may vary between lateral rhinotomy, partial maxillectomy and total maxillectomy. ITAC is a high-grade malignancy. The rates of local recurrence, lymph node metastasis and distant metastasis were found 50%, 8% and 13% in a study carried on 213 patients with ITAC, respectively, and 60% patients became exitus due to this disease. The patients who developed this tumor due to exposure to wood dust were found to have a better prognosis compared with sporadic ITAC. The well-differentiated ITACs manifested a better prognosis than solid and mucinous subtypes (1, 6). Our case was colonic type ITAC and well-differentiated, and he has been under follow-up with remission for 16 months.

CONCLUSION

Intestinal-type adenocarcinomas are the rarely seen neoplasms of the sinonasal tract. They are aggressive tumors that are generally diagnosed in the advanced stage. Histopathological subtype is an important prognostic indicator. Colonic adenocarcinoma metastasis should be ruled out by clinical history and colonoscopic examination before diagnosis of primary ITAC.

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Authorship Contributions

Concept: DGK, SU, Design: DGK, SU, Supervising: DGK, GSO, Data collection and entry: SU, Analysis and interpretation: DGK, GSO, Literature search: DGK, SU, GSO, Writing: DGK, Critical review: DGK, GSO.

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CASE REPORT
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A case of acalculous cholecystitis or *Brucella*-induced acute cholecystitis?

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Abstract

Brucella spp. is a microorganism that can cause febrile, systemic infection, especially in endemic areas. Although it causes a multisystemic involvement and creates various clinical symptoms, osteoarticular symptoms are the most common. However, *Brucella* spp. is known to be a great mimic and can cause rare, atypical presentations. In this case report, we aimed to present a 67-year-old Turkish female patient diagnosed with stony cholecystitis due to *Brucella* spp. Although rare, brucellosis can be encountered as a cause of acute cholecyst. Although there are changes in the epidemiology of brucellosis, it is useful to keep in mind brucellosis in the differential diagnosis of many diseases, in endemic areas, especially in rural areas.

Keywords: Brucellosis, *Brucella*, Cholecystitis, Endemic, Atypical presentations

INTRODUCTION

Brucellosis is a febrile, systemic infectious disease caused by bacteria of the *Brucella* genus (1,2). Especially in underdeveloped countries, both humans and animals can be commonly affected by the disease and more than 500,000 new cases have been recorded each year (2). The *Brucella* genus has 10 subspecies, four of which are human pathogens (2). When a ranking is made in terms of pathogenicity; *B. melitensis* is the most pathogenic among human pathogens, followed by *B. suis*, and the least severe form is *B. abortus* (2).

Brucellosis is a multisystemic disease and may present with many different clinical symptoms. It is most commonly presented in focal forms and is characterized by osteoarticular symptoms at a rate of 30% (3). However, it can rarely cause biliary involvement in the form of acute cholecystitis (4).

In this report, a patient presenting with acute *Brucella* cholecystitis is presented.

CASE

A 67-year-old Turkish female presented with right upper abdominal pain, nausea and vomiting of two days duration. She was living in rural area and was a farmer. She had no history of fever or jaundice. Beginning in the epigastric region, the pain later concentrated in the right upper quadrant. She was sent to our academic medical facility out of worry about choledochal pathology owing to her ongoing discomfort. Upon physical examination, vital signs were all within normal range, the right upper quadrant of the abdomen was only mildly painful, and the Murphy's sign was positive.

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White blood cell (WBC) count was 9.70 K/µL (84 % neutrophils) (4-11.0 K/µL), alanine aminotransferase (ALT) was 140 U/L (7-45 U/L), aspartate aminotransferase (AST) was 89 U/L (8-33 U/L), total bilirubin was 4.2 mg/dL (0.3-1.0 mg/dL), alkaline phosphatase (ALP) was 171 U/L (44-147 U/L), C-reactive protein (CRP) was 10 mg/dL (0.3- 1.0 mg/dL) at the time of admission to the emergency department.

Abdominal ultrasonography performed in the emergency department revealed an increase in gallbladder size, thickening of the gallbladder wall (11 cm), biliary sludge, and a few moving stones in the gallbladder.

With these findings, the patient was admitted to the general surgery service with the diagnosis of acute calculous cholecystitis and empiric treatment with ceftriaxone 2 gr/day was started. On the third day of admission to the hospital, the patient's fever started, and therefore blood cultures were taken. The patient was questioned again and it was learned that although she was a farmer, she was also engaged in animal husbandry. Although she does not consume raw milk, it was learned that he did not fully boil the milk while making cheese. In addition, it was determined that she had low back pain and weakness but did not say this because it had been going on for a long time. Brucella serology was also sent from the patient in line with this information. Brucella Wright test titer in serum was 1/160 positive. *Brucella* spp. in blood cultures was not detected, but according to the blood results, the patient was serologically diagnosed as brucellosis.

The patient received orally combination therapy of doxycycline 100 mg twice daily and rifampin 600 mg daily. Her fever subsided, her complaints completely regressed, and she was discharged after five days of therapy. The patient's treatment was completed in six weeks and stopped. She did not show signs of recurrence within six months in the subsequent follow-ups.

DISCUSSION

Brucella spp. infections can affect many systems and present in different ways (3,5). Although patients most frequently apply to infectious diseases outpatient clinics with osteoarticular symptoms, gastrointestinal system symptoms can be seen alone or in addition to other symptoms. Non-specific gastrointestinal symptoms such as anorexia, nausea, vomiting, stomach pains, diarrhea and constipation can be seen in approximately 70 % of brucellosis patients (6-8). However, in addition to these symptoms, life-threatening gastrointestinal involvements can also be detected rarely. It is possible to evaluate pancreatitis, peritonitis, colitis, intestinal obstruction, liver involvement, spleen involvement and gallbladder involvement among these serious complications (6,7). It is rare for brucellosis to affect the bile ducts, and a limited number of *Brucella* cholecystitis cases dating back to 1934 have been reported in the medical literature (3,4,9-13). In our case, the diagnosis of brucellosis could not be confirmed histologically or microbiologically, since the patient was not operated. However, the fact that our country is an endemic region and the patient lived in a rural area, was also engaged in animal husbandry, ate cheese made from unboiled milk, and had long-standing low back pain brought to mind brucellosis. Although it was thought to be calculous cholecystitis at first, fever despite antibiotics for calculous cholecystitis, positive brucella serological tests, and clinical response to brucellosis treatment suggest a case of cholecystitis caused by Brucella spp.

Brucellosis is typically transmitted by consuming raw or unpasteurized dairy products. The milk of diseased sheep, cows or goats can be contaminated with this microorganism, and if it is not pasteurized, it can be transmitted to people who eat these products (1). However, in recent years, the epidemiology of brucellosis has undergone a significant change with the spread of international travel as well as hygienic, social and political factors (14,15). The greatest significant source of contamination is still eating unpasteurized milk and dairy products, though. There is a history of consumption of unpasteurized dairy products in the cases of brucella-associated cholecystitis reported in the literature (13). There was no such history in our case, but brucellosis is an option that should always be kept in mind since we are in a brucella endemic country and the patient lives in a rural area.

Brucella spp. are located within the cell and this situation limits the antibiotic options that can be used in the treatment (1,2). Antibiotics that are active in acidic intracellular conditions are used in the treatment of brucellosis, and tetracyclines, aminoglycosides and rifampin are some of them (16). In addition to these, agents such as fluoroquinolones and trimethoprim/sulfamethoxazole can also be used as secondary options in the treatment of brucellosis (17). In studies, the most frequently used regimens in patients with a diagnosis of *Brucella* cholecystitis are doxycycline plus streptomycin or doxycycline plus rifampin, or tetracycline plus streptomycin, with treatment durations ranging from eight days to six months (3,4,9-13). Doxycycline and rifampin were used for six weeks in the treatment of our patient, and no signs of recurrence were encountered in the six-month follow-up after treatment.

CONCLUSION

In conclusion, although rare, brucellosis can be encountered as a cause of acute cholecyst. Although there are changes in the epidemiology of brucellosis, it is useful to keep in mind brucellosis in the differential diagnosis of many diseases, in endemic areas, especially in rural areas.

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