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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.

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ABOUT THE JOURNAL

Scientific Reports in Medicine is a scientific publication of Academician Publishing and published three times a year online.

It is an open access scientific journal, which publishes original contributions in medical disciplines pertaining to human medicine. In this context, the Journal publishes original researches, case reports, and reviews based on clinical and experimental studies in all areas of human medicine. It is a scientific, periodic journal based on the principles of blind peer-review process. The publication language is English. The Journal is published online three times a year on April, August, and December.

Manuscripts submitted for publication in the journal should be prepared in accordance with research and publication ethics. All manuscripts submitted to the Journal are screened in terms of originality.

All manuscripts should be submitted by online system of the Journal.

The Journal aims to;

- Publish original contributions from different scientific disciplines through the advisory board covering a wide range of 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 and experimental 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

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- 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 human medicine specialties of the topics mentioned above.

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AUTHOR GUIDELINES

Thank you for your interest in submitting your manuscript to Scientific Reports in Medicine 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.

Scientific Reports in Medicine is a scientific publication of Academician Publishing and published three times a year online.

It is an open access scientific journal, which publishes original contributions in medical disciplines pertaining to human medicine. In this context, the Journal publishes original researches, case reports, and reviews based on clinical and experimental studies in all areas of human medicine. It is a scientific, periodic journal based on the principles of blind peer-review process. The publication language is English. The Journal is published online three times a year on April, August, and December.

Manuscripts submitted for publication in the journal should be prepared in accordance with research and publication ethics. All manuscripts submitted to the Journal are screened in terms of originality.

All manuscripts should be submitted by online system of the Journal.

Subject areas include, but are not restricted to the clinical and experimental 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 human 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 (SRINMED), operated by Academician Publishing, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration

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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 manuscrpits 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.

You can contact Academician Publishing to receive Editing and Proofreading services for a fee. You can click here to contact Academician Publishing.

Our journal does not have any commercial partnership with any translation or proofreading service company, and our authors are absolutely free to make their choices as they wish.

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

Use of first person

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

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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, Methods, Results [Findings], and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection

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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

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 methods), 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.

Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. The Methods 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 [Findings] 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 methods.

The Methods 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

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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.

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 [Findings]

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 Methods 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 [Findings] 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

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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. References 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

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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.

Scientific Reports in Medicine, since the first day of its publication uses the PubMed/NLM reference style. Thus, references 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.

Reference List

The reference 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 Scientific Reports in Medicine, 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.

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.

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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.

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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 subpixel 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

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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

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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 or TIFF files.

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

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

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3. Case Reports: Brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens.

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Brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens.

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The manuscript could be of up to 2000 words (excluding references and abstract) and could be supported with up to 25 references. Care should be taken to ensure that the number of figures or tables does not exceed 5-6 each.

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EDITORIAL

The final stage of a scientific research process is to share findings to the public and the scientific community, in other words, publishing. We are aware of the importance and challenges of this stage. Gerard Piel's statement, "Science without publication is dead," effectively summarizes the significance of this matter. When defining the mechanism that creates a scientific article, a valid publication is only possible if it undergoes an objective evaluation process. A fundamental, acceptable scientific publication should be the initial explanation that contains sufficient information, enabling peers to evaluate observations, replicate experiments, and assess intellectual processes. As the journal Scientific Reports in Medicine (SRINMED), we are excited to share the thrill of launching our publication journey with our first issue, and we are pleased to share it with you, esteemed science readers. I would like to thank all the authors who contributed to our second issue.

Editor-in-Chief

Assoc. Prof. Dr. Burak METE

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Intermittent Explosive Disorder

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Abstract:
Intermittent explosive disorder is characterized by recurrent episodes of inability to resist aggressive impulses, resulting in damage to other people or other people's property. In the history of DSM, it first appeared as 'isolated explosive disorder' in DSM-III. However, with some changes in the diagnostic criteria, it is included under the title of 'destructive, impulse control and conduct disorders' in DSM-5. Although previous studies have shown it is a rare disorder, recent epidemiological studies suggest it may be more common than thought. For this reason, it is essential to master the clinical features and learn the treatment methods in order to recognize people with this disorder and apply the appropriate treatment.

Keywords: Intermittent Explosive Disorder, Impulse Control, Conduct Disorders

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Introduction

Intermittent explosive disorder (IED) is an impulse control disorder characterized by recurrent episodes of inability to resist impulses of aggression, resulting in severe aggression or destruction of other people's property.[1] Diagnoses related to impulsive aggression have been included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association since its first edition.[2] In DSM 5, IED is classified under "Disruptive, Impulse Control, and Conduct Disorders" together with pyromania and kleptomania.[3]

The DSM has argued that in order for patients with anger outbursts or impulsive aggression to be diagnosed with IED, other psychiatric disorders that can be shown to cause these behaviors should be excluded. Anger, violence, and aggression are also seen in the presence of many other psychiatric conditions, such as personality disorders, psychotic disorders, substance use disorders, and conduct disorders. IED is included in this section precisely to emphasize that impulsivity is the main component and that uncontrollable aggressive and impulsive episodes are separate from those observed in these disorders.[4] The degree of aggression observed in patients is disproportionate to the stressor that elicited the presenting picture.

Considering that IED can lead to serious public health problems, that most people with this diagnosis do not seek treatment, and that this disorder is a common behavioral disorder that can be treated with specific pharmacological or psychological interventions, the importance of not overlooking this diagnosis in outpatients and inpatients stands out.[2,4]

History

IED was first named by French psychiatrist Jean-Étienne Dominique Esquirol in 1838 under the title "impulsive monomania," a "partial insanity" related to senseless impulsive attempts.[5] When we look at the history of IED, the only adult psychiatric diagnosis in which pathological aggression is primary, it is seen that it was called "passive-aggressive personality-aggressive type" in DSM I and "explosive personality" in DSM II.[3,6] In the International System of Classification of Diseases 9th Edition Clinical Modification (ICD-9-CM), and for the first time in the history of DSM, it was officially included in DSM-III together with the diagnosis of "Isolated Explosive Disorder" within "Axis I Disorders". Moreover, in this classification, the presence of an organic cause was not considered an exclusion criterion for the diagnosis of IED. In DSM-III-R, on the other hand, "isolated explosive disorder" was removed from the classification because it was artificial, and IED retained its place in the classification.[1,4]

In DSM-IV, the diagnostic criteria for APD were generally preserved.[7,8] However, "Criterion C" (absence of impulsivity or aggression between episodes) was removed as a diagnostic criterion because it makes it difficult to diagnose people who exhibit violent and aggressive attitudes between episodes.[8] Furthermore, an exclusion criterion has been added, stating that the symptoms of a person losing their control cannot be better explained by other psychiatric disorders such as schizophrenia, antisocial personality disorder, borderline personality disorder, attention deficit hyperactivity disorder, conduct disorder, also that it should not be directly attributed to the physiological effects of a substance or a general medical condition, simultaneously, if the aggression experienced by the individual aims at gaining material benefit, self-defense, obtaining social control, emphasizing political preference, or involves a gang-related attempt, then a diagnosis of IED should not be made.[8,9] However, it is noteworthy that there is a lack of definition of how often and in what period such aggressive behaviors occur.[4]

The diagnostic criteria have not changed in DSM-IV-TR.[9] This diagnosis, which was included in the category of 'impulse control disorders not elsewhere classified' in DSM-IV and DSM-IV-TR, was included in 'disruptive, impulse control and conduct disorders' with the removal of the category of 'impulse control disorders not elsewhere

classified' in DSM-5.[8,10] In DSM-IV-TR, it is stated that the patient generally does not have symptoms of generalized impulsivity or aggression except during periods of active illness. In contrast, in DSM-5, it is stated that milder episodes may be detected between severe episodes.[9,11] DSM-IV criteria focused on physical aggression, but DSM-5 allows the diagnosis of IED in the presence of frequent verbal aggression with or without physical aggression.[6] According to DSM-5, IED is defined as a failure to resist aggressive impulses resulting in repeated acts of verbal or physical aggression. The inclusion of verbal aggression represents a significant change from previous definitions of IED in the DSM.[6]

After the diagnostic criteria were updated in DSM-5, the difference was not as high as thought in the studies evaluating the difference between the frequency of IED based on DSM-IV and DSM-5 diagnostic criteria. This situation may be associated with the DSM-5 diagnostic criteria being expanded to include verbal aggression yet being more restrictive in duration/frequency compared to the DSM-IV diagnostic criteria.[4]

Epidemiology

Although IED is stated to be a rare disorder in DSM-IV-TR, some recent epidemiological studies suggest that this diagnosis may be seen more frequently than thought.[9,12,13] The lack of a comprehensive study on this subject has prevented a definite figure from being put forward. The frequently changing diagnostic criteria for IED is the most significant factor preventing the comparison of studies. In one of the first studies conducted after IED was included as a separate diagnosis in DSM-III, 20 of 830 patients (2.4%) admitted to a university clinic over two years were diagnosed with IED.[14] IED was the primary diagnosis in only 14 (%1.7) of these patients. While evaluating the results of the study, the researchers suggested that this diagnosis, which was known to be quite rare until then, was more common and suggested that the diagnostic criteria should be evaluated individually for this purpose. Felthous et al. conducted a study on 443 male volunteers with complaints of violence and aggression and found that only 15 (3.4%) met the diagnosis of IED according to DSM-III.[15] It has been reported that 80% of the patients could not be diagnosed because of the criterion in DSM-III, which prevents patients from being diagnosed with IED if impulsive and aggressive behaviors are present between attacks. Various studies have also been conducted according to the DSM-IV diagnostic criteria, which are expected to cover a more comprehensive patient group than other versions. In a field study conducted on 253 individuals in Baltimore, the lifetime prevalence of IED, according to DSM-IV, was found to be 3.95%. In the same sample group, when IED was diagnosed according to the research criteria developed by Coccaro, in which personality disorders were not considered as an exclusion criterion, the lifetime prevalence increased by 30% to 5.14%.[16]

In a community-based survey of 9282 individuals (National Comorbidity Survey-Replication (NCS-R)), the lifetime prevalence for IED was found to be 5.4% and 7.3%, respectively, depending on the limited and comprehensive diagnostic criteria used. When the 12-month prevalence was analyzed, it was determined as 2.7% and 3.9%.[12] In a study conducted in Iraq with 4332 individuals, the lifetime prevalence of IED was 1.7%, and the 12-month prevalence was 1.5% according to DSM-IV diagnostic criteria.[17]

When other studies conducted in Turkey are examined, in an epidemiological study conducted in Sivas, IED was determined at a rate of 0.059% in a study group of 1184 cases.[18] In another clinic-based study conducted in Adana, lifelong IED was found as an additional diagnosis in 15 (14.6%) of 103 adult patients who were hospitalized in the psychiatry service of a university hospital within six months.[19] In another study conducted in Adana in 2015 with 406 patients who applied to outpatient clinic services for the first time in 6 months, the lifetime and 12-month prevalence of IED according to DSM-5 were 16.7% and 11.3%, respectively.[4]

In summary, it was stated that these differences found between the studies could be attributed to the patient groups in which the studies were conducted,

the fact that the disease could not be interrogated as much and systematically as it should be, or cultural factors; moreover, these differences could also be explained by the fact that there is no diagnostic tool that can be accepted as the 'gold standard' for APD and that the preferred research methods were not designed in a way to recognize social diversity.[2,17,20]

Etiopathogenesis

Hypotheses about the etiology of impulsive aggression and IED have been a subject of psychiatry since its inception. Since the second half of the 19th century, explanations about cases showing episodic impulsive aggression have been under two main headings. The first of these states that impulsive aggression occurs due to childhood traumas or adverse early childhood experiences that may affect the development of traits such as willpower (self-control), planning, delaying pleasure, and the power to withstand inhibition, which is extremely important in the suppression of impulsive aggression (self-prevention). The second view is that impulsive aggression is associated with imbalances or variations in the brain's functioning, mediating behavioral arousal and behavioral inhibition. This view is gaining strength, with many results supporting it in research conducted over the past two decades.[21]

Early experiences of "good enough mothering," which encourage a stage-appropriate delay of gratification, and the potential to imitate and identify with the mother are essential for normal development. Too much or too little frustration and too much or too little satisfaction can impair the normal development of the ability to anticipate frustration and delay satisfaction, which is thought to lead to impulsive aggression.[22]

A second line of work, which has yielded numerous positive findings over the last 20 years, states that impulsive aggression may result from variations or imbalances in brain mechanisms mediating behavioral arousal and behavioral inhibition. A rapidly growing body of evidence has shown that impulsive aggression may be associated with defects in the brain's serotonergic system, which inhibits motor activity.[23,24] Animal studies suggest that serotonergic neurons are involved in behavioral inhibition, thus providing impetus to explore the role of serotonin in human impulsivity. Studies on neuropsychiatric patients with localized brain lesions have shown that some bilateral lesions in the PFC may be associated with a chronic pattern of particularly impulsive aggressive behavior. Neurological studies suggest that PFC regions associated with impulsive aggression syndromes are involved in the processing of emotional information and inhibition of motor responsiveness, both of which are impaired in impulsive aggressive patients.

Interictal episodes of aggression may also occur in some people with epilepsy. In a quantitative MRI study examining such episodes among people with temporal lobe epilepsy (TLE), three groups (24 TLE patients with aggressive behaviour, 24 TLE patients without such behaviour and 35 non-patient controls) were compared and aggressive behaviour was associated with reduced frontal neocortical grey matter.[25]

Clinical observation and family history data indicate that IED is a familial disorder. In a study conducted by McElroy et al. in 1998, it was reported that approximately one-third of the first-degree relatives of IED patients had the same diagnosis. In another family study, the risk of disease was found to be 26% in relatives of IED patients, whereas this rate was 8% in relatives of the control group.[26] Twin studies have confirmed the hypothesis that both impulsivity and aggression are under significant genetic influence, but twin studies of IED itself have not been conducted.[27,28] The genetic influence of these two traits varies between 28% and 47%, and unshared environmental effects account for most of the remaining variance.

Very few neuroimaging studies have examined impulsive aggression or IED. Impulsive aggressive behavior is defined as an imbalance between excessive, aggressive impulses originating from limbic brain structures such as the amygdala and inadequate control of these impulses by cortical structures such as the orbitofrontal cortex

and anterior cingulate cortex.[29] Coccaro, et al.'s functional magnetic resonance imaging study of 20 unmedicated patients (10 patients with IED and 10 control group patients) who were shown emotionally salient facial expressions, supports this hypothesis.[30] Compared to controls, patients with IED have been shown to have increased activation of the amygdala and decreased activation of the orbitofrontal cortex towards faces expressing anger. In another perspective, unlike the healthy control group, aggressive individuals responded to angry facial expressions but failed to establish an amygdala-orbitofrontal cortex connection. This study found dysfunction in the amygdala-orbitofrontal cortex connection in subjects with a history of impulsive aggressive behavior when faced with a signal that can be considered socially threatening (angry facial expressions). In addition, it revealed the link between aggression and the problem in the functioning of the corticolimbic network. In an earlier study using fluorodeoxyglucose positron emission tomography (FDG-PET), Siever et al. found blunted glucose utilization responses to serotonin stimulation in the orbitofrontal cortex (an area associated with impulsive aggression) of IED patients. A similar finding has been reported in impulsive-aggressive individuals' anterior cingulate and anteromedial orbit cortex.[31]

Clinical Features

IED is one of several impulse control disorders, manifested by an inability to control emotions and behavior, resulting in behavior that violates social norms and the rights of others.[2] Patients with IED are periodically unable to restrain their impulses, resulting in verbal or physical aggression.[32] The aggressive behavior is unplanned and out of proportion to the provocation. It causes distress or psychosocial impairment in patients. In addition, cognitive impairment and self-harm (e.g., suicide attempts) may occur.[20]

Psychotic experiences (delusions and hallucinations) are observed in many mental disorders, including IED.[33] In a cross-country study conducted in 18 countries, individuals with a lifetime diagnosis of intermittent explosive disorder were identified, and it was found that psychotic experiences occurred in 15% of them.[34] It has been observed that psychotic experiences typically occur after the onset of IED rather than before or at the same time as its onset.

1. Aggressive behavior: The violent, impulsive outbursts that characterize IED are usually preceded by a brief prodrome period. The first impulse to attack typically occurs in response to a minor provocation but can also occur spontaneously.[15] The urge is often accompanied by a rapidly increasing tension or arousal.[35] Somatic symptoms such as paresthesia, tremors, palpitations, and chest tightness may be accompanied by irritability, anger, increased energy, racing thoughts, difficulty in communicating, and impaired cognitive functioning.[36] Little or no thought is given to the consequences of this sudden violent behavior.

Impulsive, aggressive behavior consists of one or more of the following:

- Physical hitting of other people or animals - Ranging from shoving or slapping to fist fighting, using a weapon against someone, injuring someone badly enough to require medical attention, or even murder.
- Verbal outbursts, arguments, and threats to physically attack others - It often occurs during tantrums or heated arguments, characterized by shouting and loss of control.
- Physical aggression towards objects - Ranges from throwing things, slamming doors, kicking objects to breaking objects, or injuring an animal. It often occurs during tantrums or heated arguments, characterized by shouting and loss of control.

The outburst of anger typically lasts less than 30 minutes and is often followed immediately by a feeling of relief.[2] The feelings that follow often include fatigue, dysphoria, regret, and shame.

In IED, the intensity and frequency of aggressive behavior are often inversely proportional:[2,37]

- Low-intensity (non-destructive and harmless) aggression is relatively common.
- High-intensity (destructive or injurious) aggression rarely occurs.

A retrospective study of individuals with IED (n = 380) found that approximately 70% of individuals showed both forms of aggression (low intensity/high frequency and high intensity/low frequency).[38] Approximately 20% showed only low-intensity/high-frequency impulsive aggression, and 10% showed only high-intensity/low-frequency aggression.

In patients with intermittent explosive behavior in the form of physically attacking and injuring other individuals or animals or damaging property, high-intensity aggressive behavior may occur three times a year. In contrast, verbal aggression and threats or physical aggression towards property, animals, or other individuals that does not result in physical damage or injury (i.e., low-intensity aggression) may occur on average twice a week for at least three months.[2,12,32]

A nationally representative survey in the United States found that among 463 people with a lifetime history of IED, the average number of physical (high and low intensity) and verbal outbursts was 28 per year.[12] Symptoms of general aggression may occur between explosive episodes.[35] Patients with IED may experience chronic anger on an ongoing basis as well as subthreshold events during these periods when they can resist aggressive impulses.

2. Cognitive impairment: Cognitive impairments may occur in IED. One study found that impulsive, aggressive male prisoners scored significantly lower on tests of attention, concentration, memory, and intelligence compared to a non-aggressive control group matched for age, race, and education.[39]

IED is also associated with abnormal processing of social and emotional information. Those with IED were more likely to misinterpret others' behavior, make hostile attributions about their intentions, and respond to this with negative emotions, having a more positive view of aggressive behavior compared to each control group. In addition, strategic emotional intelligence (the ability to understand what the other person is feeling and to use this information) is lower in individuals with IEDs compared to healthy controls; this deficit is likely related to abnormalities in social-emotional information processing.[40]

Clinical Prognosis

Retrospective studies show that IED is persistent and chronic. One study found that the average duration of the disease ranged from about 12 years to almost the entire life span.[2]

Treatments

A significant portion of the treatment approaches preferred in the treatment of IED was determined by considering the approaches preferred in the treatment of impulsivity or aggression observed in other psychiatric disorders. The main goal in treating IED is the complete resolution of symptoms or the creation of a picture in which only a few symptoms are mild. In cases where regression of symptoms cannot be achieved, it is aimed to ensure the safety of the person and the immediate environment and to minimize the number, frequency, and severity of attacks as much as possible. A 50% decrease in "Modified Open Aggression Scale" scores after treatment is considered as response to treatment.[20]

In the last decade, double-blind, placebo-controlled clinical trials have been conducted in patients with impulsive aggression or IED (research criteria). Early studies reported a decrease in impulsive aggressive behavior in IED patients with comorbid personality disorder, especially with fluoxetine treatment.[41]

Clinicians are advised to treat IED with CBT in addition to pharmacotherapy, based on randomized clinical trials showing the limited benefit of medication alone.[41,42]

1. Pharmacotherapy

a. Primary treatment approach

Selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line pharmacotherapy for IED in terms of demonstrated efficacy, tolerability, and ease of use. Fluoxetine is frequently preferred because it is the most commonly studied agent. However, other SSRIs are also suitable alternatives. Most randomized trials recommend 6 to 12 weeks of treatment before determining whether the drug is beneficial, depending on the duration of treatment.[41,43,44] Approximately 66% of patients are expected to respond to this treatment protocol.

The usual starting dose of fluoxetine is 20 mg once daily. An effect is expected within two to four weeks. Patients who do not respond to treatment may receive additional dose escalations of 10 to 20 mg daily every two to four weeks as tolerated until an effective dose is reached. The maximum dose is 60 mg per day.

One of the reasons why fluoxetine is preferred in the treatment of IED is a 12-week randomized trial comparing fluoxetine with a placebo in 100 patients with IED and a comorbid personality disorder (obsessive-compulsive, paranoid, or borderline).[41,43] Significantly more moderate to major improvements were observed in patients receiving fluoxetine compared to placebo (66% versus 29%). Other studies also indirectly support the use of fluoxetine to treat IED. A meta-analysis of randomized trials (3992 patients treated for various psychiatric disorders) found that significantly less impulsive aggressive behavior occurred in patients receiving fluoxetine than placebo (0.2% versus 0.7%).[45] In other randomized controlled trials, it was found that fluoxetine significantly reduced impulsive and aggressive behavior in patients with borderline personality disorder and in patients with a history of causing domestic violence and alcohol use disorder.[46,47]

In an open-ended study with 8 participants diagnosed with IED or cluster B personality disorder, it was observed that participants showing impulsive aggression decreased in aggression and irritability with the use of citalopram.[48] In another case series study, a positive response to antidepressant monotherapy using sertraline or venlafaxine was observed in 5 of 10 patients with IED, and a positive response to valproic acid or lithium was observed in 7 of 10 patients.[49]

b. Approach in the treatment-resistant patient

In IED, some patients do not respond to an SSRI within 6 to 12 weeks of starting the medication. (Response is defined as a significant improvement in the number, intensity, and frequency of symptoms, as well as stabilizing the safety of the patient and those around them.) For these treatment-resistant patients, it is recommended to taper the SSRI for one to two weeks, discontinue it, and switch to a drug from a different group, such as phenytoin, carbamazepine, or oxcarbazepine.

Phenytoin: The starting dose of phenytoin is 100 mg three times daily or 200 mg in the morning and 100 mg in the evening, depending on tolerability and compliance.[50,51] The 12-hour serum drug level should be checked two weeks after the first dose and one week after any dose change. In the majority of studies, the drug was kept at 300 mg per day, although there are no data correlating serum levels with efficacy in reducing impulsive aggression. However, patients who do not respond after two to three weeks may benefit from increasing the dose by 30 mg per day each week to 400 mg per day.

Carbamazepine, Oxcarbazepine: The starting dose of oxcarbazepine is 150 or 300 mg daily. It is increased by 150 to 300 mg daily every two to four days to a target dose of 1200 to 2400 mg daily, as tolerated.[52] The dose is divided into two doses per day. Carbamazepine is usually started at a dose of 200 mg per day in divided doses. The dose is increased by 200 mg daily every five days to reach a target dose of 800 to 1800 mg per day as tolerated. Although there are no data linking serum levels to efficacy in reducing impulsive aggression, extended-release formulations may provide more stable serum

levels. A systematic review of four randomized trials showed that oxcarbazepine and carbamazepine were superior to placebo in impulsive aggressive behavior.[53]

In IED, some patients do not respond to oxcarbazepine within 6 to 12 weeks of starting the drug. For these treatment-resistant patients, it is recommended to reduce oxcarbazepine by 300 to 600 mg every two to three days, discontinue it, and switch to a drug from a different group, such as lamotrigine, topiramate, valproic acid, or lithium. The rate of patients responding to the medication change applied in this way can be up to approximately %50.[20,44]

Lamotrigine: The starting dose of lamotrigine is 25 mg daily for the first two weeks. In the third and fourth weeks, the dose is increased to 50 mg per day in divided doses. The dose can then be titrated between 25 and 50 mg daily, once a week for each increase. This slow titration reduces the risk of Steven Johnson Syndrome, a potentially life-threatening side effect characterized by a skin rash. The target dose is 50 to 200 mg per day. In an 8-week randomized controlled trial comparing lamotrigine and placebo in 27 patients with borderline personality disorder, lamotrigine proved superior.[54]

Topiramate: The starting dose of topiramate is 50 mg per day, taken divided in half. The dose is increased by 50 mg daily each week to reach a target dose of 200 to 300 mg daily, as tolerated. Two randomized controlled trials conducted over eight weeks in patients with borderline personality disorder have demonstrated the superiority of topiramate over placebo.[55,56]

Valproate: The initial dose of valproate is 250 mg twice daily, which is increased by 250 mg daily as tolerated to reach an effective dose.[57] The maximum dose is 30 mg/kg/day. Although there are no data linking serum levels to efficacy in reducing impulsive aggression, some authorities target 12-hour serum drug levels of 80 to 120 mcg/mL to maximize efficacy.

The largest randomized controlled trial failed to prove the superiority of valproate over placebo for 12 weeks in 116 patients with IED.[57] However, other smaller studies suggest that valproate may reduce impulsive aggressive behavior.[53]

Lithium: The starting dose of lithium is usually 300 mg two or three times daily. As tolerated, the dose should be increased by 300 to 600 mg every one to five days. The aim is to achieve a therapeutic serum level, which usually occurs with a dose of 900 mg to 1800 mg per day. The target serum level is between 0.8 and 1.2 mEq/L and should generally not exceed 1.2 mEq/L. In a 12-week randomized controlled trial comparing lithium with a placebo in 59 prisoners with chronic impulsive aggressive behavior, lithium proved superior.[58]

2. Psychotherapy

Psychotherapy in IED patients is generally planned to teach these individuals to recognize and manage their moods and moments of anger. Because it is assumed that the fact that these patients are unaware of their increasing anger leads to an unbearable accumulation in the process and that a sudden and inappropriate outburst of anger follows to discharge the accumulation. Group therapy is also known to be helpful in these patient groups.[59] The "exposure" method, which is frequently used in anxiety disorders, was examined in a non-controlled pilot study for anger treatment. In the process, people developed tolerance to anger-triggering scenarios and benefited from the treatment.[59] Another study compared relaxation training alone and combined cognitive behavioral therapy and relaxation training in drivers with anger control problems. While there was no significant improvement in the general anger level in both groups, it was found that the anger levels observed while driving decreased.[60] When this study was repeated in the following years with vehicle drivers with higher anger levels, both methods provided significant improvement in general anger level. Since subjects who received only relaxation training and subjects who received both relaxation training and cognitive therapy benefited at the same level, it has been shown that only relaxation training can be considered sufficient

in treating subjects who are likely to become angry while driving.[61] Mindfulness training is a meditation technique and is another option that can be preferred during the treatment of sudden outbursts of anger without planning in patients diagnosed with IED. This technique teaches the individual how to shift attention from the current situation that causes anger to a more neutral, unrelated part of the body (such as the palms of the hands or soles of the feet) or a more irrelevant situation.

3. Cognitive Behavioral Therapy

Impulsive aggressive behaviors can be controlled with CBT.[42] CBT teaches patients how to manage triggering stimuli in the everyday environment. Specific techniques used in CBT applied in IED include:

1. Cognitive restructuring (changing faulty assumptions and dysfunctional thoughts; the patient is encouraged to examine and evaluate the validity of assumptions and thoughts in the light of all available evidence).
2. Relaxation exercises (e.g., progressive muscle relaxation exercises involving deep breathing as well as tensing and relaxing different muscle groups while imagining situations that cause anger)
3. Training in coping skills (e.g., rehearsing responses such as role-playing potentially provocative situations and avoiding them)
4. Relapse prevention (educating patients that recurrence of impulsive aggressive behavior is common and should be seen as a "slippage" rather than a failure)

CBT is most effective with highly motivated patients who value a problem-solving approach. On the contrary, it is contraindicated in patients who cannot learn the specific techniques taught (e.g., patients with moderate or severe cognitive deficits).[42]

CBT can be delivered in a group or individual format. Patients typically receive 8 to 16 sessions of therapy, but some treatment plans may require 20 sessions, each lasting approximately 60 minutes. Skills taught in therapy are practiced between sessions.

In a 12-week randomized trial comparing group CBT, individual CBT, and a control group condition in 45 patients with intermittent explosive disorder not receiving pharmacotherapy, patients receiving CBT had a clinically large and statistically significant reduction in impulsive aggressive behavior compared with the control group; minor differences between group and individual CBT were observed, which were not significant.[62]

Conclusion

Intermittent explosive disorder is characterized by recurrent episodes in which the person is unable to resist aggressive impulses. These episodes may result in damage to other people or property. Although the frequency and severity of the attacks vary, the degree of aggression observed is disproportionate to the stressor that brought about the current situation. Even though many studies have been conducted to determine the prevalence of the diagnosis, very different results have been found. It can be said that this is due to the lack of a "gold standard" diagnostic tool and the fact that research methods are not organized in a way that distinguishes social diversity, so further studies are needed in this field. Aggressive behaviors and cognitive impairment are at the center of the clinical features. These symptoms can be observed for many years in diagnosed individuals. In addition to SSRIs such as fluoxetine, many different options, such as phenytoin, carbamazepine, and lamotrigine, can be used for the treatment of the disorder, especially in treatment-resistant cases. Psychotherapy combined with pharmacotherapy will also be appropriate in terms of treatment, as it is found to be more effective than pharmacotherapy alone.

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Evaluation of The Frailty Index and Thiol-Disulphide Levels in Geriatric Orthopedic Injuries

Evaluation of The Frailty Index

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Abstract:

Backround: One of the concepts recently discussed about old age is frailty. Frailty was found to be important in determining weakness and indulgence in the elderly. Frail older people are more likely to fall and experience related orthopedic trauma. Free oxygen radicals are known to cause oxidative stress in trauma patients. The aim of this study is to report the levels of frailty and thiol disulphide homeostasis and related factors in patients with geriatric orthopedic injury who presented to the emergency department.

Methods: This study included 82 patients aged 65 and over who were admitted to the Emergency Department of Ankara City Hospital in 2020 due to orthopedic trauma, and 38 people who presented for other reasons in a control group. FRAIL Frailty scale was used to evaluate frailty. In samples from patients' venous blood, native thiol and total thiol were analyzed.

Results: The average age of the patients was 78.48 ± 7.86 (min: 65-max: 99). Of the patients, 30.8% were in the prefrail group and 56.7% were in the frail group. In patient and control group comparisons, total thiol values in the patient group were significantly lower, and disulphide, ischemia-modified albumin, index 1 and index 2 values were significantly higher in the patient group compared with the control group. There were significantly more prefrail individuals (41.5%) among orthopedic trauma patients, and frail individuals (81.6%) in the control group. There was a significant weak negative correlation between body mass index and native thiol and total thiol values.

Conclusion: Oxidative stress is increased in patients with geriatric orthopedic injuries.

Key words: Geriatric patient, orthopedic injury, oxidative stress, frailty

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INTRODUCTION

Aging is a complex condition that is difficult to define. It is a universal process that involves a progressive decline in physiological processes and a permanent decrease in all functions over time.[1] Individuals older than 65 years are defined as elderly. Old age is divided into three stages; the first stage involving ages 65-74 is the young old stage, the second stage involving ages 75-84 is the middle old stage, the third stage involving ages 85 and over is the old old stage.[2,3] Aging varies across individuals. In the evaluation of aging, not only age but the functional capacity of the individual should also be considered. In the evaluation of elderly patients, planning must be performed by assessing whether or not patients are healthy.[4] Frailty is one of the concepts discussed in relation to old age in the recent times. Frailty was found to be important in determining weakness and indulgence in the elderly. The rise in the elderly population, and the presence of multiple diseases in elderly individuals increase the prevalence of frailty in the population. Along with aging, chronic diseases increase and the medication burden shows a parallel rise.[5] While it varies between 10-25% in the general population older than 65 years, it reaches up to 30-45% above 85 years of age.[6-8] Trauma is an important cause of mortality in young adults worldwide. Rates of trauma-related causes of morbidity and mortality vary between 7% and 45%.[9] Although trauma is a significant condition for all age groups, trauma care for the elderly has a special status due to the decrease in their metabolic and physiological capacity.[10] The participation of the elderly in the daily life and social life increases their risk of experiencing trauma.[11]

As in many other patient groups, free oxygen radicals are also known to cause oxidative stress in trauma patients. Further, a review of the literature reveals that frail and prefrail conditions are associated with elevated oxidative stress and reduced antioxidant activity. Thiols are known as mercaptans and are organic compounds that are made up of a sulphur atom and a hydrogen atom attached to a carbon atom, which involve a sulfhydryl (-SH) group.[12] Disulphide bonds found in these molecules can be re-reduced to thiol groups. Because of this property, thiol/disulphide homeostasis is a sustainable reaction.[13] Thiols comprise a large portion of the total antioxidants found in our bodies and exert considerable resistance against reactive oxygen molecules.[14,15] Thiols in plasma have either prooxidant or antioxidant physiological effects and are generally accepted to be antioxidants.[16] They also play a critical role in programmed cell death, detoxification, antioxidant protection and the regulation of cellular enzymatic activity.[17] Measuring serum levels of thiol may indirectly indicate antioxidant protection.[18] Therefore, plasma total thiol (TT), native thiol (NT) and disulphide levels have gained a wider use in routine clinical diagnosis and the monitoring of certain diseases and metabolic disorders.[19] This study assesses frailty levels and thiol disulphide homeostasis levels of patients with geriatric orthopedic injuries who presented to the Emergency Department of Ankara City Hospital to investigate whether there exist differences between the patient and control groups.

MATERIALS AND METHODS

This study was conducted on individuals older than 65 years who presented to the Emergency Department of Ankara City Hospital in 2020 (March-May) with orthopedic injuries. This is a non-randomized clinical trial. The minimum sample size required for this study was determined as 87 based on the sample size analysis conducted at 80% power and a 95% confidence interval (20). One-hundred-and-twenty patients were enrolled. Of these, 82 were patients with orthopedic trauma and 38 were control subjects.

Inclusion criteria:

- Aged 65 or older with an isolated orthopedic injury
- Voluntary participation

Exclusion criteria:

- Multi-trauma patients
- Chest trauma patients

- Head trauma patients
- Non-consent to participation
- Cerebrovascular disease
- Chronic kidney disease
- Rheumatoid Arthritis
- Chronic liver disease
- Acute-chronic infection
- Presence of malignancy
- Antioxidant medication use
- Smoking
- Alcohol use
- Parkinson's, Alzheimer's disease
- Aged less than 65 years

Measurements

a) Frail Frailty Scale

The FRAIL scale was used to determine the patients' frailty states. The validity-reliability study of the FRAIL scale in Turkish was conducted in 2017 by Muradi and colleagues (20). This scale has 5 components: Fatigue, Resistance, Ambulation, Illness, and Loss of Weight. Each component is scored as 0 or 1. The total score varies between 0 and 5. Scores are evaluated as follows; 0: normal, 1-2: prefrail, 3-5: frail.[20]

b) Thiol Disulphide Homeostasis (TDH)

Patients' venous blood samples were analyzed for thiol-disulphide levels. The samples were analyzed using a Roche Cobas C 501 device, in the Emergency Biochemistry Laboratory of Ankara City Hospital. The samples were stored in a refrigerator, at -80 degrees, for 3 months. All samples were analyzed when the sample size was met. Collected blood samples were analyzed for NT, TT and disulphide levels. The indices of these measurements were calculated as follows:

Index 1= (disulphide/native thiol) x 100

Index 2= (disulphide/total thiol) x 100

Disulphide= (total thiol-native thiol) / 2

c) Measurement of Thiol-Disulphide Homeostasis Parameters

Thiol disulphide homeostasis tests were performed according to the automatic spectrophotometric method developed by Erel and Neselioglu. Firstly, disulphide bonds were reduced with sodium borohydride in order to produce free functional thiol groups. Unused reducer sodium borohydride was removed using formaldehyde in order to prevent the reduction of DTNB (5,5'-dithiobis-2-nitrobenzoic acid). Following reaction with DTNB, all thiol groups, including reduced and native thiol groups were determined. Half of the difference between total thiols and native thiols is equal to the amount of dynamic disulphide. Following the determination of the amounts of native thiol, total thiol, and disulphide; disulphide/total thiol (SS / SH + SS), disulphide/native thiol (SS / SH), and native thiol/total thiol (SH / SH + SS) percent ratios were calculated.[17,21]

Statistical Analysis

Data analyses were conducted using the SPSS 22.0 program. The Kolmogorov Smirnov test was used as a test of normal distribution. Qualitative data were presented as frequency and percentages, and quantitative data as mean, standard deviation, and median values. Data analyses used the chi-square test, Mann-Whitney U test, student's t-test, Kruskal Wallis test, One Way ANOVA, and Spearman correlation analysis. $p<0.05$ was considered significant.

RESULTS

The mean age of the 87 trauma patients who presented to the emergency department and 38 individuals in the control group was 77.87±7.80 (min:65-max:95). Sociodemographic characteristics of the patients are provided in Table 1.

Tablo 1. Sociodemographic characteristics	
Characteristic	**n/(%)**
Group patient/control	82(68.3) / 38(31.7)
Gender male/female	61(50.8) / 59(49.2)
Age 65-74/75-84/85 and older	40(33.3) / 47(39.2) / 33(27.2)
Frailty normal/prefrail/frail	15(12.5) / 37(30.8) / 68(56.7)
Trauma site pelvis/lower extremity/upper extremity	42(51.2) / 27(32.9) / 13(15.9)
Chronic disease yes/no	24(20.0) / 96(80.0)

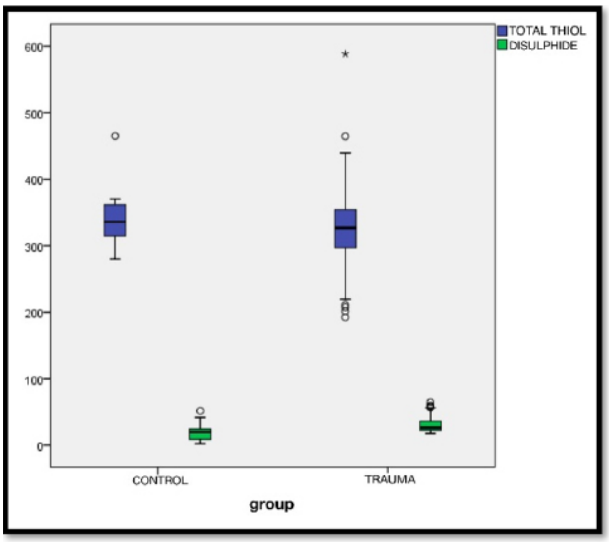
Twenty-five per-cent of these patients had quit smoking, and 75% never smoked. Of the patients, 5.8% were immobile, while 59.2% were mobile enough to fulfill basic needs and 34% showed a normal level of mobility. At least one chronic disease was present in 80% of the patients, and 80% of the patients used at least one regular medication. Comparison of frailty states according to various characteristics is provided in Table 2.

Table 2. Comparison of frailty states				
	Frailty group (n/%)			
Group	**Normal**	**Prefrail**	**Frail**	**p**
Patient	11 (13.4)	34 (41.5)	37 (45.1)	**<0.001**
Control	4 (10.5)	3 (7.9)	31 (81.6)	
Trauma site				
Pelvis	5(11.9)	15 (35.7)	22 (52.4)	
Lower extremity	4 (14.8)	9 (33.3)	14 (51.9)	**0.046**
Upper extremity	2 (15.4)	10 (76.9)	1 (7.7)	
Gender				
Male	10 (16.4)	18 (29.5)	33 (54.1)	0.423
Female	5 (8.5)	19 (32.2)	35 (59.3)	
Age				
65-74	7 (17.5)	15 (37.5)	18 (45.0)	
75-84	5 (10.6)	15 (31.9)	27 (57.4)	0.311
85 and over	3 (9.1)	7 (21.2)	23 (69.7)	

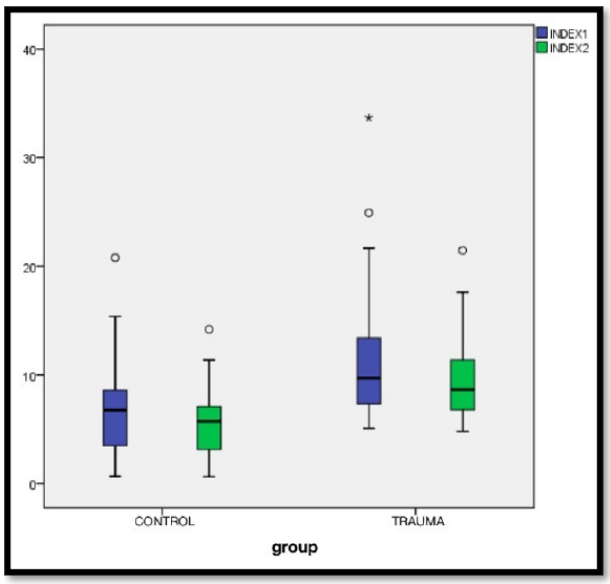
It was found that trauma and control groups were significantly different with regard to frailty states, and that, when the trauma site was considered, more patients with pelvic orthopedic traumas were in the frail group. There were no differences between frailty states in terms of gender and age. Both in the control group and in the patient group, the number of individuals who showed normal physical activity levels was significantly lower in the frail group compared with normal and prefrail groups ($p<0,05$). Comparison of patient and control groups with regard to blood thiol levels and the calculated indices is provided in Table 3.

Table 3. Comparison of TDH (Thiol Disulphide Homeostasis) between trauma and control groups					
	Trauma		**Control**		
	X±S.D.	**Median**	**X±S.D.**	**Median**	**p**
Native Thiol (umol/L)	322.4±69.6	305.8	309.3±83.8	305.6	0.450
Total Thiol (umol/L)	372.6±63.7	362.5	350.8±88.0	339.4	**0.045**
Disulphide (umol/L)	19.0±12.6	18.6	30.7±10.8	26.8	**<0.001**
Albumin (g/dl)	3.1±0.66	2.9	3.5±0.98	3.7	0.099
Index 1	6.4±4.8	5.6	10.6±5.0	9.2	**<0.001**
Index 2	5.2±3.4	4.9	9.0± 3.3	8.2	**<0.001**

The comparison of trauma and control groups revealed that total thiol levels were significantly lower and disulphide, index 1, index 2 levels were significantly higher in the trauma group compared with the control group. Distributions of TT, disulphide, index 1, index 2 levels in the patient and control groups are presented in the graphs below.



Graph 1. Total thiol and disulphide levels of trauma and control groups



Graph 2. Index 1 and Index 2 values of trauma and control groups

Blood thiol levels by frailty state are presented for patients in the trauma group in Table 4.

Table 4. Comparison of TDH (Thiol Disulphide Homeostasis) across frailty states (trauma group)							
	Normal		**Prefrail**		**Frail**		
	X±S.D.	**Median**	**X±S.D.**	**Median**	**X±S.D.**	**Median**	**p**
Native Thiol	291.1±64.7	283.7	304.7±86.4	295.5	319.0±87.0	310.1	0.629
Total Thiol	332.6±67.9	339.8	344.7±88.4	336.0	361.8±93.2	339.0	0.637
Disulphide	30.7±7.1	29.2	30.0±13.0	23.8	31.3±9.6	30.6	0.207
Albumin	3.5±0.68	3.8	3.7±1.0	3.7	3.4±1.0	3.2	0.723
Index 1	11.1±4.1	9.7	10.7±6.3	8.2	10.3±4.0	9.7	0.366
Index 2	9.5±2.9	8.6	9.0±3.9	7.5	8.9±2.8	8.5	0.398

The comparison of blood thiol levels of patients in the trauma group across frailty categories did not reveal a significant difference. Correlations between body mass index and blood thiol levels are provided in Table 5.

Table 5. Correlations between BMI (Body Mass Index) and TDH(Thiol Disulphide Homeostasis) levels

	BMI	
	r	**p**
Native Thiol	-0.188	**0.040**
Total Thiol	-0.198	**0.030**
Disulphide	-0.035	0.701
Albumin	0.073	0.425
Index1	0.092	0.319
Index2	0.102	0.269

Body mass index showed a significant weak negative correlation with native thiol and total thiol levels.

DISCUSSION

In this clinical study, the comparison of trauma and control groups showed that total thiol levels were significantly lower in the trauma group compared with the control group; and that disulphide, index 1 and index 2 levels were significantly higher in the patient group. The oxidant burden was determined to be significantly higher in the trauma group. It was found that the number of prefrail and frail individuals was significantly higher among patients with orthopedic trauma, and that the control group had significantly more frail individuals than those with a frailty state evaluated as normal. The literature reports that frailty can occur due to complex conditions involving a multitude of factors such as unintentional weight loss, reduced appetite, cognitive impairment, depression, sarcopenia, osteopenia, activation of inflammatory and coagulation systems, increase in coagulopathy and inflammatory markers, and activation of catabolic cytokines.[22] According to the information existing in the literature, frailty fractures occur at increasing rates, producing considerable economic and societal effects. Identifying the patients who are at risk, initiating effective treatment of metabolic bone disease and comprehensive planning of treatment protocols to reduce future fractures constitute an indispensable component of this process.[23] Since osteoporosis and osteoporotic fractures maintain their status as an important public health problem worldwide, the concept of osteoporosis-related frailty in the elderly is gaining wider acceptance and has prompted new studies that assess frailty in osteoporotic fractures. The assessment of frailty levels in the elderly appears to be quite useful in the evaluation and management of osteoporosis and osteoporotic fractures and the related decisions, in the context of both clinical research and health policy.[24] Osteoporosis is associated with elevated oxidative stress and free radical levels. In elderly frail individuals, elevated levels of free oxygen production were found to overcome the natural antioxidant defense mechanisms, expose individuals to hyperoxidant stress, and thus, lead to osteoporosis. Improving the antioxidant levels of these individuals can protect their bones against osteoporosis and also help accelerate the healing of fractured bones.[25]

Another important result obtained in the present study is that frail and prefrail states were more common in patients with lower extremity and pelvic traumas; while frail states were less common in patients with upper extremity traumas. Fall-related lower extremity and pelvic fractures are a common problem with significant impact on patients, caregivers, health service providers and the society. The largest burden is caused by hip fractures and

although the surgery is usually successful, many patients do not fully recover. Most individuals who sustained a hip fracture do not regain their previous activity and mobility levels, and thus, there is a higher risk of falling. Many of these patients also show higher levels of dependence; approximately 10% fail to return to their previous states.[26-28] Based on this, we can state that these fractures make the patients frailer; and that these frail states constitute a risk factor for many complications such as fractures etc. Optimizing recovery after lower extremity fractures and preventing further falls have the potential to decrease the burden on the individuals and the society.[29-31] Considering that, in the present study, frail and prefrail states were more common among patients with lower extremity and pelvic traumas; preventing the exposure of these patients to trauma, eliminating the factors that facilitate trauma and the occurrence of fractures, and in the case that fractures occur, ensuring fracture healing and regaining of previous functioning would improve the long term outcomes in these patients. As falling continues to be an important problem in the elderly populations worldwide, studies have evaluated the effects of exercise programs on avoiding further falls in fracture patients. Studies conducted by Bischoff-Ferrari and colleagues, Orwig and colleagues, and Sherrington et al. suggest that exercise programs with carefully constructed details for elderly patients with fall events should be devised.[3,33] The fact that frail and prefrail states were more common in patients with lower extremity and pelvic trauma in the present study reminds us once again that patients in these groups require a multidimensional approach. On the other hand, in our study, the number of those with normal physical activity levels were lower in the frail group than in normal and prefrail groups, both in the control and the patient group. Based on these findings, we can state that precautions taken against frailty would reduce these fractures, which have devastating effects, and that reducing these fractures would, in turn, prevent frailty.

According to literature data, frail and prefrail states are related to elevated oxidative stress and reduced antioxidant activity.[34] One of the important results of our study is that oxidative stress parameters were higher and the antioxidant status was decreased in the elderly orthopedic trauma group compared with the control group: it was found that total thiol levels were significantly lower in the patient group, and disulphide, index 1 and index 2 levels were significantly higher in the patient group compared with the control group. Oxidative stress is generally defined as a consequence of an imbalance between oxidant production and oxidant scavenging by protective mechanisms such as antioxidants. Cells that have a central role in fracture healing may be influenced, causing osteoblastogenesis to decrease, but osteoclastogenesis, which results in a net decrease in bone density, to increase. Additionally, intrinsic oxidative stress may lead to problems in bone reformation due to osteocyte apoptosis resulting from irreversible cell injury caused by excessive toxic radicals.[35,37] The dynamic thiol disulphide homeostasis state has critical roles in antioxidant production, detoxification, signal transduction, apoptosis, regulation of enzymatic activity, and transcription factor and cell signaling mechanisms.[38,39] Moreover, an increasing number of findings suggest that it has a more significant role than previously thought in a variety of diseases. Therefore, determining dynamic thiol disulphide homeostasis can provide valuable information regarding various normal and/or abnormal biochemical processes.[40,41] Accordingly, our study performed these measurements and reached highly significant results in the patient group compared with the control group. In addition to physical interventions that aim to prevent fractures and/or ensure recovery and return to previous functioning states in patients with orthopedic injuries; these data will strengthen our position in coping with complicated and multifactorial conditions such as frailty. As in many patient groups, free oxygen radicals are known to induce oxidative stress in trauma patients.[41,42] In the present study, the comparison of patient and control groups revealed that total thiol levels were significantly lower and disulphide, index 1 and index

2 levels were significantly higher in the patient group compared with the control group. Also, our study determined a significant weak negative correlation between body mass index and NT, TT levels. We can interpret these findings better if we remember that, according to literature data, obesity and oxidative stress are related, and further, that obesity is a risk factor for frailty.[43,44] We can state that both the oxidative stress levels and the frailty levels of these patients would be more favorable when the body mass index conforms to ideal levels.

In a study by Iskender and colleagues that investigated thiol homeostasis in patients with traumatic bleeding and hemorrhagic shock who presented to the emergency department and a control group; significant differences were determined, in descending order of significance, in NT, TT, disulphide, disulphide/NT, disulphide/TT, and NT/TT levels. It was found that the patient group had significantly lower native thiol, total thiol, native thiol/total thiol ratios and disulphide levels, and significantly higher disulphide/native thiol, disulphide/total thiol ratios.[42] Similar results were obtained in the present study, showing significantly lower total thiol levels and significantly higher disulphide, index 1 and index 2 levels in trauma patients compared with the control group. It can be seen that trauma modifies the thiol homeostasis. In patients with serious trauma, the amount of oxidative stress generally depends on various parameters such as total antioxidant capacity and lipid peroxidation. It was reported that monitoring the oxidant-antioxidant ratios could be a useful tool in the evaluation of the level of oxidative stress, inflammation, the severity of injury and the potential effectiveness of treatment.[45,46] In agreement with the literature data, it was found in the present study that oxidant capacity increased and antioxidant capacity decreased in trauma patients. Increasing the total antioxidant capacity in patients who present with trauma can be considered in order to improve the outcomes of treatment. A better understanding of fracture and oxidative stress mechanisms may help define the role of oxidative stress following a fracture, and perhaps, determine the contribution of antioxidants to fracture healing more clearly.[47] In the early period after a fracture, reactive oxygen species (ROS) are produced under inflammatory and ischemic conditions due to vascular and soft tissue injury, and this leads to cell death. Generally, during fracture healing, such injuries can be prevented to a great extent through the protective mechanisms and functions of antioxidant enzymes. However, excessive toxic radicals produced due to intrinsic oxidative stress can cause irreversible damage to cells associated with bone repair in the fracture healing process. Therefore, individuals with Type-2 diabetes mellitus, osteoporosis, alcohol intake, and heavy smokers are at risk for defective fracture healing due to high oxidative stress.[48] Preventing these disorders and abnormal conditions would have a positive effect on fracture healing and offer patients a healthier life by averting frail states.

We report the low number of controls in the study and the fact that the controls were recruited from individuals who presented to the emergency department as the limitations of this study. The results of this study show that oxidative stress is elevated in patients with orthopedic trauma. Prefrailty and frailty are higher among trauma patients. Improving oxidative stress, frailty and the conditions that induce frailty can have a favorable effect on the outcomes of frail patients with orthopedic injuries. All geriatric trauma patients should be evaluated multidimensionally with a perspective to prevent frailty and its negative consequences.

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Hepatocellular carcinoma: A comprehensive review of epidemiology, diagnosis, and treatment

Hepatocellular carcinoma: A comprehensive review

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Abstract: Hepatocellular carcinoma (HCC) is a primary liver cancer predominantly arising in individuals with chronic liver diseases such as cirrhosis or chronic hepatitis B virus (HBV) infection. Accounting for approximately 75% of primary liver tumors, HCC's global epidemiology is significantly influenced by HBV and hepatitis C virus (HCV) infections, alcohol and tobacco use, metabolic syndrome, diabetes, obesity, and aflatoxin B1 exposure. Preventive measures, including HBV vaccination and direct-acting antivirals for HCV, have reduced incidence rates, particularly in younger populations. Early diagnosis through surveillance in high-risk groups is critical, employing imaging modalities like ultrasound, CT, and MRI, alongside biomarkers such as alpha-fetoprotein (AFP). Prognostic assessments utilize scores like Child-Pugh and ALBI. Treatment strategies for HCC are multifaceted, involving surgical resection, locoregional therapies (e.g., transarterial chemoembolization), and systemic therapies, including targeted and immunotherapies. Despite advancements, treatment efficacy remains a challenge, necessitating ongoing research into novel therapeutic approaches and predictive biomarkers to enhance personalized treatment and improve outcomes for HCC patients.

Keywords: Hepatocellular carcinoma, Chronic liver disease, Treatment options

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Epidemiology of Hepatocellular Cancer

Hepatocellular carcinoma (HCC) is a type of liver cancer that usually occurs in individuals with chronic liver disease, especially those with cirrhosis or chronic hepatitis B virus infection. HCC accounts for around 75 percent of primary liver tumors, whereas cholangiocarcinoma makes up the majority of the remaining instances (1).

1. **Hepatitis B Virus (HBV):** HBV is a DNA virus that causes HCC by triggering chronic necroinflammatory disease in liver cells (2). It is responsible for 33% of HCC cases worldwide (3). The lifetime risk of developing HCC in HBV carriers is between 10-25%. Risk factors include male gender, advanced age, high viral load and HBV genotype (4-6).
2. **Hepatitis C Virus (HCV):** HCV, an RNA virus, causes tumor development through repetitive damage, regeneration and fibrosis. Chronic HCV infection increases the risk of HCC by 10-20 times (7) and is responsible for 10-25% of HCC cases worldwide. Risk factors include advanced age, male gender, HCV genotype and co-infections (8).
3. **Alcohol and Tobacco Use:** Chronic alcohol consumption (≥3 drinks/day) increases the risk of HCC by causing fatty liver, alcoholic hepatitis, fibrosis and cirrhosis. The annual incidence of HCC is 1-2% in patients who develop cirrhosis (9). Alcohol may have a synergistic effect with other risk factors (10). Tobacco use also increases the risk of HCC; the risk is 70% in current smokers compared to 40% in people who have quit smoking (11).
4. **Metabolic Syndrome, Diabetes and Obesity:** These factors increase the risk of HCC. Treatment of type 2 diabetes with metformin reduces the risk of HCC, while treatment with insulin and sulfanilurea increases the risk (12, 13).
5. **Non-Alcoholic Fatty Liver Disease (NAFLD):** NAFLD is one of the major reasons for the recent increase in the incidence of HCC(35). 20-30% of people with NAFLD develop non-alcoholic steatohepatitis (NASH) and 10-20% of these cases progress to cirrhosis(38,39). 70-80% of HCCs developing on the background of NAFLD develop on the background of cirrhosis and 20-30% develop without cirrhosis (14).
6. **Aflatoxin B1:** Aflatoxins produced by Aspergillus fungi, especially B1 (AFB1), increase the risk of HCC. According to a meta-analysis published in 2011, AFB1 alone increases the risk of HCC by 6 times, HBV alone by 11 times, and AFB1 and HBV together by 54 times (15).
7. **Other Factors:** Excessive iron buildup significantly elevates the risk of HCC. Notably, a higher ferritin concentration in the bloodstream is associated with a 49% increase in HCC risk. Factors such as hemachromatosis, alpha-1 antitrypsin deficiency, glycogen storage diseases, porphyrias, tyrosinemia and Wilson's disease also increase the risk of developing HCC (16).

Prevention and screening

Prevention of chronic liver disease is crucial in reducing hepatocellular carcinoma (HCC) risk. Effective strategies include hepatitis B virus (HBV) vaccination programs, which have significantly reduced HCC incidence in younger populations, and direct-acting antivirals for hepatitis C virus (HCV) elimination (17). For early detection, international guidelines recommend surveillance of high-risk populations using six-monthly abdominal ultrasound, with or without alpha-fetoprotein (AFP) testing. However, controversies persist regarding AFP's value due to varying sensitivity and specificity (18, 19).

In conclusion, while significant progress has been made in HCC prevention and early detection, continued research and public health efforts are necessary to address emerging risk factors and improve screening efficacy.

Diagnosis of hepatocellular cancer:

Early diagnosis of HCC is important. While the 5-year survival rate is 70% in patients diagnosed at an early stage and treated, this rate drops to 18% in

patients diagnosed late (20, 21). High-risk patients Cirrhosis, chronic hepatitis B and chronic hepatitis C patients with advanced fibrosis are high-risk patients in terms of HCC development. Regular surveillance is recommended in high-risk patients (22). Ultrasonography (USG) and alpha-fetoprotein (AFP) are generally used for surveillance. The Liver Imaging Reporting and Data System (LI-RADS) is used for the diagnosis of HCC. LI-RADS classifies lesions according to the likelihood of malignancy (23).

Three main imaging modalities are used in the diagnosis of HCC: Contrast-enhanced US (CEUS), triphasic contrast-enhanced CT, and dynamic contrast-enhanced MRI.Typical findings for HCC on imaging are: contrast staining in the arterial phase, contrast material excretion in the venous phase, and capsule visualization.Biopsy is recommended in lesions without typical HCC findings (LI-RADS-4) (22, 24-26).

Clinical and biochemical biomarkers in hepatocellular carcinoma:

Hepatocellular carcinoma prognosis depends on tumor characteristics and underlying liver disease. Higher serum AFP levels correlate with increased mortality and recurrence risk after resection or transplantation (27). Child-Pugh and ALBI scores evaluate liver function as prognostic factors, with post-hoc analyses confirming their role during systemic therapy (28). Molecular signatures classify HCC into proliferation and non-proliferation classes, but have limited clinical use. HCC typically has low-moderate tumor mutational burden. Liquid biopsy approaches show potential for non-invasive diagnosis and monitoring. Angiogenesis biomarkers are associated with poor prognosis but don't predict treatment response. Inflammatory markers may predict survival benefit with systemic therapy. These biomarkers collectively contribute to our understanding of HCC biology and patient outcomes, though their clinical application remains an area of ongoing research and development (29).

Treatment:

Guidelines at national and international levels provide a clear picture of the treatment options available for patients diagnosed with hepatocellular carcinoma. The Barcelona Clinic of Liver Cancer (BCLC) algorithm is the predominant staging system for hepatocellular carcinoma. It categorizes patients into five clinical stages: very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C), and terminal stage (BCLC D) (30).

Surgery:

Treatment of patients with HCC requires a multidisciplinary approach. Surgical resection is one of the curative treatment modalities and can provide a 5-year survival of more than 50% in well-selected patients (31). The stage of the disease, patient performance, liver reserve and risk factors should be evaluated when selecting surgical candidates. Methods such as Child-Pugh classification, MELD score and ICG test are used to evaluate liver reserve (32). The presence of portal hypertension and high bilirubin levels are indicators of poor prognosis. Child A patients without portal hypertension and with normal bilirubin levels are the best candidates for surgery (33). Postoperative morbidity ranges between 33-55% and mortality between 1-24%. The main complications include liver failure, bile leakage and pleural effusion [30,39,48].Tumor size, number, vascular invasion, extrahepatic involvement and liver function are the main factors affecting postoperative results (34,35).

Locoregional Therapies in Hepatocellular Cancer:

Locoregional therapies, which are usually performed by interventional radiologists, are basically divided into two groups: transcatheter embolizations (transarterial embolization [TAE], transarterial chemoembolization [TCE]), which are characterized by the delivery of chemotherapeutics or radiotherapeutics to the targeted area via the arterial route, transarterial radioembolization [TARE]) and

local (usually percutaneous) ablations (percutaneous ethanol injection [PEE], radiofrequency ablation [RFA], microwave ablation [MDA], cryoablation [KA], laser-induced thermotherapy [LITT] and irreversible electroporation [GDE]) (36).

TAE: Provides occlusion of the arteries supplying the tumor with embolic agents. Provides tumor control in BCLC class B and C patients. It can also be used for downstaging before liver transplantation (37).

TAKE: It uses a combination of chemotherapeutic and embolic agents. It is the first-line treatment in unresectable HCC (BCLC stage B). It can also be used as a bridge to surgical methods (38).

TARE: Provides delivery of radioactive microspheres to the tumor. Recommended for BCLC stage 0 or A single HCC smaller than 8 cm. Protects quality of life in patients with portal vein invasion (39).

PEE: Cell death is achieved by injecting ethanol into the tumor. It shows similar efficacy to RFA in small HCCs (<1.5 cm) (40).

RFA: Creates coagulation necrosis in tumor tissue with high frequency current. It is indicated in early stage HCC (≤3 cm, ≤3 nodules) (41).

MDA: Provides cell death by heating the tissue with microwave energy. It has similar indications to RFA, but may be more effective in larger tumors (3-5 cm) (42).

KA: Cell death is achieved by applying extremely low temperatures. It can be used safely in subcapsular high-risk HCCs Other methods such as LITT and GDE are also available, but their role in HCC treatment has not yet been fully determined (43, 44). These locoregional therapies have an important role in the management of HCC and are expected to be used more frequently as monotherapy or combination therapies in the future.

Targeted Therapies and Immunotherapy in Hepatocellular Cancer:

Surgical resection is the mainstay of treatment in HCC, but most patients are not suitable for surgery. There have been many developments in the treatment of patients with HCC (figure-1) (29). Until 2008, there was no effective treatment for advanced HCC (45, 46). Sorafenib became the standard of care in first-line treatment, showing a survival benefit in the SHARP and Asia-Pacific trials (47, 48). Lenvatinib was also an alternative to sorafenib in subsequent studies (49). In second-line treatments, regorafenib (50), cabozantinib (51) and ramucirumab (52) were found to be effective. In the IMbrave150 study, the combination of atezolizumab plus bevacizumab was superior to sorafenib in first-line treatment in Child-Pugh A patients (53). In the Himalaya study, durvalumab plus tremelimumab showed an overall survival benefit over sorafenib (54). Other targeted therapies (linifanib, tivantinib, axitinib) have been evaluated in various studies but have not entered standard treatment. In the Imbrave 050 study, atezolizumab plus bevacizumab showed a recurrence-free survival benefit in adjuvant treatment in patients with high-risk HCC (55). HCC treatment is complex and requires a multidisciplinary approach. Patients should be carefully evaluated for available treatment options.

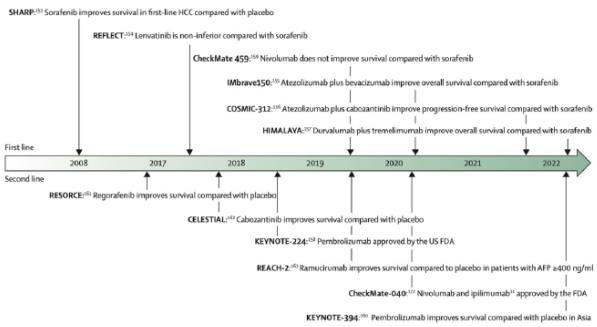

Figure 1: Milestones in the development of systemic therapy for HCC AFP=alpha-fetoprotein. FDA=Food and Drug Administration. HCC=hepatocellular carcinoma.

Conclusion:

The epidemiology of liver cancer is changing and increasingly non-viral causes are becoming dominant. Innovative approaches and preventive strategies are needed to address the increasing incidence of hepatocellular carcinoma in patients with fatty liver disease. Despite significant advances in locoregional and systemic therapy, the majority

of patients do not respond and ultimately treatment failure is likely. Consequently, there is still a need for more effective systemic therapies as well as predictive biomarkers that enable personalized and cost-effective treatment stratification. The dynamic interaction between locoregional and systemic therapy is also under investigation. Despite being one of the cancers with the worst prognosis, the coming years will be dedicated to studies that will contribute to survival leading to better outcomes.

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Evaluation of the Relationship Between Health Literacy and the Perspectives of Pregnancy on Covid-19 Vaccines During the Covid-19 Pandemic Period

Perspectives of Pregnancy on Covid-19 Vaccines

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Abstract:

Objective:1The aim of this study was to investigate the number of pregnant women who were exposed to COVID-19 during the COVID-19 pandemic their perspectives on vaccines, their vaccination status, their attitude towards vaccines, and to evaluate the relationship between their approaches and health literacy.

The population of the study, Kastamonu Training and Research Hospital and those who have at least four weeks of pregnancy who apply to İnebolu State Hospital, and covering all other trimester periods (N = 375). May 2022-Between December 2023, socio-demographic characteristics of pregnant women, obstetrics characteristics, vaccination status, attitudes and behaviors towards vaccines Survey Questionnaire in order to determine and determine health literacy levels Turkey Health Literacy Scale-32 (TSOY-32) was used. Analyses SPSS It was made using 22 software. Data Mean±Standard Deviation and percentage distribution and the Chi-square test was used in its analysis. $p < 0.05$ significance level it was considered statistically significant.

Results: The mean age of pregnant women was 28.40±5.61 and the mean gestational week was 28.405.61 22.69±11.47. In the study, 69.1% of pregnant women had COVID-19 disease. caught, 76% received COVID-19 vaccine and 9.3% were during pregnancy He was seen receiving the COVID-19 vaccine. Infecting the family of 68% of pregnant women with the disease pregnancy because they got the COVID-19 vaccine against their will, and 90.7% of them were pregnant He was seen to have given up on getting the COVID-19 vaccine. Pregnant women's TSOY-32 The mean overall index score of the scale was 23.37 ± 8.35. 55.7% of pregnant women It was determined that there was insufficient health literacy level.

Conclusion: As a result of the study, COVID-19 vaccines during the COVID-19 pandemic Health literacy of pregnant women who are determined to show approaches, attitudes and behaviors It was determined that their levels were insufficient. In line with these results, health By supporting the multidisciplinary team approach of doctors and midwives, who are among the professionals, The level of knowledge of pregnant women with low health literacy about COVID-19 vaccines It should be increased.

Keywords: Pregnancy, COVID-19, COVID-19 vaccines, Health literacy.

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INTRODUCTION

Infectious diseases that have impacted countries, continents, and even the entire world have led to the emergence of the concept of a pandemic. The pandemic declared by the World Health Organization (WHO) on March 11, 2020, due to the Coronavirus Disease 2019 (COVID-19) is seen as a serious public health issue today. (1) In the fight against the COVID-19 pandemic, early diagnosis can be achieved by using definitive diagnostic methods to minimize the transmission of the infection from infected individuals to healthy ones. This, combined with the support of antiviral drugs and vaccination practices, can help prevent the rapid spread of the virus. For pregnant women of reproductive age who are infected with COVID-19, the decision regarding the use of antiviral drugs for treatment should be made collaboratively by a multidisciplinary team and the patient herself (2). Among the pharmacological agents used in the treatment of viral infections, the antiviral drug Remdesivir is also used for treating pregnant women (3). The Academy of Breastfeeding Medicine supports the continuation of breastfeeding in infected mothers using the antiviral drug Remdesivir (4). Favipiravir, an antiviral drug that strongly inhibits the RNA-dependent RNA polymerase of RNA viruses, has insufficient data regarding its use in pregnant women and is not recommended (5). Another method used in the treatment of COVID-19 is vaccination. Vaccination plays a crucial role in minimizing the risk factors that may arise in pregnant women facing the risk of COVID-19 infection. Vaccinated pregnant women protect themselves from mortality and morbidity, and subsequently protect the fetus from neonatal mortality and morbidity. This aims to significantly reduce maternal and infant mortality, and "The American College of Obstetricians and Gynecologists (ACOG)" recommends vaccination for all women of reproductive age and breastfeeding mothers (6). Among COVID-19 vaccine types, data on the use of the inactivated CoronaVac (Sinovac) vaccine in reproductive-age pregnant women, who are at risk, are insufficient. However, the WHO supports the vaccination of reproductive-age pregnant women with the CoronaVac (Sinovac) vaccine, suggesting that clarifications about the vaccine should be made, the outcomes of vaccination versus non-vaccination should be compared, and this would contribute to increasing the awareness level of pregnant women. The WHO does not support delaying pregnancy in vaccinated reproductive-age women (7). The Pfizer-BioNTech mRNA vaccine has been found to be safe, well-tolerated, and capable of inducing both humoral and cellular immune responses against the SARS-CoV-2 virus in reproductive-age pregnant women during the second and third trimesters, as well as in newborns and breastfeeding women (8). Following vaccination, both humoral and cellular immune responses are transferred through the placenta to the fetus in pregnant women, and through breast milk to newborns in breastfeeding women, providing protective benefits. The Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG) recommend vaccination for women of reproductive age and breastfeeding mothers, and support the continuation of breastfeeding by vaccinated mothers as well as not delaying pregnancy if planned (9). Lastly, the Turkovac vaccine, which falls under the inactivated vaccine category used in our country, has been approved following an emergency use authorization application, making it the first locally produced COVID-19 vaccine in Turkey (10,11). Health literacy plays a crucial role in developing vaccination habits by helping women make informed decisions about their health, adopt positive health behaviors, and effectively utilize health services (12). This not only enables women to make conscious and accurate decisions about their own health but also helps them manage pregnancy, childbirth, and the postpartum period effectively, significantly benefiting fetal, neonatal, and child health (13).

Inadequate health literacy during pregnancy can hinder access to sufficient and quality prenatal care. It is extremely challenging for women to adhere to recommendations from healthcare professionals, such as obstetricians and midwives, and the

likelihood of making informed decisions about their own health and the fetus's health is relatively low (14). Therefore, improving problematic or limited health literacy levels through planned health education provided by a multidisciplinary team approach involving obstetricians and midwives is essential for ensuring a healthy pregnancy. Women with high health literacy levels engage in behaviors that improve the health of themselves, future generations, and the community (15).

MATERIALS AND METHODS

The study was conducted as a cross-sectional research. The study population consisted of pregnant women who visited Kastamonu Training and Research Hospital and İnebolu State Hospital between May 2022 and December 2023, including those in the early stages of pregnancy (as early as four weeks) as well as those in later trimesters. Based on the data from the study assessing the relationship between health literacy and attitudes toward COVID-19 vaccines during the COVID-19 pandemic, the sample size (power analysis) required to achieve a 95% confidence interval and 80% power was calculated to be 330 pregnant women. The study was completed with 375 pregnant women who met the inclusion criteria. Pregnant women who volunteered to participate, had at least four weeks of pregnancy, and were in any trimester and had visited the hospital were included in the study. Pregnant women with gestational age less than four weeks, those with risky pregnancy conditions, those with health problems that impeded communication (e.g., hearing or vision impairments), and those with chronic psychiatric disorders were excluded from the study.

Data Collection Tools

The research data were collected using a Questionnaire Form, which investigated the socio-demographic characteristics of the pregnant women, pregnancy information, vaccination status, attitudes towards vaccines, and their behaviors. Additionally, the Turkey Health Literacy Scale-32 (TSOY-32) was used to determine their level of health literacy.

Questionnaire Form

The research data were collected using a form consisting of a total of 33 questions: eight questions regarding the socio-demographic characteristics of the pregnant women, eight questions concerning obstetric characteristics, and 17 questions related to COVID-19 parameters. The questions were distributed across multiple-choice, closed-ended, and open-ended formats.

Turkey Health Literacy Scale-32 (TSOY-32 Scale)

The TSOY-32 Scale, designed to measure individuals' health information levels, was developed in 2016 through the adaptation of the European Health Literacy Survey (HLS-EU) into Turkish by a team led by Pınar Okyay, Filiz Abacıgil, and Hacer Harlak. This scale has been incorporated into Turkish literature. The validity and reliability of the scale in Turkey were established by Okyay and colleagues (16).

The scale, developed using a 2X4 matrix, consists of eight components divided into two dimensions: treatment and service, and disease prevention/health improvement. It includes four processes: accessing health-related information, understanding health-related information, evaluating health-related information, and using/applying health-related information (17). It comprises 32 items on a five-point Likert scale. Scores from the TSOY-32 Scale are assigned as follows: very easy (4), easy (3), difficult (2), and very difficult (1). The zero score represents the lowest health literacy level, while fifty represents the highest. The Cronbach's Alpha coefficient for the Turkish version of the scale was found to be 0.927 in the validity and reliability study (18).

Data Collection Process

Before starting the study, the necessary permissions were obtained from the Kastamonu Provincial Health Directorate. Participants were first informed about the study by the researchers, and their consent for voluntary participation was obtained. Subsequently, the participants were asked to

complete the Questionnaire Form and the TSOY-32 Scale thoroughly. Data were collected using face-to-face interviews.

Statistical Analysis

The data were analyzed using IBM SPSS 22 software. Descriptive statistics were used to summarize the data on socio-demographic, obstetric, and COVID-19 characteristics of the pregnant women, as well as the scale data, presenting them as percentages and Mean±Standard Deviation ($\bar{x}$±SD). The Chi-square test was applied in the data analysis. A 95% confidence interval and a p-value <0.05 were considered statistically significant.

RESULTS

The findings regarding the socio-demographic characteristics of the 375 volunteer pregnant women participating in the study are presented in Table 1. The average age of the pregnant women was determined to be 28.40±5.61 years, and the average gestational age was 22.69±11.47 weeks (Table 1).

Table 1. Socio-Demographic Characteristics of Pregnant Women (n: 375)

Characteristics		**Mean±SD**	**Min-Max**
Age		28,40±5,61	18-45
		n	**%**
Occupation	**Housewife** **Freelancer (Worker)** Public Employee	313 30 32	83,5 8,0 8,5
Employment Status	Employed Not Employed	64 311	17,1 82,9
Income Level	4000-6000 TL 6000-8000 TL 8000-10,000 TL 10,000-12,000 TL Above 12,000 TL	141 137 63 21 13	37,6 36,5 16,8 5,6 3,5
Income-Expense Balance	Income less than expenses Income equal to expenses Income more than expenses	239 135 1	63,7 36,0 0,3
Residence Location	Village District Center	113 198 64	30,1 52,8 17,1
Education Level	Literate Primary school graduate Middle school graduate High school graduate Bachelor's degree Postgraduate	4 43 156 131 40 1	1,1 11,5 41,6 34,9 10,7 0,3
Social Security	SSK (Social Security) Bağ-Kur (Social Security for Self-Employed) Green Card None	224 87 37 27	59,7 23,2 9,9 7,2

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

Table 2 presents findings related to the obstetric characteristics of the pregnant women. The average age of the first pregnancy for the women was 23.98±4.12 years. The average total number of pregnancies was 2.16±1.45; the average total number of births was 0.90±1.19, and the average number of living children was 0.92±1.22. It was observed that the women experienced their first pregnancy either during adolescence (19 years old and younger) or at advanced age (35 years old and older). 79.5% of the women (n=298) reported that they had not had a miscarriage before. When examining previous birth methods, it was found that 44.5% (n=167) had not given birth before. 88.5% of the women (n=332) had no history of chronic illness. The most common chronic condition was thyroid/goiter disease, which was found in 5.6% (n=21) of the women (Table 2).

Table 2. Obstetric characteristics of pregnant women (n: 375)

Characteristics	**Mean±SD**	**Min-Max**
Your pregnancy week	*22,69*±11,47	5-40
Age at first pregnancy	*23,98*±4,12	15-40
Total number of pregnancies	*2,16*±1,45	1-11
Total number of births	*0,90 ±1,19*	0-10
Number of living children	*0,92*±1,22	0-10
Characteristics	***n***	**%**
History of miscarriage Yes	77	20,5
No	298	79,5
Previous birth method Normal vaginal delivery	117	31,2
Cesarean delivery	76	20,3
Stillbirth	15	4,0
I have not given birth	167	44,5
History of chronic illness None	332	88,5
Thyroid/Goiter	21	5,6
Platelet disorder	2	0,5
Hypertension	3	0,8
Diabetes	5	1,3
Ulcerative Colitis	3	0,8
Asthma	3	0,8
Gastritis	1	0,3
Celiac Disease	2	0,5
Migraine	1	0,3
Familial Mediterranean Fever	1	0,3
Psoriasis	1	0,3

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

Table 3 shows the findings related to the COVID-19 characteristics of the pregnant women. 69.1% (n=259) of the women reported that they had contracted COVID-19, and when asked about the severity of their illness, 34.7% (n=130) indicated that they did not experience it as either mild or severe. 76% (n=285) of the pregnant women had received the COVID-19 vaccine, and among those vaccinated, 68% (n=255) did so to avoid transmitting the disease to their family. On the other hand, 24% (n=90) had not received the vaccine, and among those who did not get vaccinated, 22.7% (n=85) were afraid of the vaccine's side effects. Most of the vaccinated women, 90.7% (n=340), had not received the vaccine during pregnancy, and 82.7% (n=310) of those who did not get vaccinated did so because they were pregnant. Conversely, 9.3% (n=35) received their vaccines during pregnancy, and among those who got vaccinated during pregnancy, 6.7% (n=25) did so to ease their pregnancy process. 52% (n=195)

of the pregnant women had received two doses of the vaccine, 58.7% (n=220) preferred the BioNTech vaccine, and 43.2% (n=162) indicated that their next vaccine preference would also be BioNTech. Some pregnant women received multiple and different types of vaccines. When asked about side effects after vaccination, 41.1% (n=154) reported no side effects. 64.3% (n=241) of the women felt they did not have enough information about the vaccine, 80% (n=300) recommended the vaccine to others, and 79.5% (n=298) did not closely follow developments related to the COVID-19 vaccine (Table 3).

Table 3. COVID-19 Characteristics of Pregnant Women

Characteristics		**n**	**%**
COVID-19 infection status	Yes	259	69,1
	No	116	30,9
Condition of illness in those who contracted COVID-19	*I had a very mild case*	*51*	13,6
	It was neither mild nor severe	130	34,7
	Typeface must be same all tables	78	20,8
COVID-19 vaccination status	Yes	285	76,0
	No	90	24,0
If yes, reason for getting vaccinated	*I believe that the vaccine protected me from the illness*	221	58,9
	I trust the vaccine	*168*	44,8
	I do not want to spread it to my family	*255*	68,0
	My workplace requires me to get vaccinated	*29*	7,7
If no, reason for not getting vaccinated	*I do not believe the vaccine is protective*	41	10,9
	I think the vaccine will harm me	81	21,6
	I am afraid of the vaccine's side effects	85	22,7
	I am against vaccines	12	3,2
COVID-19 vaccination status during pregnancy	Yes	35	9,3
	No	340	90,7
If yes, reason for getting vaccinated	I got vaccinated to protect my baby	19	5,1
	I got vaccinated to make the pregnancy process more comfortable	25	6,7
	I believe the vaccine is beneficial	15	4,0
	My doctor recommended that I get vaccinated	24	6,4
If no, reason for not getting vaccinated	I don't want it because it might harm my baby	245	65,3
	I decided not to get vaccinated because I am pregnant	310	82,7
	My time to get vaccinated hasn't come yet	16	4,3
	I believe the vaccine will harm my body	186	49,6

Table 3. COVID-19 Characteristics of Pregnant Women *(Devamı)*			
Characteristics		**n**	**%**
Number of COVID-19 vaccine doses received	1	29	7,7
	2	195	52,0
	3	53	14,1
	4	8	2,1
Type of COVID-19 vaccine received	Sinovac	82	21,9
	BioNTech	220	58,7
	Turkovac	3	0,8
Next vaccine preference	Sinovac	31	8,3
	BioNTech	162	43,2
	Turkovac	92	24,5
Experience of side effects after vaccination	Yes	131	34,9
	No	154	41,1
Level of knowledge about vaccines	Yes	134	35,7
	No	241	64,3
Recommending the vaccine to others	Yes	300	80,0
	No	75	20,0
Following developments in COVID-19 vaccines	Yes	77	20,5
	No	298	79,5

Table 4 shows the findings related to the health literacy levels of pregnant women. The average general index score determined using the TSOY-32 scale for the included pregnant women was calculated as 23.37±8.35. When the health literacy levels of the 375 volunteer pregnant women participating in the study were assessed, it was found that 55.7% (n=209) had an inadequate health literacy level with a score range of 0-25, 31.2% (n=117) had a problematic-limited health literacy level with a score range of 25-33, 12% (n=45) had a sufficient health literacy level with a score range of 33-42, and 1.1% (n=4) had an excellent health literacy level with a score range of 42-50 (Table 4).

Table 4. Distribution of pregnant women in the research group according to their health literacy levels (n: 375)		
Characteristics	**Mean±SD**	**Min-Max**
Overall index score	23,37 ± 8,35	0-50
Characteristics	**n**	**%**
Insufficient health literacy	209	55,7
Problematic-limited health literacy	117	31,2
Adequate health literacy	45	12
Excellent health literacy	4	1,1
Min: Minimum, Max: Maximum, SD: Standard Deviation		

Table 5 shows the effect of pregnant women's COVID-19 vaccination status on their socio-demographic characteristics. A statistically significant difference was detected between pregnant women's COVID-19 vaccination status and their employment status ($p < 0.05$). A statistically significant difference was detected between pregnant women's COVID-19 vaccination status and their social security ($p < 0,05$). The significant difference is due to the None group, which does not have social security.

Table 5. The effect of pregnant women's COVID-19 vaccination status on their socio-demographic characteristics							
Variable	**Working Status**						**p**
	I am working		**I am not working**		**Total**		
COVID-19 vaccination status (n=375)							
Yes	**n**	56		229	285		**0,018**
	%	14,9		61,1	76,0		
No	**n**	8		82	90		
	%	2,1		21,9	24,0		
Total	**n**	64		311	375		
	%	17,1		82,9	100,0		
Variable	**Social security**						
		SSK (Social Security)	**Bağ-Kur (Social Security for Self-Employed)**	**Green card**	**None**	**Total**	**p**
COVID-19 vaccination status (n=375)							
Yes	**n**	181	63	26	15	285	**0,016**
	%	48,3	16,8	6,9	4,0	76,0	
No	**n**	43	24	11	12	90	
	%	11,5	6,4	2,9	3,2	24,0	
Total	**n**	224	87	37	27	75	
	%	59,7	23,2	9,9	7,2	100,0	
*p≤0,05 It was considered statistically significant. *Chi-square test was used.							

Table 6 shows the impact of COVID-19 characteristics of pregnant women on their health literacy levels. There was no statistically significant difference between the pregnant women's COVID-19 disease status and their health literacy levels ($p > 0.05$). There was no statistically significant difference between the disease process status and health literacy levels of pregnant women with COVID-19 ($p > 0.05$). A statistically significant difference was detected between the symptom of sore throat, which is among the symptoms experienced by pregnant women with COVID-19 during the disease process, and their health literacy levels ($p < 0.05$). The symptom of sore throat was more common in pregnant women with insufficient health literacy level, at a rate of 46.7% (n=121). A statistically significant difference was detected between pregnant women's COVID-19 vaccination status and their health literacy levels ($p < 0.05$). A statistically significant difference was detected between the workplace's willingness to be vaccinated, which was among the reasons for pregnant women vaccinated against COVID-19, and their health literacy levels ($p < 0.05$). A statistically significant difference was detected between the thought that the vaccine would harm oneself, which was among the reasons for not being vaccinated for pregnant women who had not received the COVID-19 vaccine, and their health literacy levels ($p < 0.05$). A statistically significant difference was detected between pregnant women's COVID-19 vaccination during pregnancy and their health literacy levels ($p < 0.05$). There was no statistically significant difference between the reasons why pregnant women received the COVID-19 vaccine during pregnancy, such as protecting their babies, having a comfortable pregnancy, thinking the vaccine

is beneficial, and the doctor's recommendation to be vaccinated, and their health literacy levels ($p > 0.05$). A statistically significant difference was detected between pregnant women's health literacy levels and the reasons for not getting the COVID-19 vaccine during pregnancy: thinking that it would harm their baby, not being vaccinated for time, and thinking that the vaccine would harm the body ($p < 0.05$). There was no statistically significant difference between the status of giving up vaccination due to pregnancy, which is among the reasons why pregnant women did not receive the COVID-19 vaccine during pregnancy, and their health literacy levels ($p > 0.05$). There was no statistically significant difference between the number of COVID-19 vaccine doses received by pregnant women and their health literacy levels ($p > 0.05$). A statistically significant difference was detected between pregnant women's having sufficient knowledge about vaccination and their health literacy levels ($p < 0.05$). There was no statistically significant difference between pregnant women's recommendation of vaccination to others and their health literacy levels ($p > 0.05$). A statistically significant difference was detected between pregnant women's ability to follow developments regarding the COVID-19 vaccine and their health literacy levels ($p < 0.05$).

Table 6. The impact of COVID-19 characteristics of pregnant women on their health literacy levels

Variable		Insufficient	Problematic-Limited	Satisfactory/ Excellent	Total	p
Status of contracting COVID-19 disease (n=375)						
Yes	**n**	139	81	39	259	0,198
	%	37,1	21,6	10,4	69,1	
No	**n**	70	36	10	116	
	%	18,7	9,6	2,7	30,9	
Disease process status in those infected with COVID-19 (n=259)						
I survived the disease very mildly.	**n**	30	13	8	51	0,559
	%	11,6	5,0	3,1	19,7	
My illness was neither mild nor severe.	**n**	64	47	19	130	
	%	24,7	18,1	7,3	50,2	
I overcame the disease very seriously.	**n**	45	21	12		
	%	17,4	8,1	4,6	78	
Symptoms experienced by people with COVID-19 during the disease process						
Sore throat						
Yes	**n**	121	64	27	212	**0,028**
	%	46,7	24,7	10,4	81,9	
No	n	18	17	12	47	
	%	6,9	6,6	4,6	18,1	
COVID-19 vaccination status (n=375)						
Yes	**n**	147	96	42	285	**0,014**
	%	22,8	13,9	11,2	76,0	
No	**n**	62	21	7	90	
	%	16,5	5,6	1,9	24,0	
If your answer is yes, the reason for vaccination (n=285)						
My workplace requires me to get vaccinated						

Table 6. The impact of COVID-19 characteristics of pregnant women on their health literacy levels (Continue)						
Variable		**Insufficient**	**Problematic-Limited**	**Satisfactory/ Excellent**	**Total**	**p**
Yes	**n**	1	10	18	29	**<0,001**
	%	0,4	3,5	6,3	10,2	
No	**n**	146	86	24	256	
	%	51,2	30,2	8,4	89,8	
If your answer is no, the reason for not being vaccinated (n=90)						
I think the vaccine will harm myself						
Yes	**n**	59	19	3	81	**<0,001**
	%	65,6	21,1	3,3	90,0	
No	**n**	3	2	4	9	
	%	3,3	2,2	4,4	10,0	
Status of receiving COVID-19 vaccination during pregnancy (n=375)						
Yes	**n**	15	11	9	35	**0,045**
	%	4,0	2,9	2,4	9,3	
No	**n**	194	106	40	340	
	%	51,7	28,3	10,7	90,7	
If your answer is yes, reason for vaccination (n=35)						
I was vaccinated to protect my baby						
Yes	**n**	9	6	4	19	0,907
	%	4,0	2,9	2,4	54,3	
No	**n**	6	5	5	16	
	%	17,1	14,3	14,3	45,7	
I was vaccinated to have a comfortable pregnancy.						
Yes	**n**	11	8	6	25	1,000
	%	4,0	2,9	2,4	71,4	
No	**n**	4	3	3	10	
	%	11,4	8,6	8,6	28,6	
I think the vaccine is useful						
Yes	**n**	7	6	2	15	0,381
	%	20,0	17,1	5,7	42,9	
No	**n**	8	5	7	20	
	%	22,9	14,3	20,0	57,1	
My doctor suggested I get vaccinated						
Yes	**n**	9	9	6	24	0,581
	%	25,7	25,7	17,1	68,6	
No	**n**	6	2	3	11	
	%	17,1	5,7	8,6	31,4	
If your answer is no, the reason for not being vaccinated (n=340)						
I don't want it because it will harm my baby						
Yes	**n**	154	71	20	245	**<0,001**
	%	45,3	20,9	5,9	72,1	
No	**n**	40	35	20	95	
	%	11,8	10,3	5,9	27,9	

Table 6. The impact of COVID-19 characteristics of pregnant women on their health literacy levels (Continue)						
Variable		**Insufficient**	**Problematic-Limited**	**Satisfactory/ Excellent**	**Total**	**p**
I gave up getting vaccinated because I was pregnant						
Yes	**n**	180	94	36	310	0,472
	%	52,9	27,6	10,6	91,2	
No	**n**	14	12	4	30	
	%	4,1	3,5	1,2	8,8	
It's not time for me to get vaccinated						
Yes	**n**	4	9	13	16	**0,027**
	%	1,2	2,6	0,9	4,7	
No	**n**	190	97	37	324	
	%	55,9	28,5	10,9	95,3	
I think the vaccine will harm my body						
Yes	**n**	119	49	18	186	**0,017**
	%	35,0	14,4	5,3	54,7	
No	**n**	75	57	22	154	
	%	22,1	16,8	6,5	45,3	
Number of COVID-19 vaccine doses you have received (n=285)						
1	**n**	19	8	2	**29**	0,217
	%	6,7	2,8	0,7	10,2	
2	**n**	99	65	31	195	
	%	34,7	22,8	10,9	68,4	
3	**n**	25	22	**6**	**53**	
	%	8,8	7,7	2,1	18,6	
4	**n**	4	1	3	8	
	%	1,4	0,4	1,1	2,8	
Having sufficient knowledge about vaccination (n=375)						
Yes	**n**	**35**	**65**	**34**	**134**	**<0,001**
	%	9,3	17,3	9,1	35,7	
No	**n**	174	52	15	241	
	%	46,4	13,9	4,0	64,3	
Status of recommending vaccination to the public (n=375)						
Yes	**n**	158	100	42	300	0,055
	%	42,1	26,7	11,2	80,0	
No	**n**	51	17	7	75	
	%	13,6	4,5	1,9	20,0	
Status of following COVID-19 vaccine developments (n=375)						
Yes	**n**	8	37	32	77	**<0,001**
	%	2,1	9,9	8,5	20,5	
No	**n**	201	80	17	298	
	%	53,6	21,3	4,5	79,5	
*p≤0.05 was considered statistically significant. *Chi-square test was used.						

DISCUSSION

We obtained some important data by applying the TSOY-32 scale in the study, which examined the relationship between variables such as socio-demographic characteristics, obstetric characteristics, vaccination status and attitudes and behaviors towards vaccines and health literacy levels of pregnant women. In studies using the TSOY-32 scale, it was observed that the average TSOY-32 scale general index score of pregnant women was between 34.49±9.14 and 58±8.15 (19,20). Although there are many studies on the COVID-19 pandemic, there is insufficient research on its relationship with health literacy. In the study, it was determined that there was a significant relationship between employment status, which is among the socio-demographic characteristics that affect the status of pregnant women to receive the COVID-19 vaccine. When the literature was examined, a significant relationship was observed between the acceptance of the COVID-19 vaccine by those with high income levels (21). In the study, it was determined that there was a significant relationship between social security status, which is among the socio-demographic characteristics that affect the status of pregnant women to receive the COVID-19 vaccine. In order to examine the effect of nursing students' COVID-19 vaccine literacy and socio-demographic characteristics on their COVID-19 vaccine attitudes, Gökşen et al.'s (2023) descriptive and relational study included 503 nursing students and found that 64.2% (n) =323) had social security, while 35.8% (n=180) did not have social security. In the study, no significant relationship was seen between nursing students' attitudes towards COVID-19 vaccination and social security (22). The study determined that there was a significant relationship between the status of COVID-19 vaccination in pregnant women and their health literacy levels. ACOG recommends vaccination for all pregnant women of reproductive age, breastfeeding mothers, and women planning to become pregnant (6). Vaccine administration is among the protective and preventive measures against the COVID-19 pandemic (23). In a study conducted in our country by Goncu Ayhan et al. (2021), when we look at the attitudes of pregnant women regarding COVID-19 vaccines, 37% of them are positive about being vaccinated, and among the reasons for not being vaccinated for pregnant women who have not been vaccinated, the most common reasons for not being vaccinated are lack of information about the safety of vaccines and their risk to the fetus. It has been determined that there is a possibility of harm (Goncu Ayhan et al., 2021) In a recent systematic review by Shamshirsaz et al. (2021), although the rate of pregnant women getting the COVID-19 vaccine was observed to be low, the frequency of getting the COVID-19 vaccine was higher among pregnant women who had Tdap (tetanus, diphtheria, acellular pertussis) and seasonal influenza vaccines, which are among the inactive vaccines. It has been found to be excessive (24). The study determined that there was a significant relationship between the status of pregnant women receiving the COVID-19 vaccine during pregnancy and their health literacy levels. In Demir's (2023) study, which was conducted using the phenomenology design, one of the qualitative research methods, in which they included 10 pregnant women, in order to examine the thoughts of pregnant women about coronavirus infection and COVID-19 vaccines, specifically against vaccination, ten pregnant women participating in the study were asked about their thoughts about COVID-19 vaccines. Six of them stated that their pregnancy status did not affect their COVID-19 vaccination status, five stated that they were affected by their spouse's vaccination status, four stated that they did not receive sufficient assurance from anyone about the vaccine, ten stated that they were most worried about their baby, and nine stated that COVID-19 vaccines were not safe during pregnancy (25). Therefore, presenting information about vaccination practices during pregnancy and the effects of vaccines in a transparent manner will help alleviate the concerns of pregnant women about vaccination. The study determined that there was no significant relationship between the number of COVID-19 vaccine doses, vaccine types and

next vaccine preferences of pregnant women and their health literacy levels. In a descriptive study by Aloğlu and Sönmez (2021) in which they included 1708 volunteers, male and female, aged 18 and over, in order to examine the impact of the COVID-19 pandemic on individuals and their attitudes towards the COVID-19 vaccine, 56.8% of the participants It was determined that while 43.2% of the population wanted to get vaccinated, 43.2% did not want to have it, 20.5% preferred the CoronaVac (Sinovac) vaccine, 24.7% preferred the BioNTech vaccine and 47% preferred the local vaccine, the Turkovac vaccine (26) In the study, it was determined that there was a significant relationship between pregnant women's ability to have sufficient knowledge about vaccination and their health literacy levels. When the literature was examined, it was seen that pregnant women's increased confidence in COVID-19 vaccines and adequate knowledge about vaccines were an important factor in positively changing attitudes towards vaccines (27). In another study, it was determined that posts on social media, as well as doctors, who are among the health professionals who are effective in gaining knowledge about the vaccine, are also an important factor in affecting the society's perspective on the vaccine (28). In the study, it was determined that there was no significant relationship between the status of pregnant women recommending the vaccine to others and their health literacy levels. In a descriptive study by Özkan and Yiğit (2022) in which they included 63 health care workers at family health centers in the central districts of Kayseri, in order to determine the attitudes of primary health care workers towards the COVID-19 vaccine and the relationship between COVID-19 disease perceptions during the coronavirus epidemic, 95% It was determined that 2.2% (n=60) recommended the vaccine to their patients, while 4.8% (n=3) did not recommend the vaccine to their patients (29). The study determined that there was a significant relationship between pregnant women's ability to follow developments regarding the COVID-19 vaccine and their health literacy levels. In order to examine the impact of the COVID-19 pandemic on individuals and individuals' attitudes towards the COVID-19 vaccine, Aloğlu and Sönmez's (2021) descriptive study included 1708 volunteers, women and men aged 18 and over, and found that developments regarding the COVID-19 vaccine were 38% higher. 1.1% (n=650) from TV, 31.1% (n=531) from the internet, 28.2% (n=481) from social media, 2.1% (n=36)) from their close circle and 0.6% (n=10) from newspapers (26).

Limitations of the study

Since the study is based on the statements of pregnant women, effects such as information and recall biases may occur. Since the study is carried out from a single center, there may be problems in the generalizability of the data to the universe. For this reason, a larger sample size can be reached.

CONCLUSION AND SUGGESTIONS

As a result of the study, it is observed that the health literacy levels of pregnant women who were determined to have an approach, attitude and behavior towards COVID-19 vaccines during the COVID-19 pandemic period were insufficient. In line with these results, the multidisciplinary team approach of doctors and midwives, who are health professionals, should be supported and the knowledge level of pregnant women with low health literacy about COVID-19 vaccines should be increased. In the pre-pregnancy period, women should be supported to increase their confidence in the vaccine by identifying the content, importance and possible side effects of COVID-19 vaccines, misconceptions about vaccination and the real reasons and reservations underlying refusing to be vaccinated, and providing them with the necessary training. Due to the importance of informed women educated before pregnancy in providing accurate, reliable and effective information during pregnancy, birth, breastfeeding and the postpartum period, it will contribute to preventing anti-vaccine thoughts, developing vaccine awareness and increasing trust in vaccines. Guiding pregnant women in the risk population group and increasing their awareness is

also important for the continuity of immunization during the pandemic process. It has been observed that increasing the awareness levels of pregnant women will contribute to their approach, attitude and behavior towards vaccines and the pandemic period.

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Hemoglobinopathy Awareness Among Middle and High School Students in Karataş, Turkey

Hemoglobinopathy Awareness Among Middle and High School Students

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Abstract: **Objective:** Hemoglobinopathies are complex and inherited genetic disorders with no definitive cure; however, preventive measures such as genetic counseling and premarital screening may dramatically reduce their prevalence. Therefore, having sufficient information about the mentioned preventive measures is crucial.

Methods: All students attending middle and high schools were included without a sample selection. A survey form was administered to students in order to evaluate their knowledge level and attitudes regarding hemoglobinopathies. The results were evaluated using Chi-square and logistic regression analysis with 95% confidence interval (CI).

Results: The total number of students agreeing to participate in the study was 877. The mean age of the participants was 14.8 ± 1.5 years; 50.5% of them were male.Of the participating students, 40.3% were previously informed about hemoglobinopathies.The lowest correct response rate among questions in terms of students' knowledge about hemoglobinopathies was observed in the question that asked the transmission route of the disorders with 13.7%.In the multivariate analysis, maternal education level (OR=1.417; 95% CI) and knowing an affected patient (OR=4.215; 95% CI) were associated with a greater likelihood of being previously informed.

Conclusions: The correct rates of the responses given by the participating students to the questions about hemoglobinopathies varied. Students who were previously informed about hemoglobinopathies gave a higher rate of correct answers. Organizing and sustaining educational particularly genetic basics of the disorders to students, who are the parents of the future, may be useful in combating hemoglobinopathies.

Keywords: Hemoglobinopathies, Awareness, School Health, Middle School Students, High School Students

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INTRODUCTION

Hemoglobinopathies (sickle-cell disorders and thalassemias) refer to a group of diseases caused by genetic disorders that affect the formation of the normal hemoglobin chain (1). According to the World Health Organization (WHO), about 5% of the world population are healthy carriers of a gene for thalassemia or sickle-cell anemia. However, there are more than 300,000 annual births with severe forms of these diseases worldwide, the majority being in countries with low or middle income (2). According to data of the Turkish National Hemoglobinopathy Council and the Ministry of Health, there were 1.4 million thalassemia carriers in Turkey in 2006. Additionally, the prevalence of both β-thalassemia and sickle cell anemia carriers was particularly high in cities such as Hatay, Antalya and Adana, which are located on the Mediterranean shore (3,4). A control program has been recommended by the WHO for hemoglobinopathies because there is no definitive cure. The control program comprises prenatal diagnosis, raising awareness of the public, carrier screening and genetic counseling (5). Henceforward, in many of the affected countries worldwide, premarital screening programs have been put into practice. Countries such as Italy, Canada, Greece, the United Kingdom and Cyprus have used such programs. As a striking example, the thalassemia prevalence in Cyprus has been reduced from very high levels to trifling levels after the implementation of a screening program (6).The achievements in these programs have also shown the importance of enlightenment about the diseases because insufficient awareness and knowledge regarding hemoglobinopathies may act as obstacles to prevention and testing for hemoglobinopathies. Cultural and psychosocial concerns may lead to disclosure of disease status (7,8). All these suggest that, increasing awareness about the nature and transmission of these disorders may help individuals to make healthy decisions in terms of risky situations. Therefore, in this paper, our goal was to investigate the knowledge of middle and high school students towards hemoglobinopathies and to determine their preventive behaviors in Karataş, Adana, where the disorders are prevalent.

METHODS

Design and data collection

The study was planned in a cross-sectional design and it took place in Karataş, Adana, which is a city in the Çukurova Region. In this study, a survey form evaluating the knowledge level and attitudes of students in terms of hemoglobinopathies and their status of being previously informed about the disorders was used. In Karataş, there were 3 middle schools and 2 high schools at the time of the study. The total number of students attending these 5 schools was 1058. We opted not to choose a sample and aimed to reach all students between the 7^{th} and 12^{th} class. Before the questionnaires were given to the students, all classes were visited by the researcher with a guidance teacher and information about the questionnaire was given. In addition, an illuminated proclamation paper was distributed to the students to be completed by their parents. The questionnaire was administered to students who brought the illuminated proclamation paper the next day. For the ones who forgot to bring the illuminated proclamation paper, one last survey was conducted the day after. Of the 1058 students, 877 (82.9 %) agreed to participate in the study. The data were collected during October-December 2015.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) for Windows software was used in order to manage data and perform statistical analysis. The results were evaluated using Chi-square and logistic regression analysis, assuming $p<0.05$ to be statistically significant.

Ethical considerations

Official approvals were obtained from the Provincial Directorate of Education and the Governorship of Adana for the study.

RESULTS

The total number of students agreeing to participate in the study was 877. The mean age of the participants was 14.8 ± 1.5 years; 50.5% of them were male. It was found that 10.7% (n=94) of the students' mothers and 4.3% (n=38) of the students' fathers were illiterate. One hundred twenty-five (14.3%) of the participants perceived their economic status as very bad or bad, 61.5% (n=539) were perceived it as moderate, and 24.2% (n=213) perceived it as good or very good. Of the participants, 11.1% (n=97) expressed that they knew a patient with hemoglobinopathy around them, 77.4% (n=679) did not know a patient with hemoglobinopathy and 11.5% (n=101) were unsure whether there was a hemoglobinopathy patient around them (Table 1).

Table 1. Sociodemographic characteristics of the participants

Sociodemographic Characteristics	n	%
Sex		
Female	434	49.5
Male	443	50.5
Age group (years)		
12 to 14	384	43.8
15 to 17	463	52.8
18 or above	30	3.4
Educational status of the students' mothers		
Illiterate	94	10.7
Literate only (not primary school graduate)	116	13.2
Primary school graduate	372	42.4
Middle school graduate	173	19.8
High school graduate	95	10.8
University graduate	27	3.1
Educational status of the students' fathers		
Illiterate	38	4.3
Literate only (not primary school graduate)	102	11.7
Primary school graduate	338	38.5
Middle school graduate	214	24.4
High school graduate	145	16.5
University graduate	40	4.6
Perceived economic status		
Very bad	20	2.3
Bad	105	12.0
Moderate	539	61.5
Good	196	22.3
Very good	17	1.9
Existence of a known hemoglobinopathy patient		
Yes	97	11.1
No	979	77.4
Unsure	101	11.5

Of the participating students, 40.3% (n=353) were previously informed about hemoglobinopathies, the remainder was not. The lowest correct response rate among questions in terms of students' knowledge about hemoglobinopathies was observed in the question that asked the transmission route of the disorders with 13.7% (n=120). This indicates that vast majority of the participants did not know that the disorders were inherited. On the other hand, 70.8% (n=621) of the participating students correctly stated that the diseases affected both males and females. The distributions of accurate answers about hemoglobinopathies are shown in Chart 1. The accurate answer rates were significantly altered according to their status of being previously informed. These findings show that informing students about the disorders plays an important role in their knowledge level regarding hemoglobinopathies (Table 2). Of the participants, 80.7% (n=663) were willing to gain knowledge about hemoglobinopathies at schools, and 74.6% (n=607) were keen to learn whether they were carriers. Of the participants, 72.0% (n=559) expressed that they would change their future decisions in case of a risky situation caused by these disorders. A significant difference was found between participants who were and were not previously informed in terms of changing their future decisions in case they were affected by the disorders (Table 3).

Our results revealed that informing participants may play a key role in altering their level of knowledge and attitudes. Considering this fact, we performed a regression analysis to determine which factors affected the status of being previously informed. The following variables were associated with a greater likelihood of being previously informed: maternal education level and presence of a known affected patient. However, being a middle or high school student, fathers' education level, and economic status perception were not found to be associated with being previously informed about hemoglobinopathies in the regression model (Table 4).

Table 2. Students' accurate answer rates according to status of being previously informed

Questions	Correct answer of not previously informed(n=524)		Correct answer of previously informed(n=353)		P-value**
	n	%*	n	%*	
Which system of body do these disorders affect?	191	36.5	256	72.5	<0.001
How do these disorders transmit?	42	8.0	78	22.1	<0.001
Is it possible to be a carrier of these disorders ?	213	40.6	237	67.1	<0.001
Which sexes do these disorders affect?	359	68.5	262	74.2	0.068
Where do these disorders occur mostly in Turkey?	189	36.1	216	61.2	<0.001
Do you think these disorders are preventable?	199	38.0	178	50.4	<0.001
What is an important risk for the disorders ?	115	21.9	187	53.0	<0.001
Are these disorders are curable?	157	30.0	143	40.5	0.01

*The values are in n (%)
**Calculated using Pearson's Chi-square test

Table 3. Attitude and behavioral pattern of students about hemoglobinopathies according to being previously informed					
Attitudes and Behaviors	**Not previously informed**		**Previously informed**		**P-value****
	n	%*	n	%*	
Willing to be informed at school [a]	390	80.4	273	81.0	0.831
Willing to learn their carrier status [b]	347	73.4	260	76.2	0.351
Would change future plans in case of a risky situation [c]	293	65.7	266	80.6	<0.001

*The values are in column percentage of valid answers
**Calculated using Pearson's Chi-square test
[a] 55 missing data
[b] 63 missing data
[c] 101 missing data

Table 4. Factors affecting the status of being previously informed					
Factors				**95% C.I.for O.R.**	
	B	**p**	**O.R.**	**Lower**	**Upper**
Education (middle school-high school)	0.259	0.102	1.296	0.950	1.768
Mothers' education level	**0.349**	**0.049**	**1.417**	**1.001**	**2.007**
Fathers' education level	0.026	0.878	1.026	0.736	1.431
Economic status perception	0.059	0.725	1.061	0.762	1.477
Presence of a patient around	**1.439**	**<0.001**	**4.215**	**2.640**	**6.731**

DISCUSSION

Our aim in this study was to emphasize the importance of raising knowledge and awareness about hemoglobinopathies beacuse insufficient knowledge and awareness are major obstacles in regards to prevention (6,7,8).As mentioned before both thalassemias and sickle cell anemia is prevalent in Adana (3,4).Therefore, we decided to conduct the study in Karataş, Adana which is in the Çukurova region of Turkey. By doing this, we aimed to measure the level of knowledge and awareness in a region where the disorders are common.Our results indicate that the lowest level of knowledge regarding hemoglobinopathies was about the transmission of the disorders. Only 13.7% of students knew that hemoglobinopathies were inherited disorders. This rate was even lower for students who had not been informed about hemoglobinopathies before. In a survey of high school students in Hatay in 2009, 18.5% of students with no previous education about hemoglobinopathies and 44.8% of students previously informed about hemoglobinopathies knew that the diseases were inherited (9). Later in 2016, a similar study conducted on 8th and 9th graders in Hatay reported that about 30% of the students could specify that hemoglobinopathies were inherited disorders (10). In a study conducted in Antalya between 1998 and 1999, 10.7% of 11th graders stated that thalassemia was a result of carrier marriage (11). Another study conducted on 8th graders in Burdur reported that over 80% of the students knew that thalassemia was not contagious (12). Although the rate seems higher in the Çatak et

al. study than in other studies, the question asked in the study was whether thalassemia was contagious or not, which may explain why the rate was higher. Except for the study conducted in Burdur, it would not be wrong to state that knowledge levels about the transmission of hemoglobinopathies in middle school and high school students in Turkey are low. Another remarkable finding in our study is that nearly two thirds of the students did not know that the consanguineous marriage was a risk for hemoglobinopathies. Similar findings were also found in two studies conducted in Hatay (9,10). This is particularly important in our country where consanguineous marriage is frequent. Consanguineous marriage is a risk factor for many genetic disorders, including sickle cell anemia and thalassemia (13,14,15). Consanguineous marriage rates in Turkey have been between 20% and 25% over the last 25 years (16). Taken together, the lack of knowledge about the transmission of the disorders and not recognizing consanguineous marriage as a risk, may obstruct the path to screening and health consultancy and hinder using preventive measures. We believe educational interventions regarding the genetic transmission of common inherited disorders are necessary, especially in regions where consanguineous marriages are frequent. In our study, previously informed students gave more accurate answers to questions regarding the level of knowledge about illnesses than previously uninformed students (see Table 2). A study conducted on university students in Kocaeli reported that there was an evident augmentation in knowledge level regarding hemoglobinopathies after an informative course (17). Likewise, a study conducted on risk groups in 2009 reported that, after an infotainment session, participants understood the genetic transmission of hemoglobinopathies (18). All these suggest that it is important to inform students to raise awareness about the disorders.In our study, when students' attitudes towards hemoglobinopathies were evaluated, the percentages of students who were willing to gain knowledge, establish whether or not they were carriers, and be alert to risky situations in the future were 80.7%, 74.6%, and 72.0%, respectively. The rates found in our study were slightly lower than those observed in two studies conducted in Hatay (9,10). The rate of previously informed students who stated that they would change their future decisions in case of a risky situation was significantly higher than those who were not previously informed. Likewise, in a study performed in Iran, it was found that the desired attitudes of high school students towards diseases were increasing with higher knowledge levels (19). It may be useful to include courses into schools' curricula regarding these diseases because it is a prerequisite to raise awareness among the public to develop preventive behaviors.Informing students about hemoglobinopathies plays a key role in both students' level of knowledge and positive attitudes. In this study, higher maternal education levels and existence of a known patient with hemoglobinopathy were found as independent factors that positively affected the status of being previously informed. Consistent with our findings, Miri-Moghaddam et al. also reported that as parents' educational level increases, the students' positive attitude level towards hemoglobinopathies became augmented (19). Similarly,(9) and (10) reported that the rate of students' being previously informed status were significantly higher in those who knew an affected person. The fact that positive attitudes of the students were augmented with higher maternal education levels suggests that educating mothers about the disorders may also be beneficial in raising the awareness of students.This study was conducted in a region where the disorders are prevalent. Also, all middle and high schools in Karataş were included in the study. However the study has some limitations. Since the data were collected using a questionnaire, memory factors may affect the responses to the questionnaires. Additionally, the carrier status of the students was not questioned.

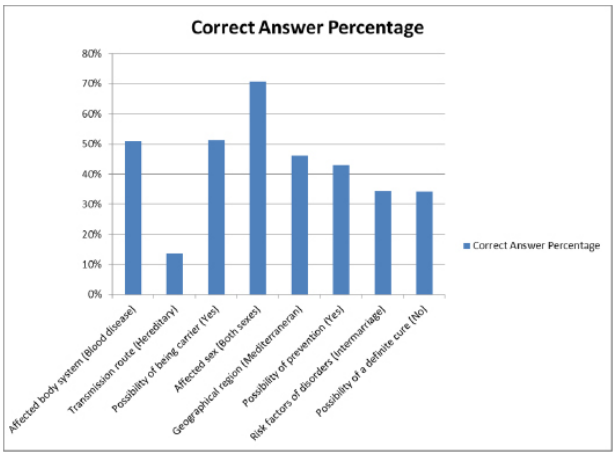

Chart 1. Students' accurate answer rates to questions about hemoglobinopathies

Limitations

This study only provides an idea about the awareness of students in Karataş, a district of Adana, and cannot be generalized. If a more appropriate sample representing Adana is selected, the representativeness will increase. In addition, the fact that a scale measuring knowledge or awareness about hemoglobinopathy was not used in the study causes limitations when interpreting the results.

CONCLUSIONS

The rate of correct responses of the participating students to questions about hemoglobinopathies varied between 13.7% and 70.8%. The subject they were least informed about was the transmission route of the disease, and the subject they were most informed about was that it could affect both genders. Students who had previously been informed about hemoglobinopathies gave a higher rate of correct responses. Students with a higher level of maternal education and those who knew about the existence of a person affected by the disease increased the likelihood of having been informed before. It may be recommended that training be planned on this subject in order to increase students' awareness of this issue.

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Evaluation of Circulating Tumor DNA and Carcinoembryonic Antigen Levels and Relationship with Clinicopathological Risk Factors and Prognostic Indices in Colorectal Cancer Patients

ctDNA and CEA Relationship in Colorectal Cancer

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Abstract: **Objective:** Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide. Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for CRC management, offering real-time insights into tumor burden and genetic mutations. This study investigates the correlation between carcinoembryonic antigen (CEA) levels, ctDNA, clinicopathological factors, and treatment outcomes in early and advanced CRC patients.

Methods: The study retrospectively analyzed data from CRC patients, including those with early-stage disease who underwent curative treatment and those with metastatic disease. ctDNA levels, demographic data, and clinical parameters such as CEA, inflammatory indexes, and tumor characteristics were evaluated to determine correlations with treatment outcomes.

Results: The study included 20 patients, with 60% diagnosed at the metastatic stage. Among metastatic patients, the liver, bone, and lung were the most common metastasis sites. When the ctDNA levels of the patients were evaluated, the mean value was found to be 9.96±12 in patients with early stage (stage 2-3) colon cancer, while it was 9.75±13 in metastatic stage disease. No significant relationship was found between ctDNA levels in both early-stage disease and metastatic stage disease (p 0.903). Additionally, when the relationship between ctDNA levels and early-stage relapse was examined, no significant relationship was found between the ctDNA levels and early- stage relapse and patients who did not develop relapse (p 0.167). While CEA and ctDNA levels were measured, they did not demonstrate a significant relationship with treatment outcomes.

Conclusion: Despite its potential, the integration of ctDNA as a routine biomarker in CRC care faces challenges, including variability in measurement techniques and cost-effectiveness. However, ctDNA's ability to guide personalized treatment strategies and monitor disease recurrence holds promise. The study's findings align with previous research, suggesting ctDNA as a poor prognostic indicator, though further research is needed. ctDNA represents a significant advance in CRC management, offering non-invasive, real-time insights into tumor dynamics. Ongoing research is expected to solidify its role in personalized treatment planning, potentially leading to more effective and tailored therapies for CRC patients.

Key words: colorectal cancer, circulating DNA, tumor markers

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INTRODUCTION

Colorectal cancer (CRC) is a significant contributor to cancer-related illness and death globally. Studies have highlighted circulating tumor DNA (ctDNA) as a valuable biomarker for managing, diagnosing, and treating CRC. It has been demonstrated to be useful in assessing treatment response in advanced-stage disease and in determining the need for adjuvant treatment as well as treatment escalation or de-escalation in early-stage disease. CtDNA, which consists of freely circulating tumor-derived DNA fragments in the blood, offers several advantages over traditional laboratory-based biomarkers and radiological evaluations. One of its key benefits is the ability to provide real-time information on tumor burden and genetic changes, which is crucial in CRC for timely detection of disease recurrence or treatment response. The concept of 'minimal residual disease', commonly used in hematological malignancies, is also applicable to solid organ malignancies with ctDNA detection. In early-stage patients undergoing curative treatment like surgery, detecting measurable levels of ctDNA in the circulation is an important indicator for diagnosis and disease recurrence, impacting the need and timing of adjuvant treatment. CtDNA analysis can help identify driver mutations in the tumor, guiding personalized treatment strategies such as targeted therapies or immunotherapies. By evaluating ctDNA-based mutations from the circulation, clinicians can improve the effectiveness of treatment and patient survival rates by detecting the dominant colonic features in the tumor. However, the expanded use of ctDNA testing has presented some challenges, such as the lack of standardized measurements, variations in test sensitivity and specificity, and unresolved cost-effectiveness issues.

In this study, we aimed to assess the correlation of carcinoembryological antigen (CEA) levels, clinicopathological risk factors, and ctDNA levels with treatment outcomes in patients with early and advanced CRC.

METHODS

We began by reviewing the records of both early-stage and advanced-stage CRC (Colorectal Cancer) patients who underwent ctDNA testing at our hospital between 2015 and 2022. The inclusion criteria were as follows: patients over 18 years old who had received curative treatment, had undergone ctDNA testing, and tested positive for ctDNA; and patients diagnosed at the metastatic stage with measurable ctDNA levels before treatment were also included in the study. Among early-stage CRC patients, those who had ctDNA testing after curative treatment, tested positive, and were considered for adjuvant therapy were included. In metastatic CRC patients, treatment-naive individuals with measurable ctDNA levels were evaluated. In addition to pre-treatment ctDNA testing, demographic data such as patients' age, gender, comorbidities, diagnosis date, stage at diagnosis, and treatments received were examined. Simultaneously with the submission of ctDNA levels for both metastatic and early-stage diseases, full blood counts, inflammatory indices, tumor markers such as CEA, and biochemical parameters were included in the evaluation.

The correlation between ctDNA levels at the time of diagnosis and pathological features, prognostic indices at diagnosis, and tumor marker values were assessed. For early-stage patients who underwent surgery, the correlation between ctDNA levels measured before adjuvant therapy and the likelihood of disease recurrence was evaluated. In metastatic patients, ctDNA levels were correlated with the location and number of recurrences. Additionally, the correlation between ctDNA levels and molecular test results was evaluated in metastatic patients.

The data were transferred to the computer environment with SPSS v20.0 program and descriptive analysis was performed. Data were presented as mean (mean) ± standard deviation (SD), median, lower value (LV), upper value (UV), number (n) and percentage (%).

RESULTS

In this study, 20 patients diagnosed with early and advanced stage colorectal cancer who were followed up and treated at Çukurova University medical oncology clinic were included. 5 (%25) of our patients were female and 15 (%75) were male. Their average age was 53. While 12 (%60) of our patients were diagnosed at the metastatic stage, the remaining 8 (%40) patients were diagnosed as early stage disease. Only 8 of metastatic patients were recognized as denovo metastatic disease. When the patients were evaluated according to their metastasis areas, the most common were liver, bone and lung metastases, while lymph node and peritoneal metastases were less common. While 6 (%30) of the patients did not have an additional comorbid disease, 14 (%70) patients had an accompanying comorbid disease. The most common comorbidity was the combination of type-2 diabetes, hypertension and ischemic heart disease. When evaluated according to tumor location, 6(%30) patients were located in the right colon and 14 (%70) patients were located in the left colon. 14 patients (%70) were in the rectosigmoid region, 3 patients (%15) were in the transverse colon, 3 patients (%15) were in the cecum and hepatic flexura. While 8 (38.1%) of the patients did not undergo primary-directed surgery, 12 patients (57.1%) underwent primary-directed surgery. The average number of lymph nodes removed in the patients was over 15. R0 surgical margins were obtained in all patients. When both early stage and advanced stage patients were examined in terms of targeted mutations, 9 patients (%45) were found to be RAS mutant, 1 patients (%5) were found to be BRAF mutant, while 3 patients (%15) were found to have both RAS and BRAF was detected as wild. Only 1 of our patients had a familial syndrome, which was Lynch Syndrome. Since the patient was diagnosed at an early stage and did not develop recurrence, other advanced genetic molecular investigations and MSH status could not be evaluated. When microsatellite instability was evaluated in all patients, they were found to be stable (MSS). No patient was considered unstable (MSH). The demographic characteristics of the patients are detailed in Table 1.

All early-stage patients received adjuvant chemotherapy. The most commonly used chemotherapy regimens are; FOLFOX was preferred in 46.1% of cases, CAPOX, preferred in 38.4%, and single-agent capecitabine, preferred in 15.38%. When the treatment durations were examined, 3 patients (38%) received 3-month adjuvant treatment, while 5 patients (62%) received 6-month treatment (Figure 1). It was observed that 3 of the early-stage colon cancer patients included in the study developed recurrent disease with distant metastasis after the completion of adjuvant treatment.

When the metastatic patients included in the study were evaluated, 8 of the patients had de nova metastatic disease. The most common areas of metastasis in these patients were the liver, lungs and bones. There were no cases of single-organ metastasis. When first-line treatment options in metastatic stage disease were examined, FOLFOX was the most frequently applied regimen with 42.9%, while FOLFIRI was preferred as the second most common regimen with 14.3%. Monotherapy with capacitabine was used in 1 patient with 4.8%, FOLFIRINOX triplet regimen was preferred in 1 patient with 4.8%. Regarding the use of biological agents accompanying chemotherapy, biological agents could not be administered to 5 patients due to various complications. However, biological agents were added to the existing chemotherapy backbone in 7 patients. When examining the preferred biological agents, Bevacizumab was the most frequently used, at a rate of 42.9%. Less commonly, Cetuximab and Panitumumab were used, respectively.

Table 1. Baseline Characteristics of Patients With Colorectal Cancer

Characteristic	Patients (n:20)
Cancer Stage	
Stg-2	4 (%20)
Stg-3	4 (%20)
Stg-4	12 (%60)
Sex	
Men	15 (%75)
Women	5 (%25)
Age,median (range),y	53
Localization	
Left Colon and Rectum	14 (%70)
Right Colon and Transverse	6 (%30)
Mutations	
K/N/H RASm	9 (%45)
BRAFm	1 (%5)
MSS	13 (%65)
MSI	0
Unknown	7(%35)
Prior Adjuvant chemotheraphy	
Stg-2	4 (%20)
Stg-3	4 (%20)
Stg-4 (relapse recurrent)	4 (%20)
Metastatic Site	
Liver	8 (%40)
Lung	3 (%15)
Bone	2 (%10)
Lymph node	5 (%25)
Peritoneal	2 (%10)
Pathological Findings	
Histology Adenocarcinoma	19 (%95)
Mucinous carcinoma	1 (%5)
Differentiation	3(%15)
Well dif.	7 (%35)
Moderately dif.	2 (%10)
Poorly dif.	8 (%40)
Unknown	10 (%50)
LVI (positive)	10 (%50)
PNI (positive)	4 (%20)
Metastatic Lymph node	3 (%15)
N0	1(%5)
N1	
N2	
Surgery	
Elective Surgery	11(%55)
Emergency Surgery	1(%5)

*Abbreviations: MSI, microsatellite instability; MSS, microsatellite stability; LVI, lymphovascular invasion;PNI; perineural invasion

Only 3 patients diagnosed at the early stage were alive when overall survival was examined. The remaining 17 patients had died due to disease-related or other causes. CEA values at the time of diagnosis could not be evaluated in 6 patients due to inaccessibility, and were evaluated in 14 patients. The mean CEA mean values at the diagnosis were found to be 7.12 (>3). While C-reactive protein (CRP) levels at the time of diagnosis could not be evaluated in 6 patients due to lack of data, they were assessed in 14 patients. The mean CRP levels at diagnosis were 26.1 (>0.8). When the ctDNA levels of the patients were evaluated, the mean value was found to be 9.96±12 in patients with early stage (stage 2-3) colon cancer, while it was 9.75±13 in metastatic stage disease. No significant relationship was found between ctDNA levels in both early stage disease and metastatic stage disease (p 0.903). Additionally, when the relationship between ctDNA levels and early stage relapse was examined, no significant relationship was found between the ctDNA levels and early stage relapse and patients who did not develop relapse (p 0.167). When overall survival and ctDNA levels were evaluated, the mean ctDNA levels of the 3 patients who survived were 5.49, while the mean ctDNA levels of the 18 patients who had died were found to be 10.15. Although the ctDNA levels of surviving patients were numerically half of those in deceased patients, there was no statistical significance (p = 0.498). Similarly, when ctDNA levels were compared with CEA and CRP levels, no statistical significance was reached.

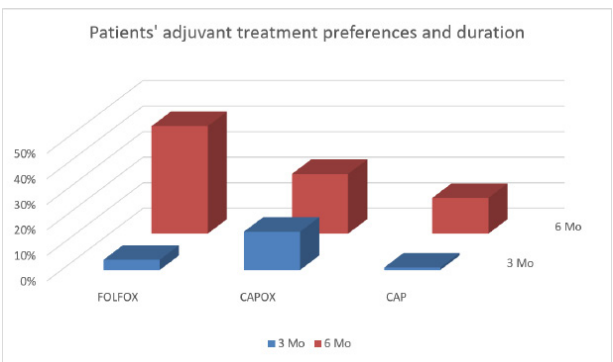

Figure 1. Patients Adjuvant Treatments and Durations

DISCUSSION

In this study, the aim was to investigate the relationship between circulating tumor DNA (ctDNA) levels, clinicopathological risk factors, and treatment outcomes in patients with early and advanced colorectal cancer (CRC), and to present these findings as survival data. Our cohort provides valuable insights into the potential role of ctDNA as a prognostic and predictive biomarker in the management of CRC.

Cell-free nucleic acids are fragments of extracellular DNA (cfDNA) or RNA (cfRNA) that can be detected in a variety of body fluids (1). These may be due to tumor apoptosis, necrosis or paraneoplastic releases. These tumor-associated nuclear fragmentations are called 'circulating tumor DNA' or 'circulating tumor RNA' when found in the blood or lymphatic circulation (2). Their half-life is approximately 114 hours. Depending on these half-lifes, ctDNAs constitute 0.1%-10% of cfDNAs (3,4). An increasing number of studies describe the potential uses of circulating tumor DNA (ctDNA) in the care of patients with colorectal cancer. However, unlike tissue biopsy, it has rapidly become widely used in the clinic because it is noninvasive, represents heterogeneous structures, and is easy and reproducible. Although the most common and well-known use of ctDNA is in blood, many other body fluids such as cerebrospinal fluid, saliva, pleural effusion, ascites, and urine samples can also be used(5-8). A number of different analytes are being investigated with different technologies, including not only these but also circulating tumor cells, tumor-educated platelets, exosomes, circulating nucleic acids, proteins and metabolites (9). Unfortunately, the detectable amount of ctDNA measured is closely related to tumor volume. For example, ctDNA has been shown to be detectable in 10–15% of patients with curatively treated stage II disease and 50–90% of patients with metastatic colorectal cancer(10-12). In our study, we examined ctDNA levels in blood, which is the most commonly analyzed source. Numerous studies have been heterogeneous, showing varied analyses and outcomes. However, more recent comprehensive studies indicate that ctDNA will soon be integrated into the routine care of both advanced and early-stage colorectal cancer patients, providing crucial guidance in patient management. There are many ongoing studies aiming to incorporate ctDNA usage in both early-stage and advanced-stage colorectal cancer treatment. When reviewing studies on why ctDNA is important in the early stages or how it can be integrated, the underlying hypothesis typically revolves around post-operative management (13). In patients receiving curative treatment, the objective is to provide prognostic and predictive insights into which patients should receive adjuvant therapy, how long it should last, and whether genomic analysis is warranted in early-stage disease (14-17). Additionally, ctDNA monitoring may enable the detection of early recurrences even before they become apparent on radiological scans in patients who have undergone curative treatment (18,19). In metastatic disease, ctDNA could be used to monitor treatment response, guide the selection of targeted therapies, identify resistance mutations that emerge post-treatment, and assess clonal evolution. As mentioned earlier, ctDNA levels tend to be higher in metastatic settings compared to early-stage disease. Although our study showed numerically higher ctDNA levels in metastatic cases, statistical significance was not reached, likely due to the heterogeneity of our patient group and the small sample size. Other studies have examined how ctDNA levels vary according to the site of metastasis (20).

The Gozila study, examined ctDNA levels at the metastasis site in colorectal cancers with single-organ metastasis. According to the study, the site with the lowest ctDNA level was peritoneal metastasis (21). In another study, higher ctDNA levels were observed in patients with liver metastases and tumor masses greater than 1 cm (22). Although this study did not include a sufficient number of patients with single-site metastases, ctDNA levels were found to be higher in patients with visceral metastases, aligning with findings from other studies.

CEA and other laboratory clinical risk factors evaluated in the early-stage disease group have been examined in many studies with ctDNA levels. Unfortunately, it has been shown that neither pathological risk factors nor laboratory markers such as CEA are sufficient to determine the risk of recurrence in patients. In fact, in the recent Galaxia and Dynamic studies, it has been proven that clinicopathological risk factors alone are not sufficient. In our study, when ctDNA measurements made before adjuvant treatment in earlystage patients were compared with clinicopathological risk factors of the patients, no statistically significant relationship was detected. Again, when both the amount of ctDNA measured in early-stage disease and metastatic-stage ctDNA elevations were examined, it was detected at lower rates compared to metastatic disease due to the lower disease burden in early-stage disease and the decrease in ctDNA secretions due to the disappearance of the primary tumor and the decrease in ctDNA levels secreted due to the primary mass. However, when the ctDNA levels of early-stage colon cancer patients and metastatic-stage colon cancer patients were examined in our study, although numerically higher levels were detected in metastatic-stage disease, this did not reach statistical significance. However, we think that this insignificance is due to the insufficient number of our patients. In a study examining the relationship between ctDNA and CEA after adjuvant treatment in early-stage disease and recurrence, 83% of patients with both ctDNA and CEA elevations after treatment subsequently experienced recurrence, while only 1 (17%) of patients with high CEA levels but negative ctDNA, experienced recurrence (23). In a different study evaluating imaging, CEA and ctDNA levels in terms of recurrence in resected early-stage colon cancer cases, it was observed that ctDNA testing did not provide a definite advantage over standard imaging and CEA measurement in the follow-up of resected colorectal cancer patients. In the study, the sensitivity of ctDNA in patients with recurrence was determined as 53.3%, imaging had a sensitivity of 60.0% and The sensitivity of CEA levels alone was 20.0%, while in the combined evaluation of ctDNA and imaging and CEA levels, the sensitivity of the combination was determined as % 73.3 (**24**).In this study, CEA levels could not be reached in 1 of 5 patients diagnosed with early-stage disease and who experienced recurrence, while 3 patients had CEA levels within the normal range, and only 1 patient had CEA elevation consistent with ctDNA. All 4 of the patients had high CEA levels at the time of diagnosis and before treatment.

Studies have confused the question of whether adjuvant treatment decisions should be made based on ctDNA or standard clinicopathological risk factors. In the latest ESMO 2024 study, it is suggested that if there is no correlation between ctDNA and standard clinicopathological risk factors, standard risk factors are still valid and treatment decisions should be made accordingly, and the obtained ctDNA results should be integrated into these risk factors (25). In our study, when the standard clinicopathological risk factors of patients who relapsed after early-stage curative treatment with ctDNA were evaluated, they constituted a high-risk patient group, similar to these finding.

Although many studies on ctDNA and colon cancer have been conducted to date, the first and only phase-3 randomized trial is the 'Dynamic' study. The results of this study are highly significant and are expected to bring about substantial changes in patient treatment management. The Dynamic study demonstrated that patients in the ctDNA-guided treatment arm received less chemotherapy compared to those in the standard treatment arm, which was based on clinicopathological risk factors. Despite this reduction in chemotherapy, the recurrence-free survival (RFS) outcomes at the 2-year follow-up were non-inferior. Additionally, when both ctDNA positive and negative arms receiving systemic treatment were compared, the ctDNA positive arm showed worse RFS. his suggests that the use of ctDNA can help prevent overtreatment, while also emphasizing the need for more intensive treatment in patients with high or positive ctDNA levels in the future (26). In our study, out of 9 early-stage patients

who received adjuvant treatment and had high ctDNA levels, only 3 did not experience recurrence, while the remaining 6 developed recurrence. Similar to other studies, our findings confirm that elevated ctDNA is a poor prognostic indicator.

This study, despite its contribution to the literature, also has serious deficiencies. First of all, the inclusion of both early and advanced stage disease groups, being a heterogeneous group, the low number of samples in both groups, the fact that ctDNA levels were only checked once and could not be evaluated during follow-up, and the lack of a control group in both arms are the deficiencies of our study.

CONCLUSIONS

In conclusion, ctDNA holds great promise as a valuable biomarker in the management of colorectal cancer, as it does in many other solid organ malignancies. Its ability to provide real-time and consistent information on tumor burden and associated driver genetic mutations, combined with the simplicity and non-invasiveness of its measurement through a blood test, represents a significant paradigm shift in the diagnosis, treatment, and monitoring of CRC patients. With ongoing research, we believe ctDNA will enhance the potential for personalized treatment planning, guiding decisions on when to intensify treatment or adopt a wait-and-see approach.

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