ODÜ TIP DERGİSİ

ODU MEDICAL JOURNAL

August 2024 Volume 11 Issue 2 e-ISSN 2148-6816

ODU TIP DERGİSİ

ODU MEDICAL JOURNAL

(ODU MED J)

ODU TIP DERGİSİ/ODU MEDICAL JOURNAL
(ODU MED J)

ODU Medical Journal is published by Faculty of Medicine of Ordu University on behalf of Ordu University and provides DOI free of charge.

The content of all topics can be accessed as full text free of charge at https://dergipark.org.tr/tr/pub/odutip/archive.

e-ISSN 2148-6816

ODU Tıp Dergisi/ ODU Medical Journal

Editorial office:

Ordu University, Faculty of Medicine

Republic Campus

52200, Ordu, TÜRKİYE

Telephone: +90 452 234 50 10
Fax: +90 452 226 52 55
Email: haticehancii@gmail.com

Web site: https://dergipark.org.tr/tr/pub/odutip
Publication Date and Place: 31/08/ 2024, ORDU, TÜRKİYE
Publication Type: Online
Index: Index Copernicus, Google akademik, Medline, Europub, DRJI

Open Access Policy

ODU Medical journal implements an open access policy in line with the rules of the Budapest Open Access Initiative (BOAI).

According to BOAI rules, open access is defined as “the full text of these articles being available for any user to read, download, copy, distribute, print, search or link to and browse through”.

All studies published in the ODU Medical Journal can be accessed by all internet users as of the publication date. No fee is charged from those who download the studies published in the journal.

Aim and Scope

Aim: ODU Medical Journal is an international journal and publishes clinical and scientific original research. ODU Medical Journal, published by Ordu University, publishes research articles, case reports and reviews that include fundamental innovations in health education.

The aim of the journal is to contribute to the international literature with clinical and experimental research articles, case reports and reviews in the field of health sciences.

The target audience of the journal is all scientists working in the field of health and graduate students and researchers in this field.

Scope: ODU Medical Journal is an open access and independent international journal based on impartial double-blind peer-review principles. The publication languages of the journal are English. The journal is published every four months in April, August and December and a volume is completed in three issues.

ODU Medical Journal adheres to the standards in publication ethics in research in health science and also adopts the ethical publishing principles published by Scientific Research and Publication Ethics Directive of the Council of Higher Education, Committee on Publication Ethics (COPE), Directory of Open Access Journals (DOAJ), Open Access Scholarly Publishers Association (OASPA) and the World Association of Medical Editors (WAME).

The authors are not charged for the evaluation and publication of the article.

Publication Ethics Statement

ODU Medical Journal adheres to the standards in publication ethics in research in health science and also adopts the ethical publishing principles published by Scientific Research and Publication Ethics Directive of the Council of Higher Education, Committee on Publication Ethics (COPE), Directory of Open Access Journals (DOAJ), Open Access Scholarly Publishers Association (OASPA) and the World Association of Medical Editors (WAME). The address for the principles

expressed under the title of Principles of Transparency and Best Practice in Scholarly Publishing is given below.

https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing

Submitted studies must be original, unpublished, and not in the evaluation process of another journal. Each article is double-blindly evaluated by one of the editors and at least two referees. Plagiarism, duplication, false authorship/denied authorship, research/data fabrication, article slicing, publishing by slicing, copyright infringement and concealment of conflict of interest are considered unethical behaviors.

All articles that do not comply with ethical standards are removed from the publication even if accepted. This also applies to articles with possible irregularities and inconsistencies detected after publication.

Research Ethics

• Compliance of the articles with ethical rules is the responsibility of the authors.

• The ethical standards of the Declaration of Helsinki must be complied with in studies on humans.

• Consideration should be given to ethical principles in the design, review and conduct of research.

• The research team and participants should be fully informed about the purpose of the research, the rules of participation and the risks, if any.

• Confidentiality of the information and answers given by the research participants should be ensured. Research should be designed in such a way as to preserve the autonomy and prestige of its participants.

• Those who will participate in the research should take part in the research voluntarily and should not be under any coercion.

• The research should be planned in a way that does not put the participants at risk.

• Research should be clear and unambiguous about its independence. If there is a conflict of interest, it should be stated.

• In experimental studies, written informed consent must be obtained from participants who decide to participate in the research. The consents of the legal guardians of children, ones under guardianship and those with a confirmed mental illness must be obtained.

• If the study will be carried out in an institution or organization, the necessary approval must be obtained from this institution or organization.

• In studies with human, it should be stated in the “methods” section that “informed consent” was obtained from the participants and ethics committee approval was obtained from the institution where the study was conducted.

Authors Responsibility

Compliance of the articles with scientific and ethical rules is the responsibility of the authors. The author must provide assurance that the article is original, has not been previously published elsewhere, and is not under consideration for publication elsewhere and in another language. Applicable copyright laws and agreements must be observed. Copyrighted material (for example, tables, figures, or large quotations) should be used with appropriate permission and acknowledgements. The work of other authors, contributors, or references should be used appropriately and cited in references.

All authors must have a direct academic and scientific contribution to the submitted manuscript. So, “author” is someone who contributes to the conceptualization and design of a published research, the obtaining, analysis or interpretation of data, writing the article or critically reviewing it in terms of content. Other conditions for being an author are planning or executing and/or revising the work on the manuscript.

Funding, data collection, or overall supervision of the research group alone does not confer authorship. All individuals listed as authors must meet all the criteria listed, and any individual who meets the above criteria may be listed as an author. The order of the authors’ names should be a joint decision. All authors must indicate the author rank on the Copyright Agreement Form signed. All individuals who did not meet the criteria for authorship but contributed to the study should be listed in the "acknowledgments" section. Examples of these are people who only provide technical support, help with writing, just provide general support, and financial and material support.

All authors must declare financial relationships, conflicts of interest, and competition of interest that have the potential to affect the results of the research or scientific evaluation. If an author detects a significant error or inaccuracy in his or her published article, it is the responsibility to immediately contact and cooperate with the editor for correction or retraction of these inaccuracies.

Editor and Reviewer Responsibilities

The editor-in-chief evaluates articles regardless of the authors' ethnicity, gender, sexual orientation, nationality, religious beliefs, and political philosophy. S/he ensures that the articles submitted for publication undergo a fair double-blind peer-review. S/he guarantees that all information regarding the submitted articles will remain confidential until the article is published. The editor-in-chief is

responsible for the content and the overall quality of the publication. If necessary, it should publish an error page or make corrections.

The editor-in-chief does not allow any conflict of interest between authors, editors and referees. It has full authority to appoint a referee and is responsible for making the final decision on the articles to be published in the journal.

Reviewers should not have conflicts of interest with the research, the authors and/or the financial supporters of the research. They should reach an impartial judgment as a result of their assessment. They should ensure that all information regarding the submitted manuscripts is kept confidential and should report any copyright infringement and plagiarism on the part of the author to the editor. The referee should notify the editor of this situation and state that s/he cannot be a referee in cases where the subject of the article is not his area of expertise or s/he cannot return on time.

Reviewers and editorial board members cannot discuss articles with other people. Attention should be taken to keep the identity of the referees confidential. In some cases, with the decision of the editor, the comments of the relevant referees for the manuscript can be sent to other referees who comment on the same manuscript.

PUBLİCATİON POLİCY

The authors undertake that their publications are created in accordance with all universal ethical rules, and research is accepted accordingly.

Authors are responsible for all statements in their work. Submitted studies should be prepared in accordance with the writing rules of the journal. Studies that do not comply with the spelling rules are rejected or sent back to the authors for correction.

The journal reserves the right to make language corrections in accepted studies without changing the content and meaning.

The journal accepts the research provided that it has not been published in another journal or publication.

All authors must state their affiliation with persons or organizations that may have a conflict of interest. If there is support received for the study, it should be stated in detail. Conflicts of interest should also be stated on the title page.

In the management and publication processes of the journal, the publication principles of the "International Committee of Medical Journal Editors (ICMJE)" and "Committee on Publication Ethics (COPE)" are taken into consideration.

Evaluation process

-Only manuscripts uploaded to the journal's system are evaluated. Studies sent via e-mail will not be evaluated.

-All submitted works go through pre-evaluation, language editing, statistics editing and referee evaluation processes. The evaluation process is carried out by the editor of the journal.

Preliminary Evaluation Process

After the manuscript is uploaded to the journal, the pre-evaluation process begins. At this stage, the editor examines the manuscript in terms of content, form, suitability for the aim and scope of the journal. As a result of this review, the editor

• may decide that the study is not suitable for the journal and reject the study.

• may resend the work to the responsible author for corrections.

• may send it to the language editor and can request correction.

• may evaluate by sending it to the statistical consultant. After this evaluation, the editor may request corrections from the author.

• may refer the article to the referees and initiates the referee evaluation process.

Peer Review Process

All articles in the journal are subject to **double-blind peer** review. To ensure the objective evaluation process, each article is evaluated by at least two independent referees who are experts in their fields. In cases where there is no consensus among the referees, the article is evaluated by the third referee. In the decision-making processes of all articles, the editor-in-chief makes the final decision.

Revision

Authors should mark the changes they made in the main text in color when submitting the article revision files. The responses to the referees should be specified in a separate Word file. Revised articles should be sent to the journal within one month following the decision. If the revised version of the article is not uploaded within the specified time, the revision option may be canceled. If authors need additional time for revision, they should submit their publication requests to the journal before the end of one month.

The manuscripts accepted for publication are checked again for grammar, punctuation and format. Accepted manuscripts are arranged in accordance with the publication format of the journal, and the final version is sent to the responsible author in pdf format before publication and approval is received for publication. Authors should review their article and give approval for publication. If

any correction is required in the article other than the publication format, the correction request is notified to the editor at haticehancii@gmail.com. Correction requests are evaluated by the editor and reported to the responsible author. Articles that are not approved by the corresponding author will not be published.

Plagiarism

The similarity rate control of the articles should be made on iThenticate and should be at most 20%, excluding the "References" section.

The journal is published online only.

The journal is free of charge and no publication fee is requested from the researchers.

The journal is published by Ordu University.

Journal contact

haticehancii@gmail.com

General Rules

ODU Medical Journal is an open access and independent international journal based on impartial double-blind peer-review principles. The publication languages of the journal are English and Turkish. The journal is published every four months in July, November and March and a volume is completed in three issues. ODU Medical Journal adheres to the standards in publication ethics in research in health science and also adopts the ethical publishing principles published by Scientific Research and Publication Ethics Directive of the Council of Higher Education, Committee on Publication Ethics (COPE), Directory of Open Access Journals (DOAJ), Open Access Scholarly Publishers Association (OASPA) and the World Association of Medical Editors (WAME).The authors are not charged for the evaluation and publication of the article.

SUBMISSION POLICIES

Submission of a paper to ODU Medical Journal indicates that it deals with previously unpublished original material and is not intended for publication elsewhere. Articles submitted under multiple authorship are reviewed with the assumption that all listed authors agree with the submission and a copy of the final manuscript has been approved by all authors. Once a manuscript has been accepted, it should not be published elsewhere in the same form or in another language without the written consent of the editors and publisher. If citations from other copyrighted works are included, the author(s) must obtain written permission from the copyright holders and cite the references(s) in the article. The layout and style of the article must strictly follow the instructions. No revisions or updates will be included once the manuscript has been accepted and submitted to the publisher (unless approved by the editors).

SUBMISSION GUIDELINES

The articles sent online at https://dergipark.org.tr/tr/pub/odutip are reviewed in ODU Medical Journal. Manuscripts submitted online are quickly assigned to referees. Authors can view the status of their articles as they progress through the review process via individual author centers on this website. Editing notification of each article will be sent to the relevant author by e-mail on the day of decision. You can create your account for online submission by going to https://dergipark.org.tr/tr/login. If this is your first time for submission and you don't have an existing account, you'll need to create a new one. If you are unsure whether you have an account or have forgotten your password, enter your email address in the password assistance section on the login page. If you do not have an account, click the create account link in the upper right corner of the login page. Then, you will be able to submit and monitor the progress of your articles. After

logging in, you will be presented with a link to the main menu and your author center. You can submit your manuscript from the author center. At the end of a successful submission, you will receive an e-mail confirming that the article has reached the journal. If this does not happen, please send an email to haticehancii@gmail.com. To submit your manuscript online, please prepare the text and images according to the instructions listed below. At the end of each step, you can enter and exit the manuscript submission process. However, after you submit the manuscript, you cannot edit it. Web submission is required and the instructions are available at https://dergipark.org.tr/tr/pub/odutip/writing-rules.

COPYRIGHT TRANSFER AGREEMENT

A signed COPYRIGHT PUBLICATION FORM must be sent by all authors during manuscript submission.

ODU Medical Journal

Editorial Office

Faculty of Medicine, Ordu University

Cumhuriyet Campus

52200, Ordu, TÜRKİYE

Phone: +90 (452) 226 52 14-5234

Fax: +90 (452) 226 52 28

E-mail: haticehancii@gmail.com

Authors should write their information exactly (Full address, telephone and fax numbers, e-mail address and ORCID number).

PREPARATION OF THE ARTICLE

The corresponding author should submit the manuscript as described below:

• Files you need to add:

1. Title page
2. Full text
3. Tables
4. Figures/Graphics
5. Copyright Form
6. Similarity report (Similarity should be at most 20%.)
7. Cover letter
8. Ethics committee approval/consent in case reports

• When parasites, bacteria, viruses and fungi are mentioned in the main text and references, genus and species names should be written in italics and genus names should be written in capital letters.

• Abbreviations should be expanded when first mentioned and used consistently thereafter.

• Graphic files: Each figure should be a separate file.

• All figure files must be presented in sufficiently high resolution.

It is the responsibility of the authors to create the appropriate files for the electronically submitted manuscripts as stated above. The editorial office cannot convert beyond the supported file types.

ORGANIZATION OF THE MANUSCRIPT

Manuscripts should be prepared electronically using "Time News Roman" font, formatted according to A4 page size, mono-spaced throughout, with 2.5 cm margins on all sides and 12 point font. Words should not be hyphenated to fit on one line. Pages should be numbered.

A. Title page: The title page should be separate and prepared as follows.

The title page should be in Turkish and English, and the full and short title should be written.

If it has been presented in congress and symposium, it should be stated.

The names of the author(s), their affiliations and ORCID numbers should be stated.

Example: Ülkü Karaman1, Yeliz Kaşko Arıcı2, Cemil Çolak3

1-First author's institution, mail, ORCID no.

2-Second author's institution, e-mail, ORCID no.

3-Third author's institution, e-mail, ORCID no.

Corresponding author's name, address, telephone (including mobile phone number) and fax numbers and e-mail address.

Ethics Committee Approval: Ethics committee approval for this study was obtained from …… University Clinical Research Ethics Committee (Ethical committee date and no:…..)

Author Contributions: Concept - …… ..; Design …… ..; Audit …… ...; Data Collection and/or Processing - …… ...; Analysis and/or Interpretation - ……; Source Search……; Spelling……; Critical Review ……

Acknowledgement:

Conflict of interest:

Financial support:

B. What should be in the main text

1. Abstract, 2. Keywords, 3. Introduction, 4. Methods, 5. Results, 6. Discussion, 7. Conclusion, 8. References, 9. Tables and Figures.

1. Abstract: The first page should include Turkish and English abstracts and keywords. Abstracts of Original Articles should be structured with subtitles (Objective, methods, results and conclusion) (200-400 words on average).

2. Keywords: Enter at least 3-6 keywords and avoid general and plural terms and multiple concepts. These keywords will be used for indexing purposes. Key words should be written under Turkish and English abstracts. Turkish keywords should be written from http://www.bilimterimleri.com and English keywords should be written from https://www.nlm.nih.gov/mesh/meshhome.html.

3. Introduction: General information about the research, and the rationale and objectives of the research should be clearly stated in this section.

4. Methods: This section should contain all the details necessary to reproduce the experiments. When using experimental animals, the methods section should clearly state that adequate precautions have been taken to minimize pain or discomfort.

5. Results: This section should present the results and interpret them clearly and concisely. Results should generally be presented descriptively and supported by figures.

6. Discussion: It should be discussed with the findings obtained using the published literature.

7. Conclusion: In this section, the conclusions obtained from the manuscript and recommendations should be written.

8. Literature references:

While citing the references, attention should be paid to cite studies originating from Türkiye and the national journals (www.atifdizini.com).

References should be listed in the text in order of occurrence and should be indicated "in parentheses" where relevant.

References should be written according to the "Vancouver" system of the American National Library of Medicine (US National Library of Medicine; http://www.nlm.nih.gov/).

Examples: Hypotension is one of the most common and critical problems in hemodialysis patients (1, 2).

References

When citing publications, the latest and most up-to-date publications should be preferred.

All references cited in the text should be listed at the end of the article in alphabetical order by the first author followed by the year of publication.

If reference is made to a prepress publication, DOI number must be given.

The accuracy of the sources is the responsibility of the author. References should include only print or press articles.

Unpublished data, submitted articles or personal communications should be cited in the text only. Personal interviews must be documented with a letter of consent.

All items in the list of references should be cited in the text and conversely, all references in the text should be presented in the list.

Journal title abbreviations should conform to the abbreviations adopted by the Series Title Abbreviations List, CIEPS / ISDS, Paris, 1985 (ISBN 2-904938-02-8).

Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus / MEDLINE / PubMed.

For citations with one to six authors, the names of all authors should be written. For articles with more than six authors, “et al.” should be written after six names are written. The surnames of the authors should be written in full and the initials of their names should be capitalized without any punctuation marks.

Reference examples:

Journal: Stephane A. Management of Congenital Cholesteatoma with Otoendoscopic Surgery: Case Report. J Med Sci 2010;30(2):803-7.

Levine WC, Pope V, Bhoomkar A, Tambe P, Lewis JS, Zaidi AA, et al. Increase in endocervical CD4 lymphocytes among women with nonulcerative sexually transmitted diseases. J Infect Dis. 1998;177(1):167–174.

Chapter of an edited book: Hornbeck P. Assay for antibody production. In: Colign JE. Kruisbeek AM, Marguiles DH, editors. Current Protocols in Immunology. New York: Greene Publishing Associates; 1991. p. 105-32.

A single-authored book: Fleiss JL. Statistical Methods for Rates and Proportions. Second Edition. New York: John Wiley and Sons; 1981. p. 105-32.

An editorial book: Balows A. Mousier WJ, Herramaflfl KL, editors. Manual of Clinical Microbiology. Fifth Edition. Washington DC: IRL Press. 1990. p. 105-32.

Paper: Entrala E, Mascaro C. New structural findings in Cryptosporidium parvum oocysts. Eighth International Congress of Parasitology (ICOPA VIII); October 10-14; Izmir-Türkiye: 1994. p. 1250-75

Thesis: Erakinci G. Searching for antibodies against parasites in donors. Izmir: Ege University Health Sciences Institute. 1997.

Electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

FIGURES AND TABLES

Figures:

Figures should be numbered with Arabic numerals according to the order of occurrence in the text; for example: Figure 1, Figure 2, etc. Note and explanation should be written where the graphic or figure should be in the manuscript and it should be sent as a separate file in JPG format. If figures (or other small parts) of articles or books already published elsewhere are used in the articles submitted to the ODU Medical Journal, the written permission of the relevant authors and the relevant publisher should be attached to the article. In these cases, the original source should be mentioned in the figure description. The article should not contain any information that may indicate a person or institution. All submitted figures must have a clear resolution and large size (minimum dimensions: 100 × 100 mm) to avoid delays in the evaluation process.

Tables: Tables should be created with titles and explanations. Tables should appear in the main document, follow the references, and be numbered in the order in which they are cited in the main text. Each of the numeric data tables should be typed (single-spaced) and numbered sequentially with Arabic numerals (Tables 1, 2, etc.); for example: Table 1, Table 2, etc. in the text. The title of each table should appear above it. A detailed description of its contents and footnotes should be given below the body of the table. Corrections: Authors should mark the changes they made in the main text in color when submitting the article revision files. The responses to the referees should be specified in a separate Word file. Revised articles should be sent to the journal within one month following the decision. If the revised version of the article is not uploaded within the specified time, the revision option may be canceled. If authors need additional time for revision, they should submit their publication requests to the journal before the end of one month.

FINAL STATEMENT OF THE ARTICLE BEFORE PUBLICATION AND OTHER NOTES TO CONSIDER

Final version of the manuscript before publication

The final version of the manuscript will be sent as pdf by e-mail before publication. Only the printer's errors can be corrected. At this stage, no changes or additions will be allowed to the edited manuscripts. It should be noted that editing is solely the responsibility of the authors. A form with questions from the copy editor can be attached to the proofs. Please answer all questions and make

any necessary corrections or additions. Corrections in reviews must be returned by email within 48 hours of receipt. If the publisher does not receive any response from the authors after 3 days, it will be assumed that there are no errors to be corrected and the manuscript will be published.

Page rates

The journal is free and does not charge any publication fee from the authors.

The journal is published online only.

The similarity rate control of the articles should be made on iThenticate and should be at most 20%, excluding the "References" section.

The editorial board has the authority to make the necessary revisions (without making any changes in the context) in the manuscript format that does not comply with the above-mentioned conditions.

TYPES OF ARTICLES

Studies submitted to the journal are accepted as Original research, Short paper and Case report,

a) Research articles: Prospective, retrospective and all kinds of experimental studies

Structure

Title

Abstract should be structured (Objective, Methods, Results, and Conclusion) (200-400 words)

Keywords

Introduction

Methods

Results

Discussion

Conclusion

Acknowledgement

References (up to 40)

Except for the references and the English abstract, the full text should not exceed 4500 words.

b) Case Report: These are articles that differ in diagnosis and treatment, which are rarely seen. They should be supported by adequate photographs and diagrams.

Structure

Title

Abstract (average 100-300 words)

Keywords

Introduction

Case report

Discussion

Conclusion

Acknowledgement

References (up to 20)

Except for the references and the English abstract, the full text should not exceed 2200 words.

c) Review

Structure

Title

Abstract (average 150-400 words)

Keywords

Introduction

The review also includes subtitles suitable for the text.

Conclusion

Acknowledgement

References (up to 50)

Except for the references and the English abstract, the full text should not exceed 6550 words.

ODU TIP DERGİSİ/ODU MEDICAL JOURNAL
(ODU MED J)

AUGUST 2024 **VOLUME 11** **NUMBER: 2**

CONTENTS

EDITORIAL

PREFACE

With the philosophy that success is dependent on continuity and stability, we take pride in sharing another issue of our magazine with you on this journey. Each new year opens new doors for the medical community. With every scientific advancement, we aim to make our mark through our magazine. Your valuable contributions of scientific studies and writings will elevate our magazine to even greater heights in the academic arena. Hoping that this issue of our magazine, with its rich content penned with different perspectives, interesting topics, and current approaches, will contribute to all our readers, I wish you enjoyable readings.

Dr. Hatice Hanci

Editor-in-Chief

ODU TIP DERGİSİ/ODU MEDICAL JOURNAL (ODU MED J)

August 2024;11(2):68-77

ARAŞTIRMA MAKALESİ/ RESEARCH ARTICLE

DOI: 10.56941/odutip.1492859

Usability of Ordinal Logistic Regression Analysis for Beck Depression Inventory

Canan Demir[1], Siddik Keskin[2], Hamit Mirtagioglu[3], Yildirim Demir[4]

[1]VanYüzüncü Yıl University, Van Health Services Vocational School, Health Technician Department, Van, Turkiye,
[2]Van Yüzüncü Yıl University, Faculty of Medicine, Department of Biostatistics, Van, Turkiye
[3]Bitlis Eren University, Faculty of Arts and Sciences, Department of Statistics, Bitlis, Turkiye
[4]Van Yüzüncü Yıl University, Faculty of Economics and Administrative Sciences, Department of Econometrics, Van, Turkiye

Received: 31 May 2024, Accepted: 14 August 2024, Published online: 31 August 2024

Abstract

Objective: In the study; For the Beck Depression Scale, the usability of the Ordinal logistic regression model was evaluated, taking into account the situation in which this scale was ordinal.

Materials and Methods: The study was conducted in the first and second-year students of the University of Van Yüzüncü Yıl, Health Services Vocational School. A total of 664 volunteer students who accepted to participate in the study were included in the study, and no sample was taken from the population. The students were asked 8 questions including socio-demographic characteristics, as well as questions of the 21-item Beck Depression Scale. Depression status with 4 order categories (Normal-Mild-Moderate-Severe) was taken as the dependent variable in the study, and the relationship of other socio-demographic variables with the depression status variable was examined.

Results: In the study, Nagelkerke pseudo R^2 value, one of the goodness of fit criteria, was found to be 0.062. In addition, the model fit criterion -2LL (Log-likelihood) test statistic ($p<0.05$) was found significant.

Conclusion: As a result, the usability of ordered logistic regression analysis in determining the relationships between the variables and depression was emphasized.

Keywords: Beck depression inventory, Statistical analysis, Ordinal logistic regression analysis

Beck Depresyon Ölçeği İçin Sıralı Lojistik Regresyon Analizinin Kullanılabilirliği

Özet

Amaç: Çalışmada; Beck Depresyon Ölçeği için, bu ölçeğin ordinal olduğu durum dikkate alınarak Ordinal lojistik regresyon modelinin kullanılabilirliği değerlendirilmiştir.

Materyal ve Metot: Çalışma, Van Yüzüncü Yıl Üniversitesi Sağlık Hizmetleri Meslek Yüksekokulu birinci ve ikinci sınıf öğrencileri ile gerçekleştirilmiştir. Çalışmaya katılmayı kabul eden toplam 664 gönüllü öğrenci çalışmaya dahil edilmiş, evrenden örneklem alınmamıştır. Öğrencilere sosyo-demografik özellikleri içeren 8 sorunun yanı sıra 21 maddelik Beck Depresyon Ölçeği soruları sorulmuştur. Çalışmada bağımlı değişken olarak 4 sıra kategorili (Normal-Hafif-Orta-Şiddetli) depresyon durumu alınmış ve diğer sosyo-demografik değişkenlerin depresyon durumu değişkeni ile ilişkisi incelenmiştir.

Bulgular: Çalışmada uyum iyiliği ölçütlerinden Nagelkerke yalancı R^2 değeri 0.062 olarak bulunmuştur. Ayrıca model uyum kriteri -2LL (Log-likelihood) test istatistiği ($p<0.05$) anlamlı bulunmuştur.

Sonuç: Sonuç olarak, değişkenler ile depresyon arasındaki ilişkilerin belirlenmesinde sıralı lojistik regresyon analizinin kullanılabilirliği vurgulanmıştır.

Anahtar Kelimeler: Beck depresyon ölçeği, İstatistiksel analiz, Sıralı lojistik regresyon analizi

Suggested Citation: Demir C, Keskin S, Mirtagioglu H, Demir Y. Usability of Ordinal Logistic Regression Analysis for Beck Depression Inventory. ODU Med J, 2024;11(2): 68-77.

Address for correspondence/reprints:

Yildirim Demir

Telephone number: +90 (505) 452 33 29

E-mail: ydemir@yyu.edu.tr

INTRODUCTION

Depression is defined as a mental disorder affecting more than 264 million individuals worldwide (1). Depression is based on unwillingness and inability to enjoy daily activities, which they previously did willingly and fondly (2). In addition, there are negative self-concept symptoms such as fatigue, sleep and appetite disorders (3).

Depression can occur at any age and can affect all kinds of people, young, old, rich and poor (1). Current studies show that depression is caused by the interaction of genetic, biological, environmental and psychological factors (4). Life events such as childhood troubles, loss and unemployment contribute to the development of depression. The effects of depression can be reflected in the daily life and interpersonal relationships of the person and cause his/her performance in school and/or work life to decrease (5).

Depression is predicted to be a globally widespread disease that has a great burden on the population. The 21-item Beck Depression Inventory (BDI) was first proposed by Beck et al. and has been used in more than 7,000 studies to date. This scale is one of the most popular tools used worldwide to assess depressive symptoms (6).

Various statistical methods are used to evaluate the depression scale. However, depression scales tend to form asymmetric distributions. Therefore, commonly used traditional statistical methods such as t-test and linear regression may not be suitable. Therefore, in the study, For the Beck Depression Scale, the usability of the Ordinal logistic regression model was evaluated, taking into account the situation in which this scale was ordinal.

METHODS

After the approval of the Ethics Committee; the study was conducted in the first and second-year students of the University of Van Yüzüncü Yıl, Health Services Vocational School in the spring semester of the 2014-2015 academic year. A total of 664 volunteer students who accepted to participate in the study were included in the study, and no sample was taken from the population. The students were asked 8 questions (age, class, department, gender, marital status, number of siblings, residence and income status) including socio-demographic characteristics, as well as questions of the 21-item Beck Depression Scale (BDI). The categorical variables discussed in the study and the descriptive statistics (number and percentage) of these variables are summarized in Table 1.

Table 1. Variables considered in the study and descriptive statistics

Variable	Category (n=664)		%
Gender	Female	377	56.8
	Male	287	43.2
Class	1	441	66.4
	2	223	33.6
Marital status	Single	604	91.0
	Married	60	9.0
Place of residence	Dorm	239	36.0
	At home with friends	84	12.7
	At home with family	249	37.5
	At home with relatives	22	3.3
	Alone at home	70	10.5
Number of siblings	<3	124	18.7
	3-5	308	46.4
	6-10	193	29.1
	>10	39	5.8
Income	<1000	267	40.2
	1000-2000	215	32.4
	2000-3000	106	16.0
	>3000	76	11.4
Department	Anesthesia	69	10.4
	Dialysis	20	3.0
	First and Emergency Aid (Normal)	117	17.6
	First and Emergency Aid (Night)	115	17.3
	Perfusion	23	3.5
	Radiotherapy	26	3.9
	Medical Documentation and Secret	112	16.9
	Medical Laboratory	62	9.3
	Medical Imaging	41	6.2
	Elderly care	79	11.9

Logistic regression analysis shows that when the dependent variable is binomial (successful-unsuccessful, yes-absent, patient-healthy) or multinomial (Married-widowed-single, low-medium-high), it is an analysis method used to determine the relationship between the dependent variable (response variable) and explanatory (independent) variables (7,8).

In logistic regression analysis; instead of the value of the response variable, the probability of one of the values that this variable can take is estimated. Therefore, logistic regression analysis is mathematically based on probability, logarithm of odds and odds.

Odds: it is the ratio of the probability of occurrence (p) to the probability of absence (q).

Odds Ratio (OR): OR, which is a summary measure of the relationship between two variables, is the ratio of two probabilities to each other.

Ordinal Logistic Regression: The dependent variable Y is categorised as 0, 1 or 2. Assuming that the ordinal dependent variable Y categorised as 0, 1, 2, ..., K can take K +1 values, it is necessary to decide which category to use as the reference value. An extension of this is to take $Y = 0$ as the reference or baseline outcome and construct logit functions that compare other categories with it (9). The two logit functions are expressed by two models given in Equations (1) and (2).

$$g_1(x) = ln\left[\frac{P_r(Y=1|x)}{P_r(Y=0|x)}\right]$$

$$= \beta_{10} + \beta_{11}x_1 + \beta_{12}x_2 + \cdots + \beta_{1p}x_p$$

$$= x'^{\beta_1} \quad (1)$$

$$g_2(x) = ln\left[\frac{P_r(Y=2|x)}{P_r(Y=0|x)}\right]$$

$$= \beta_{20} + \beta_{21}x_1 + \beta_{22}x_2 + \cdots + \beta_{2p}x_p$$

$$= x'^{\beta_2} \quad (2)$$

Given the covariate vector, the conditional probabilities of each outcome category are as follows

$$P_r(Y=0|x) = \frac{1}{1+e^{g_1(x)}+e^{g_2(x)}} \quad (3)$$

$$P_r(Y=1|x) = \frac{e^{g_1(x)}}{1+e^{g_1(x)}+e^{g_2(x)}} \quad (4)$$

$$P_r(Y=2|x) = \frac{e^{g_2(x)}}{1+e^{g_1(x)}+e^{g_2(x)}} \quad (5)$$

A general expression for conditional probability in the categorical model is given by Equation (6).

$$\pi_j(x) = P_r(Y=j|x) = \frac{e^{g_j(x)}}{\sum_{k=0}^{2} e^{g_k(x)}} \quad (6)$$

Where both vector β_0 and $g_0(x)$ are equal to 0.

We denote a general expression for the probability that the outcome is equal to k conditional on a vector, x, of p covariates as $Pr[Y=k|x] = \emptyset_k(x)$. Logits are

$$g_k(x) = ln\left[\frac{\pi_k(x)}{\pi_0(x)}\right] = \beta_{k0} + x'\beta_k \quad (7)$$

for $k = 1, 2, \ldots, \mathrm{K}$

The basic procedure consists of the following steps:

Expressions defining model-specific logits are used to construct an equation describing $\emptyset_k(x)$ as a function of the unknown parameters. The values of K +1 dimensional multinomial result values, $z' = (z_0, z_1, \ldots, z_k)$, are occurred the ordinal output as $z_k = 1$ if $y = k$ and $z_k = 0$ otherwise. It follows that only one value of z is equal to 1. The general form of the likelihood for a sample of n independent observations, (y_i, x_i), $i = 1, 2, \ldots, n$ is

$$l(\beta) = \prod_{i=1}^{n} [\emptyset_0(x_i)^{z_{0i}} \emptyset_1(x_i)^{z_{1i}} \times \ldots \times \emptyset_K(x_i)^{z_{Ki}}] \quad (8)$$

Where we use "β" somewhat imprecisely to denote both the p slope coefficients and the K model-specific intercept coefficients. It follows that the log-likelihood function is

$$L(\beta) = \prod_{i=1}^{n} z_{0i} ln[\emptyset_0(x_i)] + z_{1i}[\emptyset_1(x_i)] + \cdots + z_{Ki} ln[\emptyset_K(x_i)] \quad (9)$$

An estimator of the covariance matrix of the estimated coefficients can be obtained in the usual way by taking the inverse of the negative of the matrix of second-order partial derivatives with respect to $\hat{\beta}$.

The log-likelihood function is used to compare predicted and observed values. Using the likelihood functions, estimated values can be expressed as follows.

$$D = 2\, ln \frac{Likelihood\ of\ current\ model}{Likelihood\ of\ saturated\ model} \quad (10)$$

The D (Likelihood Ratio or Deviance) statistic, which corresponds to the sum of squares error in linear regression, plays an important role in judging the goodness of fit (9, 10).

Beck Depression Scale (BDS): It is a 21-item self-assessment scale that was developed by Aron T. Beck et al. in 1961 and measures the risk of depression and symptoms of depression in

adults (11). The Turkish reliability and validity study of the scale was conducted by Hisli, and it was stated that it could be used to measure depression symptoms in university students (12).

Scoring and evaluation of the Beck depression scale: Beck depression scale is an easy test to score and evaluate. First of all, all the numbers marked in the sentence groups consisting of four items are added together and the total score obtained is determined. Then this score is found in the rubric below.

- 0-9: Shows normal level
- 10-18: Shows signs of mild depression
- 19-29: Indicates moderate depression
- 30-63: Shows signs of severe depression.

Depression status with 4 order categories (Normal-Mild-Moderate-Severe) was taken as the dependent variable in the study, and relationship of other socio-demographic variables with the depression status variable was examined.

RESULTS

Ordered Logistic Regression Analysis Results

In the study, the last categories of categorical variables included in the model were taken as reference categories.

Model fit criteria for sequential logistic regression analysis are given in Table 2. As seen in Table 2; -2LL (Log-likelihood) test statistic was found to be significant ($p<0.05$).

Table 2. Model fitting analysis for ordinal logistic regression

Model	Chi-Square	-2 Log Likelihood	df	p
Intercept Only		1425.130		
Final	36.618	1388.512	24	0.048
False R^2 values				
McFadden = 0.022, Nagelkerke = 0.062, Cox and Snell = 0.057				

The Nagelkerke false R^2 value, one of the measures of goodness of fit, was found to be 0.062 in the study. In R^2 statistics; the log-likelihood value of the model, which includes only the model constant term, is accepted as the general sum of squares, and the likelihood value for the entire model is accepted as the sum of error squares. Thus, the probability ratio expresses the success of the complete model compared to the model containing only the fixed term. The likelihood is between 0 and 1. Thus the logarithm of the likelihood is less than or equal to zero. If the model contains a very low likelihood ratio value, the logarithm of likelihood will be large. Thus, the small value of the logarithm of the likelihood indicates that the complete model is better than the model containing only the constant term (13).

When Table 3 was examined, the effect of the variables of department, class, age, marital status, number of siblings, place of residence and income on the level of depression was not found statistically significant, while the effect of the gender factor was significant ($p <0.05$). According to this, assuming that other variables are kept constant, it can be said that female

students are 1,559 times more likely to be depressed than male students. However, although it was not found statistically significant; Students studying in the primary and emergency aid (evening education) department were approximately 1.8 times more likely to be depressed than those studying in the dialysis department, and students studying in the dialysis department were approximately 1/0,178 = 5.6 times more likely to be depressed than those studying in the medical imaging department. Similarly, students under 25 tend to be 1.2 times more likely to be depressed than students over 25, and students staying home with friends tend to be 2.06 times more likely to be depressed than other students. When the tendency to depression is examined by income level; it can be said that students with an income of less than 1000 Lira tend to be 1.4 times more depressed than students with an income of over 3000 Lira.

Table 3. Ordinal logistic regression analysis summary results

Variable	Category	Exp(β)	P	95% Confidence Interval	
				Lower B.	Upper B.
Department	First and Emergency Aid (Night)	1.824	0.190	0.741	3.891
	Medical Documentation and Secret	1.061	0.901	0.419	4.054
	Medical Imaging	0.528	0.236	0.183	4.933
	Anesthesia	1.182	0.729	0.459	4.17
	Elderly care	1.094	0.853	0.42	4.233
	Medical Laboratory	1.292	0.608	0.484	4.396
	Perfusion	1.110	0.859	0.356	5.533
	Radiotherapy	1.315	0.637	0.421	5.566
	First and Emergency Aid (Normal)	1.071	0.880	0.435	3.902
	Dialysis				
Class	1	1.048	0.772	0.761	1.621
	2				
Age	17-25	1.201	0.612	0.593	2.899
	>25				
Gender	Female	1.559	0.006	1.136	1.611
	Male				
Marital status	Married	0.899	0.767	0.445	2.888
	Single				
Number of siblings	<3	0.552	0.165	0.238	3.555
	3-5	0.758	0.494	0.341	3.327
	6-9	0.659	0.311	0.294	3.378
	>10				
Place of residence	Dorm	1.504	0.147	0.866	2.298
	At home with friends	1.545	0.364	0.604	4.127
	At home with family	1.171	0.636	0.609	2.679
	At home with relatives	2.061	0.136	0.796	4.204
	Alone at home	1.520	0.151	0.858	2.371
	Other				
Income	<1000	1.451	0.209	0.81	2.415
	1000-2000	1.183	0.571	0.661	2.409
	2000-3000	1.267	0.463	0.672	2.603
	>3000				

DISCUSSION

In the study, descriptive information about ordinal logistic regression method was given and the usability of the method in determining the relationship between depression and some demographic characteristics in students was evaluated. The likelihood ratio statistic, which shows the overall significance of the model with the variables included in the model, was found to be significant ($p < 0.05$). Among the variables, the relationship between the gender factor and the level of depression was found to be significant. Also, although it was not found statistically significant; department, age, place of residence, and income level variables were observed to be potential risk factors for depression level.

In a study by (14); The relationship between the socio-demographic characteristics of individuals and their happiness levels was analyzed with sequential logistic regression analysis and it was emphasized that happiness levels may differ in terms of socio-demographic characteristics by years, but still basically similar results. In a study by (15), ordered logistic regression analysis was used to determine the factors affecting students' happiness. The goodness of fit of the model was evaluated with Cox and Snell, Nagelkerke, McFadden tests and it was emphasized that the factors affecting the happiness of the students were “age”, “satisfaction with the department”, “peace in the family” and “the opinion that the city of Sivas is suitable for students”. In a study by (16), ordered logistic regression analysis was preferred to determine the reasons for student absenteeism. It was emphasized that GPA and weekly course hours are significantly associated with absenteeism tendency. On the other hand, used the sequential logistic regression model to determine the factors that may have an impact on the overall satisfaction level of students studying at Atatürk University (17).

Another method used in many different fields such as binary and multinomial logistic regression analyses is the ordinal logistic regression method. The method is also known as the proportional probability model because it includes log probabilities and transformations used during prediction. The use of the ordinal logistic regression model relies on the presence of large dependent variables and the fulfillment of model assumptions (18, 19). On the other hand, ordered logistic regression analysis can be considered as an extension of the simple (binary) logistic regression model. In simple logistic regression, the logarithm of odds for the occurrence or occurrence of the event in the variable taken as the response variable is modeled as a linear combination of independent or explanatory variables. However, this modeling approach ignores the order of the categorically dependent variable. The ordered logistic regression model overcomes this problem by

using the cumulative categories of the dependent variable in calculating the logarithm of odds. Thus, interpretation of the coefficients calculated for ordinal logistic regression differs from multinomial and binary logistic regression (20).

Ordinal logistic regression includes the assumption of proportional odds, as well as the assumption that the categories of the response variable are ordered and that there is no multiple correlations between the explanatory variables. The proportional odds assumption expresses that the effect of explanatory variables is the same or equal in computing the logarithm of each odds. In this case, a single model will be sufficient for the coefficients. If this assumption is not satisfied, different models are needed to describe the relationship between each pair of outcomes. However, this assumption does not apply to the constant term, as the constant term takes different values for each equation.

CONCLUSION

As a result, as in depression levels, the response variable may be ordered in many areas, and the relationships between these variable and explanatory variables can be linear or nonlinear. In such cases, ordinal logistic regression analysis can be used as an appropriate approach to determine the relationship between variables.

Ethics Committee Approval: Ethic committee approval report was obtained from Yüzüncü Yıl University, Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (Date and number: 10.03.2015 / 21)

Peer-review: Externally peer-reviewed.

Author Contributions: Idea- Equal; Design - Equal; Control - Equal; Data Collection and/or Processing - Equal; Analysis and/or Interpretation - Equal; Literature Review - Equal; Spelling - Equal; Critical Review – Equal

Conflict of Interest: The authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study has not received no financial support.

REFERENCES

1. Anonymous 1. World Health Organization. Depression fact sheets. https://www.who.int/health-topics/depression#tab=tab_1. Accessed 05 April 2020.
2. Bedaso A, Kediro G, Yeneabat T. Factors associated with depression among prisoners in southern Ethiopia: a cross-sectional study. BMC Research Notes 2018; 11: 637-6.
3. Palmer GA, Happe MC, Paxson JM, Jurek BK, Graca JJ, Olson SA. Psychometric properties of the Beck Depression Inventory-II for OEF/OIF veterans in a polytrauma sample. Military Medicine 2014; 179: 879-884.
4. Anonymous 2. National Institute of Mental Health, Depression, Transforming the

understanding and treatment of mental illness. https://www.nimh.nih.gov/health/topics/depression/index.shtml#part_145397. Accessed 02 April 2020.

5. Taycan O, Kutlu L, Çimen S, Aydın N. Relation between sociodemographic characteristics depression and burnout levels of nurse working in university hospital. Anatolian Journal of Psychiatry 2006; 7: 100-108.
6. Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. Brazilian Journal of Psychiatry 2013; 35: 416-431.
7. Gok AC, Özdemir A. Forecasting the sector portions of banks by logistic regression analysis. Dokuz Eylül University Journal of Faculty of Business 2011; 1: 43-51.
8. Alpar R. Applied multivariate statistical methods. Ankara, Delta Yayıncılık; 2013.
9. Liu X. Applied Ordinal Logistic Regression Using Stata: From Single-Level to Multilevel Modeling. London, Sage Publications; 2016.
10. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression. New York, John Wiley & Sons; 2013.
11. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of General Psychiatry 1961; 4: 561-571.
12. Hisli N. The reliability and validity of Beck depression inventory for university students. Turkish Journal of Psychology. 1989; 7:3-13.
13. Akın HB, Şentürk E. Analysing levels of happiness of individuals with ordinal logistic analysis. Oneri 2012; 10: 183-193.
14. Keskin S. Overview of pseudo r-square measures. Güler A (Editor) Current Academic Studies in Health Sciences, Cetinje, IVPE, 2018. p.1-9.
15. Goktolga ZG, Karakıs E. Determination of the Relationship between Students' Economic Status and Their Happiness by Ordinal Logistic Regression Method: The Case of Cumhuriyet University. EconWorld2017@Paris Proceedings, Paris, France; 2017, July 25-27.
16. Ugurlu CT, Usta HG, Şimşek AS. Absence trend of undergraduates: logistic prediction. Kastamonu Education Journal 2018; 26: 345-349.
17. Orcanlı K, Oktay E. Pirim M. Investigation of Factors Affecting Satisfaction with Time-Use: Example of Atatürk University Students. Journal of Graduate School of Social Sciences 2019; 23: 797-825.
18. Eygu H, Gulluce A. Determination of customer satisfaction in conservative concept hotels by ordinal logistic regression analysis. Journal of Financial Risk Management 2017; 6: 269-284.
19. Eygu H, Kılınç A. The research of factors that affects on life satisfaction: the sample of

Kayseri province. OPUS International Journal of Society Researches 2020; 16: 3591-3618.

20. Turgut V. Investigation of sequential logistic regression model. Van Yuzuncu Yil University, Institute of Health Sciences 2020.

ODU TIP DERGİSİ/ODU MEDICAL JOURNAL (ODU MED J)

August 2024;11(2):78-90

ARAŞTIRMA MAKALESİ/ RESEARCH ARTICLE

DOI: 10.56941/odutip.1512185

Analysis of Acute Abdomen in Trauma Patients: Mortality Factors and Impact of the COVID-19 Pandemic on Admissions

Mustafa Alpaslan[1], Sultan Ozselcuk[1]

[1] Nevsehir State Hospital, Clinic of Emergency Medicine, Nevsehir, Turkiye

Received: 08 July 2024, Accepted: 26 August 2024, Published online: 31 August 2024

Abstract

Objective: To analyze the patients who developed acute abdomen due to trauma, to evaluate the factors affecting mortality and to examine the impact of the COVID-19 pandemic process on patient admissions.

Method: The study was conducted retrospectively by analyzing the patients who applied to the emergency department of a secondary healthcare institution between 01.01.2019-31.12.2023 (5 years) and developed an emergency surgical abdomen secondary to trauma and were hospitalized and treated. All age groups were included in the study. Demographic data, type of trauma, type of treatment, site of injury, laboratory data, length of hospitalization and mortality status were analyzed. Comparative analysis of the injured regions according to the type of trauma was performed. Data of patients who were discharged and those who died were compared. Data collection was performed through hospital electronic data.

Results: The study evaluated 123 patients. The majority of patients were male (%78.9). The mean age was 36.43±14.81 years and the most common age range was 21-40 years (60.2%). At the time of presentation to the emergency department, the most common Glasgow Coma Score was 11-15 (83%). The most common reason for presentation was traffic accident (40.7%). Post-traumatic injuries to more than one organ or region in the abdomen were most common (28.5%). Surgical procedures were performed in 65.9% of the patients. The mean duration of hospitalization was 7.14±5.40 days. Hemoglobin and platelet levels were found to be significantly lower at the time of admission in the patients who died ($p<0.05$). Mortality rate was 9.8%.

Conclusion: In patients with abdominal trauma, the type of injury, Glasgow Coma Score at admission and laboratory data are effective in predicting mortality. It should be kept in mind that especially in patients with blunt trauma and in cases of multiple trauma, intra-abdominal injuries may progress more insidiously and may be missed.

Key Words: Emergency Department, Blunt abdominal trauma, Penetrating abdominal trauma, Mortality

Travma Hastalarında Akut Batın Analizi: Mortalite Faktörleri ve COVID-19 Pandemisinin Yatışlar Üzerindeki Etkisi

Özet

Amaç: Travmaya bağlı akut batın gelişen hastaların analizi ile mortaliteyi etkileyen faktörlerin değerlendirilmesi ile COVID-19 pandemi sürecinin hasta başvurularına etkisini incelemektir.

Yöntem: Çalışma retrospektif olarak 01.01.2019-31.12.2023 (5 yıl) tarihleri arasında ikinci basamak bir sağlık kuruluşunun acil servisine başvuran ve travmaya sekonder acil cerrahi batın gelişen, yatırılarak tedavi altına alınan hastaların analizi ile yapıldı. Çalışmaya tüm yaş grupları dâhil edildi. Hastalarda demografik veriler, travma tipi, tedavi tipi, yaralanan bölge, laboratuar verileri, hastanede yatış süresi ve mortalite durumu analiz edildi. Travma tipine göre yaralanan bölgelerin karşılaştırmalı analizi yapıldı. Taburcu olan ve ölümle sonlanan hastaların verileri karşılaştırıldı. Veri toplama işlemleri ise hastane elektronik verileri üzerinden yapıldı.

Bulgular: Çalışmada 123 hasta değerlendirildi. Hastaların %78.9'u erkekti. Yaş ortalaması 36.43±14.81 olup en sık hasta yatışı 21-40 yaş aralığındaydı (%60.2). Acil servise başvuru anında Glaskow Koma Skoru en sık 11-15 (%83) aralığında oldu. En fazla trafik kazası nedeniyle başvuru olduğu görüldü (%40.7). Travma sonrası en fazla batın içinde birden fazla organ ya da bölgede yaralanma olduğu görüldü (%28.5). Hastaların %65.9'una cerrahi işlem uygulandı. Hastanede ortalama yatış süresi 7.14±5.40 gün oldu. Eksitus olan vakalarda başvuru anında hemoglobin düzeyi ve trombosit düzeyinin anlamlı derecede düşük olduğu görüldü ($p<0.05$). Mortalite oranı %9.8'di.

Sonuç: Karın travmalı hastalarda yaralanmanın tipi, başvuru anında gözlenen Glaskow Koma Skoru ve laboratuar verileri mortaliteyi öngörmede etkili olmaktadır. Özellikle künt travmalı hastalarda ve multi travmalı vakalarda karın içinde meydana gelen yaralanmanın daha sinsi şekilde ilerleyebileceği ve atlanabileceği unutulmamalıdır.

Anahtar kelimeler: Acil Servis, Künt abdominal travma, Penetran abdominal travma, Mortalite

Suggested Citation: Alpaslan M, Ozselcuk S. Analysis of Acute Abdomen in Trauma Patients: Mortality Factors and Impact of the COVID-19 Pandemic on Admissions. ODU Med J, 2024;11(2): 78-90.

Address for correspondence/reprints:
Mustafa ALPASLAN
Telephone number: +90 (507) 148 38 94
E-mail: mustafalpaslan@gmail.com

INTRODUCTION

Head, neck, thorax and abdominal injuries are the leading causes of trauma-related deaths, respectively. Deaths due to abdominal injuries constitute approximately 15-20% of trauma-related deaths (1-5). Although abdominal trauma is less lethal than head and chest trauma, it remains important because it is the trauma group with the highest rate of preventable deaths when early diagnosis and treatment is performed (1-3). Early deaths in abdominal trauma are usually due to massive hemorrhage. Late mortality and morbidity are due to infection and sepsis (1-3).

Injuries are caused by direct or motion effect of trauma, compressive effect, stretching and tearing effect. Hemorrhage in solid organs, internal perforation, hemorrhage and peritoneal contamination may develop (6). It has been reported that solid organ injuries are more predominant in blunt traumas while hollow organs are more commonly injured in penetrating injuries (1-3,5,6). Retroperitoneal injuries are usually asymptomatic at the beginning and may present late (6).

The two main causes of abdominal injuries are blunt trauma and penetrating injuries. Although blunt abdominal traumas usually present as multiple injuries, the most common causes are falling from a height, assault, occupational accidents and motor vehicle accidents (1-3). The most commonly injured solid organs in blunt abdominal trauma are the spleen and liver. Since they usually occur in multiple injuries, awareness may occur later in the diagnosis and treatment process compared to penetrating injuries (5).

The two most common causes of penetrating injuries are penetrating and cutting instrument injury (PCII) and firearm injury (FI). While the probability of injury in the intra-abdominal organs is 90-98% in gunshot wounds, this rate is 55-60% in FI (1-3,5). The mortality rate in penetrating abdominal trauma is around 2-13% (7).

COVID-19 disease has spread from Asia to Europe and America in a short period of time and the World Health Organization (WHO) declared a "Pandemic" on March 11, 2020 (8). In the literature, it has been reported that the epidemiologic distribution of forensic cases differs in the presence of situations such as disasters and pandemics (9).

Emergency departments are usually the first port of call for trauma and forensic cases. Patient management is very difficult especially in PCII and FI. Early diagnosis and treatment is very important in patients with acute abdomen due to trauma. In this study, we aimed to analyze the

patients who developed acute abdomen due to trauma, to evaluate the factors affecting mortality and to evaluate the effect of the COVID-19 pandemic process on such patient admissions to the emergency department.

METHODS

This retrospective study was conducted in a health institution providing secondary health care services. The time interval determined in the study was between 01.01.2019-31.12.2023 (5 years) and was performed by analyzing the patients with traumatic acute abdominal condition who were hospitalized from the emergency department to the general surgery, urology and gynecology and obstetrics clinics during this period. All age groups were included in the study. Demographic data (age, gender), type of trauma (traffic accident, PCII, FI, etc.), type of treatment (conservative, surgical, blood product replacement, etc.), site of injury (liver, spleen, small intestine, etc.), laboratory data (hemogram and biochemical parameters), 'Glasgow Coma Score' (GCS) on arrival, length of hospitalization and mortality status were analyzed. The impact of the COVID-19 pandemic on the number of cases in the specified time interval and the cases seen in this process were analyzed. Comparative analysis of the injured areas according to the type of trauma was performed. Data of patients who were discharged and those who died were compared. Data collection was done retrospectively through hospital electronic data. The data obtained were entered into the study form.

RESULTS

In this study, the number of patients who developed acute abdomen due to trauma and were hospitalized and followed up was 123. 78.9% of the patients were male. The mean age was 36.43±14.81 years and the most common age range was 21-40 years (60.2%). The proportion of patients evaluated as forensic cases was 90.2%. At the time of presentation to the emergency department, the most common GCS was in the range of 11-15 (83%). Surgical procedures were performed in 65.9% of the patients. The proportion of patients initially admitted to intensive care unit was 69.9%. The mean duration of hospitalization was 7.14±5.40 days. The majority of the patients were hospitalized for 1-7 days (64.2%). Of the patients analyzed in the study, 90.2% were discharged and 9.8% died. General data of the patients are given in Table 1.

When the distribution of patient hospitalizations by year is analyzed, the highest number of hospitalizations was in 2023 (35.7%) (Figure 1). According to the distribution given in Figure 1, patient hospitalizations showed a significant decrease after 2019 and then increased again in 2023.

Table 1. General data

		n(%)
Gender	Male	97 (78.9)
	Female	26 (21.1)
Average age		36.43±14.81
Age range	0-20	8 (6.5)
	21-40	74 (60.2)
	41-60	34(27.6)
	61-80	4 (3.3)
	81-100	3 (2.4)
Forensic Case		111 (90.2)
Glasgow Coma Score*	1-5	19 (15.4)
	6-10	2 (1.6)
	11-15	102 (83.0)
Treatment	Conservative	42 (34.1)
	Surgery	81 (65.9)
Blood Products Replacement**		
Erythrocyte (Units)	1-3	20 (16.3)
	4-6	8 (6.5)
	7-10	2 (1.6)
Fresh Frozen Plasma (Unit)	1-3	16 (13.0)
	4-6	3 (2.4)
Hospitalization	Service	37 (30.1)
	Intensive care	86 (69.9)
Length of Stay (days/ average)		7.14±5.40
Length of Hospitalization (days)	1-7	79 (64.2)
	8-15	34 (27.6)
	16-23	7 (5.2)
	24-30	3 (2.4)
Result	Discharged	111 (90.2)
	Excitus	12 (9.8)

*The value evaluated at the time of the patient's admission to the emergency department
**Number of blood products received by the patient in the emergency department and during the entire hospitalization period. Patient ratios were evaluated according to the number of all patients.

Analysis of the mechanisms of trauma revealed that traffic accidents (TA) were the most common cause of acute abdomen (40.2%). When we analyzed the regions injured after trauma, it was observed that most of the injuries occurred in more than one organ or region in the abdomen (28.5%). Spleen (21.1%) and liver (17.9%) were the most commonly injured organs. There was no

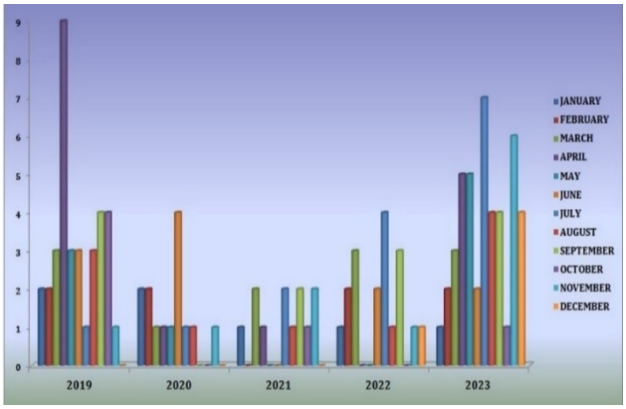

Figure 1. Distribution of the number of cases by year and month

significant difference in the type of trauma according to the year of presentation (p=0.286).There was also no significant difference between the regions of injury according to the years of presentation (p=0.364) (Table 2). There were significant differences when the injured areas were compared according to the trauma types (p=0.000) (Table 3).

The results of the comparison according to mortality status are given in Table 4. Accordingly, GCS was found to be significantly lower at the time of admission in patients with excitus (p=0.000). In laboratory data, blood glucose level and white blood cell level at admission were significantly higher in patients with excitus (p<0.05). Hemoglobin level and platelet level were found to be significantly low at the time of admission in patients with excitus (p<0.05). Blood product replacement was significantly higher in patients with excitus (p<0.05). When the length of hospitalization was analyzed, patients with excitus stayed in the hospital for a shorter time than those who were

discharged (p<0.05). In Table 5, mortality status was compared according to trauma types and injured regions and it was seen that deaths due to TA were significantly higher (p=0.005). In the comparison made according to the injured regions, it was observed that patients with injuries in more than one organ or region were more fatal (p=0.032).

Table 2. Comparison of trauma type and injured areas by years

Trauma Type / Year, n(%)	2019	2020	2021	2022	2023	Total	p
Traffic Accident	17 (48.6)	3 (21.4)	6 (50)	5 (27.8)	19 (43.2)	**50 (40.7)**	0.286 (χ^2: 18.664)
Penetrating and Cutting Instrument Injury	10 (28.6)	4 (28.6)	3 (25)	9 (50)	15 (34.1)	**41 (33.3)**	
Firearm Injury	4 (11.4)	2 (14.3)	2 (16.7)	3 (16.7)	4 (9.1)	**15 (12.2)**	
Falling	1 (2.9)	4 (28.6)	1 (8.3)	1 (5.6)	2 (4.5)	**9 (7.3)**	
Blunt Impact	3 (8.6)	1 (7.1)	0 (0)	0 (0)	4 (9.1)	**8 (6.5)**	
Injured Organ / Region							
Multiple Organs or Regions	10 (28.6)	3 (21.4)	5 (41.7)	6 (33.3)	11 (25)	**35 (28.5)**	0.364 (χ^2: 46.651)
Spleen	11 (31.4)	3 (21.4)	2 (16.7)	3 (16.7)	7 (15.9)	**26 (21.1)**	
Liver	3 (8.6)	1 (7.1)	3 (25)	2 (11.1)	13 (29.5)	**22 (17.9)**	
Anterior Abdominal Wall	3 (8.6)	4 (28.6)	1 (8.3)	4 (22.2)	0 (0)	**12 (9.8)**	
Small intestine	3 (8.6)	2 (14.3)	0 (0)	1 (5.6)	4 (9.1)	**10 (8.1)**	
Retroperitoneum	0 (0)	0 (0)	1 (8.3)	1 (5.6)	4 (9.1)	**6 (4.9)**	
Mesentery	3 (8.6)	0 (0)	0 (0)	0 (0)	2 (4.5)	**5 (4.1)**	
Column	1 (2.9)	1 (7.1)	0 (0)	0(0)	1 (2.3)	**3 (2.4)**	
Pancreas	1 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (0.8)**	
Gallbladder	0 (0)	0 (0)	0 (0)	1 (5.6)	0 (0)	**1 (0.8)**	
Stomach	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.3)	**1 (0.8)**	
Rectum	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.3)	**1 (0.8)**	
Total	**35 (100)**	**14 (100)**	**12 (100)**	**18 (100)**	**44 (100)**	**123 (100)**	

χ^2:Chi-square test analysis was used to compare two different groups and p<0.05 was accepted as significant.

Table 3. Comparison of injured areas with trauma type

Injured Area / Trauma Type, n(%)	Traffic Accident	PCII*	FI*	Fall	Blunt Trauma	Total	p
Multiple Organs or Regions	14 (40)	9 (25.7)	9 (25.7)	2 (5.7)	1 (2.9)	**35 (100.0)**	**0.003** (χ^2:74.240)
Spleen	16 (61.5)	3 (11.5)	1 (3.8)	4 (15.4)	2 (7.7)	**26 (100.0)**	
Liver	14 (63.6)	3 (13.6)	1 (4.5)	1 (4.5)	3 (13.6)	**22 (100.0)**	
Anterior Abdominal Wall	2 (16.7)	9 (75)	1 (8.3)	0 (0)	0 (0)	**12 (100.0)**	
Small Intestine	2 (20)	6 (60)	2 (20)	0 (0)	0 (0)	**10 (100.0)**	
Retroperitoneum	1 (16.7)	4 (66.7)	0 (0)	0 (0)	0 (0)	**5 (100.0)**	
Mesentery	0 (0)	2 (40)	1 (20)	1 (20)	1 (20)	**5 (100.0)**	
Column	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)	**3 (100.0)**	
Pancreas	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100.0)**	
Gallbladder	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100.0)**	
Stomach	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	**1 (100.0)**	
Rectum	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	**1 (100.0)**	
Total	**50 (40.7)**	**41 (33.3)**	**15 (12.2)**	**9 (7.3)**	**8 (6.5)**	**123 (100.0)**	

*PCII: Penetrating and Cutting Instrument Injury, FI: Firearm Injury

χ^2:Chi-square test analysis was used to compare two different groups and p<0.05 was accepted as significant.

Table 4. Comparison of Clinical Characteristics and Laboratory Data Between Discharged and Deceased Trauma Patients

		Discharge, n(%)/mean±SD	Excitus, n(%)/mean±SD	p*
Age		35.98±14.21	40.5±19.87	0.309
Gender	Male	90 (92.8)	7 (7.2)	0.067
	Female	21 (80.8)	5 (19.2)	
Glasgow Coma Score		13.79±3.37	5±4.67	**0.000**
Laboratory Data**				
Glucose (mg/dL)		107-154	137.7-239.2	**0.003**
Urea (mg/dL)		24-37	24.2-41	0.772
Creatinine (mg/dL)		0,7-1,06	0.7-0.97	0.937
Total Bilurubin (mg/dL)		0,3-0,6	0.1-0.47	0.088
Direct Bilurubin (mg/dL)		0,1-0,2	0.1-0.15	0.281
AST (U/L)		22-82	69-335	0.051
ALT (U/L)		18-64	25-293	0.137
GGT (U/L)		13-34	9.5-23.2	0.382
LDH (U/L)		285-602	288.2-813.2	0.197
CRP (mg/L)		1-3	0.9-2	0.451
White Blood Cell (10^3/mm^3)		7-12	8.2-16.8	**0.028**
Hemoglobin (g/dL)		12,6-15	7.0-11.9	**0.000**
Platelet (10^3/mm^3)		233-330	129.5-239.5	**0.040**
Neutrophils / Lymphocytes (%)		1,3-5	2.4-8.9	0.250
Blood Product Replacement (units)***				
Erythrocyte		0.57±1.45	3.08±3.02	**0.000**
Fresh frozen plasma		0.21±0.73	1.41±1.83	**0.000**
Length of Hospitalization (days)		7.49±5.39	3.91±4.56	**0.029**

*Student t test analysis was performed in the comparison between the two groups and $p<0.05$ was accepted as significant.
**Values seen at the time the patient presented to the emergency department. Laboratory data are given as 25th and 75th percentile values.
***The number of blood products given to the patient during the treatment process in the emergency department and the hospitalized clinic.

Table 5. Comparison of discharged and deceased patients according to trauma type and injury site

Trauma Type	Discharge, n(%)	Excitus, n(%)	p
Traffic Accident	39 (78.0)	11 (22.0)	**0.005** (χ^2:14.947)
Penetrating and Cutting Instrument Injury	41 (100.0)	0 (0.0)	
Firearm Injury	14 (93.3)	1 (6.7)	
Falling	9 (100.0)	0 (0.0)	
Blunt Impact	8 (100.0)	0 (0.0)	
Injured Organ / Region			
Multiple Organs or Regions	27 (77.1)	8 (22.9)	**0.032** (χ^2:21.094)
Spleen	24 (92.3)	2 (7.7)	
Liver	21 (95.5)	1 (4.5)	
Anterior Abdominal Wall	12 (100.0)	0 (0.0)	
Small Intestine	10 (100.0)	0 (0.0)	
Retroperitoneum	6 (100.0)	0 (0.0)	
Mesentery	5 (100.0)	0 (0.0)	
Column	3 (100.0)	0 (0.0)	
Pancreas	0 (0.0)	1 (100.0)	
Gallbladder	1 (100.0)	0 (0.0)	
Stomach	1 (100.0)	0 (0.0)	
Rectum	1 (100.0)	0 (0.0)	
Total	111 (90.2)	12 (9.8)	

χ^2:Chi-square test analysis was used to compare two different groups and $p<0.05$ was accepted as significant.

DISCUSSION

The abdomen is known to be the third most frequently injured region after the head and extremities in trauma-related injuries. Traumas in the abdomen are usually secondary to blunt trauma (1-3). The most common blunt traumas are injuries caused by TA. It has been reported that penetrating traumas are most commonly caused by FI and PCII (1-3,5). In our study, it was observed that TA injuries were the most common (40.7%). In our study, the second most common injuries were caused by PCII (33.3%), followed by FI (12.2%). Similarly, Acar et al. reported that the most common cause of abdominal trauma was due to TA with a rate of 80.3% (10). In the same study, it was observed that the second most common cause of abdominal trauma was injuries due to PCII (4.8%) (10). In similar studies conducted in the literature, Tekesin et al. 138.352 trauma patients and reported that 55% had blunt abdominal trauma and 10.1% had penetrating abdominal injury (11). In the study by Ozpek et al. the most common causes of blunt abdominal trauma were motor vehicle accidents (62%) and falling from height (27%) (12). In studies on abdominal traumas in children, it was reported that the most common type of trauma was falling from a height (13,14).

In the literature, it has been reported that the most commonly injured intra-abdominal organs in blunt abdominal trauma are liver, spleen and kidney, respectively (15-17). In our study, the most common injury occurred after TA and when evaluated together with isolated blunt trauma, the most common injuries were observed in the liver and spleen (Table 3). In the study by Acar et al. liver injury (55.8%), spleen injury (41.9%) and kidney injury (18.6%) were the most common injuries (10). In the study by Yasak et al. titled 'Investigation of children with solid organ injury after blunt abdominal trauma', the most commonly injured solid organs were liver (44.5%), spleen (34.2%) and kidney (10%), respectively (14). It has been reported that the injury rate of intestinal organs is higher in penetrating abdominal trauma. It has been reported that the most commonly injured solid organ is the spleen followed by the liver (2,19). In our study, the small intestine was the most commonly injured organ as a result of penetrating injury. The most commonly injured solid organs in penetrating injuries were liver and spleen in equal proportions (Table 3). In a study by Kurt et al. on penetrating sharps injuries to the abdomen, it was reported that the most common organ repaired by surgeons was the small intestine (19). In the study by Acar et al. intestinal organ perforation due to penetrating injuries was observed more frequently (10). In a study by Saylam et al. on injuries seen after FI in terrorist attacks, it was reported that the most

commonly injured organ in the abdomen was the small intestine (20).

In studies conducted in our country on abdominal injuries, it was reported that males were exposed to trauma at a higher rate than females (10-14, 19, 20). In our study, the rate of male patients was significantly higher than that of females (78.9%). In our study, we observed that the most common age range was 21-40 years and the mean age was 36.43±14.81. Similarly, in a study on risk factors affecting mortality in abdominal trauma, the mean age was reported to be 36.08±16.01 (21). In the study conducted by Acar et al. the mean age was reported as 41±18.4 years (10). Our study was similar to the literature in this respect. We think that the higher incidence of such traumas and injuries in the male gender and in the young adult age group is related to the fact that men and young adults are more active in social life and have a higher risk of encountering trauma compared to women and people in other groups.

In our study, we evaluated patient hospitalizations over a five-year period. During this period (2019-2023), the world experienced the COVID-19 pandemic. In this study, when we examined whether the pandemic process had an effect on patient admissions and hospitalizations, we observed that the number of patients decreased with the onset of the pandemic towards the end of 2019 and there was a rapid increase in the number of patients with the end of the pandemic (Figure 1). In the study by Güven et al. on the rates of forensic cases seen in the emergency department during the pandemic period, it was observed that the number of cases decreased rapidly with the onset of the pandemic and the number of cases was higher than before with the end of the pandemic (22). Similarly, in our study, the number of cases increased more than before after the end of the pandemic. In our study and in the study conducted by Güven et al. it was observed that this effect was especially evident in the TA and PCII cases (22). In our country, we think that there was a decrease in trauma cases due to restrictions in people's social lives and curfew practices during the pandemic process, and with the freedom that came with the end of the pandemic and the psychological effects of the process, we think that forensic case rates are higher than before.

Decreases in hemoglobin and hematocrit values in abdominal traumas are indicative of massive bleeding in the abdomen and have an important place in the clinical follow-up of the patient (23). In our study, we found that hemoglobin levels measured at the time of admission were significantly lower in patients with excitus compared with patients who were discharged. We also observed that hemoglobin levels were significantly lower in patients with low GCS at the time of admission ($p=0.005$). In the study by Acar et al. hemoglobin and hematocrit values

were significantly lower in patients with solid organ injury and high trauma score (10). Liver function tests and renal function tests, which are analyzed in routine biochemical parameters in abdominal traumas, may also be instructive about solid organ injuries (23). In the study of Acar et al. serum transaminase values were found to be significantly higher in patients with liver injury (10). In our study, transaminase values were significantly higher in patients with isolated liver injury (p=0.033).

In this study, we examined the effect of laboratory data at the time of admission on mortality and found that there was a decrease in serum hemoglobin and platelet levels and a significant increase in white blood cell, glucose and C-reactive protein (CRP) levels in cases that ended in death (p<0.05). In a similar study conducted by Gönültas et al. serum lactate dehydrogenase (LDH) and aspartate transminotransferase (AST) levels were significantly higher in patients with excitus (23).

We think that GCS evaluated at admission in patients with abdominal trauma is effective in predicting clinical course and mortality. In this study, the GCS value was 13.79±3.37 in patients who were discharged, whereas it was significantly lower in those who were excluded and was 5±4.67. Acar et al. reported that the GCS value was lower in patients with high trauma score (10). In a study in which patients admitted to the emergency department with gunshot wounds were evaluated, it was observed that the GCS of deceased patients was significantly lower (24).

In our study, we found that transfusion of blood products was performed at a significantly higher rate in patients with excitus (Table 4) (p=0.000). Similarly, in a similar study, it was observed that a significantly higher rate of blood product replacement was performed in patients with excitus (21).

Considering the length of hospitalization of the patients, Acar et al. reported that patients with high trauma scores were hospitalized longer (p<0.05) (10). In the study conducted by Gönültas et al. the duration of hospitalization was significantly lower in patients with excitus (21). In our study, the duration of hospitalization was shorter in cases that ended in death (p=0.029).

In recent years, with the development of computed tomography and the increase in intensive care services, conservative follow-up of patients has become more prominent. As a matter of fact, conservative treatment has become more prominent in stable cases in order to avoid surgical complications (25). However, surgical procedure comes to the forefront in penetrating injuries and unstable blunt trauma cases (2,5). In our study, 65.9% of the patients were treated surgically. However, similar to the literature, surgical treatment is predominant in

penetrating injuries and conservative treatment in blunt injuries (p=0.000). In one study, the majority (79.1%) of patients with solid organ injuries due to blunt trauma were treated conservatively (10). In a similar study, 70.8% of patients presented with blunt abdominal trauma and the proportion of patients who underwent surgical procedure was 83.2% (21).

Hypovolemic shock, peritonitis, septic shock and multi-organ failure are among the causes of death in patients with abdominal trauma (1,2,5,15). Mortality rates in abdominal trauma have been reported to vary between 12.6% and 21.3% (26-28). The mortality rate in blunt abdominal injuries is higher than penetrating injuries (5). In our study, the mortality rate was 9.8% and 11 patients (91.6%) after TA and one patient (8.4%) after FI were excused. In our study, the mortality rate due to blunt trauma was higher and especially the mortality rate was higher in patients with injuries to more than one organ or region (Table 5). Mortality in penetrating abdominal trauma is due to sudden death at the scene due to blood loss or complications in the late postoperative period and multiorgan failure developing due to trauma (12). In a study by Aldemir et al. 1048 patients with abdominal penetrating trauma were analyzed and mortality rate was reported as 10.1% (29). In patients with abdominal trauma, the mortality rate was 4.7% in the study by Acar et al. (10) and 19.4% in the study by Gönültas et al. (21).

CONCLUSION

In conclusion, in patients with abdominal trauma, the type of injury, GCS at presentation and laboratory data are effective in predicting mortality. It should be kept in mind that especially in patients with blunt trauma and in cases with multitrauma, intra-abdominal injury may progress more insidiously and may be missed. In our study, we found that the most common type of trauma in patients with abdominal trauma who developed acute abdomen was traffic accident. We would like to emphasize that patients with injuries due to traffic accidents, which is one of the most common reasons for admission to emergency departments, should be especially careful in terms of acute abdomen when evaluating patients.

Study Limitations

In the study, all patients who underwent conservative treatment and surgical procedure were evaluated and only patients who were hospitalized from the emergency department were analyzed.

Ethics Committee Approval: Prior to the study, the approval of 'Hacıbektas Veli University Non-Interventional Clinical Research Ethics Committee' numbered 2024/06 and dated 21/03/2024 was obtained.

Author Contributions: Conception - Mustafa Alpaslan, Sultan Ozselcuk; Design - Mustafa Alpaslan, Sultan Ozselcuk; Supervision - Mustafa Alpaslan; Data Collection and/or Processing - Sultan Ozselcuk; Analysis and/or Interpretation - Mustafa Alpaslan; Literature Search - Mustafa Alpaslan; Writing - Mustafa Alpaslan; Critical Review - Mustafa Alpaslan

Conflict of Interest: The authors reported no conflict of interest.

Financial Disclosure: The authors did not declare financial support.

Ethical Statement: The authors declare that they comply with research and publication ethics.

REFERENCES

1. French LK, Gordy S, O. John Ma. Abdominal trauma. In Tintinalli JE, Stapczynski JS, Ma OJ, Yealy DM, Meckler GD, Cline DM (eds): Emergency Medicine a comprehensive study guide. 8th ed. New York: The Mac Graw Hill Companies, 2015.
2. Isenhour JL, Marx J. Advances in abdominal trauma. Emerg Med Clin N Am. 2007; 25: 713-33.
3. Poletti PA, Mirvis SE, Shanmuganathan K, Takada T, Killeen KL, et al. Blunt abdominal trauma patients: can organ injury be excluded without performing computed tomography? J Trauma. 2004; 57: 1072-81.
4. Mama N, Jemni H, Achour AN, Sidiya OC, Kadri K, Gaha M et al. Abdominal trauma imaging. Derkel F, Editor. Abdominal surgery. Intech, Open access. 2012.Doi: 10.5772/50426
5. Ozkan S. Abdominal Injuries. Emergency medicine in all aspects: Diagnosis, treatment and practice book. Ed: Zeynep Kekec. 3rd Edition, Akademic Medical Bookstore, 2013, p:859-66.
6. El Wakeel AM, Habib RM, Ali AN. Role of CT in Evaluation of blunt abdominal trauma. International Journal of Medical Imaging. 2015; 3: 89-93.
7. Ntundu SH, Herman AM, Kishe A, Babu H, Jahanpour OF, Msuya D, et al. Patterns and outcomes of patients with abdominal trauma on operative management from northern Tanzania: a prospective single centre observational study. BMC Surg. 2019;19: 69.
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 15; 395 (10223): 497-506.
9. San I, Usul E, Bekgöz B, Korkut S. Effects of COVID-19 Pandemic on emergency medical services. Int J Clin Pract. 2021; 75(5): e13885.
10. Acar E, Ozkan S, Genc S, Altun S. Evaluation of adult abdominal trauma patients and intra-abdominal solid organ injuries. Phnx Med J. 2020; 2(2):90-7.

11. Tekesir K, Basak F, Sisik A, Caliskan YK. Epidemiology of trauma with analysis of 138.352 patients: Trends of a singlecenter, Haydarpasa Numune Med J. 2019; 59(2): 181-5.
12. Ozpek A, Yucel M, Atak I, Bas G, Alimoglu O. Multi variate analysis of patients with blunt trauma and possible factors affecting mortality. Ulus Trauma Emergency Surg. 2015; 21:6: 477-83.
13. Akdeniz S, Okur MH, Goya C. Demographic, clinical and laboratory results of patients with blunt liver trauma: A retrospective review of 2006-2016. Dicle Med J. 2020; 47(2): 366-76.
14. Yasak IH, Giden R. Investigation of children with solid organ damage after blunt abdominal trauma. Journal of Harran University Faculty of Medicine. 2022; 19(3): 600-4.
15. Salimi J, Ghodsi M, Zavvarh MN, Khaji A. Hospital management of abdominal trauma in Tehran, Iran: a review of 228 patients. Chin J Traumatol. 2009; 12: 259-62.
16. Demetriades D, Hadjizacharia P, Constantinou C, Brown C, Inaba K, Rhee P, et al. Selective non operative management of penetrating abdominal solid organ injuries. Ann Surg. 2006; 244: 620-8.
17. Yanar H, Ertekin C, Taviloglu K, Kabay B, Bakkaloglu H, Guloglu R. Nonoperative treatment of multiple intra-abdominal solid organ injury after blunt abdominal trauma. The Journal of Trauma 2008; 4: 943-8.
18. Dodiyi-Manuel A, Jebbin NJ, Igwe PO. Abdominal injuries in university of port harcourt teaching hospital. Niger J Surg 2015; 21:18-20.
19. Kurt F, Acele S, Sezer C. Penetrating stab wounds to the abdomen: Results in our secondary care center. J For Med 2020; 34(2):62-8.
20. Saylam N, Uyanık B, Buz M, Buyukyılmaz T, Demir Y, Algedik Gürsoy D. Gunshot wounds due to a terrorist attack. Anatolian J Emerg Med. Mart 2019; 2(1): 18-23.
21. Gonultas F, Kutluturk K, Gok AFK, Barut B, Sahin TT, Yilmaz S. Analysis of risk factors of mortality in abdominal trauma. Ulus Trauma Emergency Surg. 2020; 26(1): 43-9.
22. Guven O, Demireller M, Kurt BF, Yesil O. The effect of the COVID-19 pandemic on emergency department forensic applicatıons: a study in Turkey's western border. HMJ. 2023; 3(3): 16-23.
23. Bilgic I, Gelecek S, Akgun AE, Ozmen MM. Predictive value of liver transaminases levels in abdominal trauma. Am J Emerg Med. 2014; 32: 705-8.
24. Akbalık S. Analysis of Patients Applying to the Emergency Department with Gunshot Wounds, Master's thesis, Bezmialem Vakif University, Institute of Health Sciences, Department of Disaster Management,

Disaster Management Master's Program, Istanbul, 2022.

25. Raza M, Abbas Y, Devi V, Prasad KV, Rizk KN, Nair PP. Non operative management of abdominal trauma-a 10 years review. World J Emerg Surg. 2013; 8: 14.
26. Girgin S, Gedik E, Tacyılmaz IH. Evaluation of surgical methods applied in kunt liver trauma. Ulus Trauma Emergency Surg. 2006; 12: 35-42.
27. Koksal O, Ozdemir F, Bulut M, Aydin S, Almacıoglu ML, Ozguc H. Comparison of trauma scoring systems for predicting mortalty in firearm injuries. Ulus Trauma Emergency Surg. 2009; 15: 559-64.
28. Duzgun AP, Ozmen MM, Salyam B, Coşkun F. Factors influencing mortality in traumatic ruptures of diaphragm. Ulus Trauma Emergency Surg. 2008; 14: 132-8.
29. Aldemir M, Tacyıldız I, Girgin S. Predicting factors for mortality in the penetrating abdominal trauma. ActaChirBelg 2004; 104: 429-34.

ODU TIP DERGİSİ/ODU MEDICAL JOURNAL (ODU MED J) August 2024;11(2):91-98

DERLEME / REVIEW DOI: 10.56941/odutip.1507480

A confusing situation in the clinic practice: Isolated maternal hypothyroxinemia

Zekeriya Keskin[1]

[1] Şarkışla State Hospital, Clinic of Internal Medicine, Sivas, Turkiye

Received: 30 June 2024, Accepted: 26 August 2024, Published online: 31 August 2024

Abstract

Isolated maternal hypothyroxinemia (IMH) is a common problem in the clinic practice. There is a normal maternal thyroid stimulating hormone (TSH) level with a low maternal free thyroxine (FT4) level. The aim of this review is to explain IMH in the light of current literature and to contribute to clinicians in the management of IMH. Iodine deficiency is the most important factor in etiology. The effects of IMH on the pregnant women and the fetus are not clear. However, it is a serious concern among clinicians, especially considering the importance of the effect of thyroid hormones on fetal brain development. As for the treatment of IMH, the number of studies conducted is not sufficient and there is no consensus and evidence on levothyroxine treatment. However, there is a consensus on iodine supplementation and it is recommended to take 250 mg of iodine daily. As a result, IMH is a problem that should be taken seriously during pregnancy and care should be taken regarding its diagnosis and treatment. Additionally, more research is needed on the effects and treatment of IMH on pregnant women and fetal health.

Key Words: Isolated maternal hypothyroxinemia, Thyroid hormone, Pregnant, Fetus, Iodine deficiency

Klinik pratikte kafa karıştıran bir durum: İzole maternal hipotiroksinemi

Özet

İzole maternal hipotiroksinemi (İMH) klinik pratikte sık görülen bir sorundur. Düşük anne serbest tiroksin (FT4) düzeyi ile birlikte normal bir anne tiroid stimulan hormon (TSH) düzeyi mevcuttur. Bu derlemenin amacı İMH'nin güncel literatür eşliğinde gözden geçirilmesi ve İMH'nın yönetiminde klinisyenlere katkıda bulunmaktır. Etyolojide en önemli etken olarak iyot eksikliği bulunmaktadır. İMH'nın gebe ve fetüs üzerindeki etkileri net değildir. Ancak tiroid hormonlarının özellikle fetal beyin gelişimi üzerindeki etkisinin önemi düşünüldüğünde klinisyenler arasında ciddi bir endişe kaynağıdır. İMH tedavisinde ise yapılan çalışma sayısı yeterli olmayıp levotiroksin tedavisi konusunda fikir birliği ve kanıt yoktur. Ancak iyot takviyesi konusunda görüş birliği vardır ve günlük 250 mg iyot alınması önerilir. Sonuçta İMH gebelikte ciddiye alınması gereken, tanı ve tedavisi konusunda dikkatli olunması gereken bir problemdir. Ayrıca İMH'nın gebe ve fetüs sağlığı üzerine etkileri ve tedavisi konusunda daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: İzole maternal hipotiroksinemi, Tiroid hormonu, Gebe, Fetüs, İyot eksikliği

Suggested Citation: Keskin Z. A confusing situation in the clinic practice: isolated maternal hypothyroxinemia. ODU Med J, 2024;11(2): 91-98.

Address for correspondence/reprints:

Zekeriya Keskin

Telephone number: +90 (536) 686 69 14

E-mail: zekeriyakeskinsh@gmail.com

INTRODUCTION

Thyroid hormones are very important for the healthy maintenance of pregnancy and fetal development. Placental and fetal development are related to maternal thyroid hormones. Untreated maternal hypothyroidism poses a high risk for pregnancy and the baby (1). In the first trimester, thyroid hormones are supplied from the mother to the fetus via the placenta. Although thyroid hormone is secreted from the fetus in the second trimester, most of the hormones are provided by the mother. Therefore, hypothyroidism, especially in the first trimester, seriously affects the growth of the fetus. Hypothyroidism during pregnancy; includes clinical hypothyroidism, isolated maternal hypothyroxinemia (IMH) and subclinical hypothyroidism (2). IMH is defined as a normal maternal thyroid-stimulating hormone (TSH) level with a maternal free thyroxine (FT4) level below the 5th or 10th percentile of the reference range (3).

The prevalence of IMH has been tried to be determined by various studies, and it varies between 1.3% and 23.9% due to reasons such as different gestational ages, iodine deficiency status and ethnic differences. It has been detected more frequently in countries with iodine deficiency and in countries where specific reference ranges for pregnant women are not applied (4).

The aim of this review is to examine IMH which is commonly seen in the clinic practice and where there is often confusion in its management, in the light of current literature and to contribute to clinicians in the management of IMH.

Thyroid Gland Physiology During Pregnancy

During pregnancy, the demand for the mother's thyroid hormones increases significantly. Human chorionic gonadotropin (HCG), secreted by the placenta, increases thyroid hormone production by directly stimulating the TSH receptor. Thus, a decrease in TSH and a small, temporary increase in FT4 occurs in the first trimester. Since thyroid binding globulin (TBG) synthesis increases 2.5 times under the influence of estrogen, more thyroid hormone production is needed to maintain adequate FT4 levels (5). Additionally, there is increased renal clearance of iodine, an important element of thyroid hormones. It increases thyroid gland production by approximately 50% to compensate for the increased thyroid hormone need during pregnancy. In order to achieve this increase, the maternal thyroid gland must have sufficient iodine support and also there must be no significant underlying autoimmunity problem (6).

Etiology of IMH

The etiology of IMH is not fully determined and understood. Potential risk factors for IMH include iodine deficiency, increased affinity of TBG to thyroxine, increased placental 5-deiodinase type 3 activity, and placental angiogenic factors (7). Thyroid autoimmunity has not been identified as a risk factor (4). Additionally, many studies have

determined that obesity creates a predisposition to IMH and that negative metabolic parameters like fasting plasma glucose, triglycerides and plasma glucose and insulin resistance (HOMA-IR), are associated with IMH (4,8,9).

Effects of IMH on Pregnant and Baby

The effects of IMH during early pregnancy are not clear. However, there are concerns about its negative effects on both mother and baby. While overt hypothyroidism is associated with obstetric complications such as fetal losses, preeclampsia, spontaneous miscarriages, and gestational hypertension, there is no consensus on the perinatal effects of IMH (10). In two studies conducted with large study groups, no relationship was found between IMH and adverse perinatal events (11,12). In a study conducted with 2864 pregnant women, pregnant women in the 1st trimester and 2nd trimester were examined separately, and no association of IMH with pregnancy outcomes was found (13).

There are studies with findings contrary to these studies. In a study conducted with more than 10,000 patients, IMH in the first trimester was associated with premature birth and macrosomia, while IMH in the second trimester was associated with gestational diabetes mellitus (14). In a study conducted in China, it was observed that IMH may increase maternal hypertensive events (15). There are also studies showing that IMH causes preterm birth (16,17).

When looking at its effects on the baby, there are studies showing that IMH causes macrosomia (14,15,18). On the contrary, IMH has also been shown to cause low birth weight. Additionally, in the same study, IMH was associated with fetal distress and musculoskeletal anomalies (19).

Considering the importance of the effects of thyroid hormones on fetal brain development, especially in the first trimester, it is thought that IMH may have a negative effect on fetal brain development in this period (20). In two studies, it was stated that there was a decrease in the psychomotor test scores of children of mothers diagnosed with IMH, especially in the first trimester (21,22). Contrary to these views, there are studies showing that IMH does not affect the neurodevelopment of babies (19,23).

Treatment

There is no consensus and evidence on the treatment of IMH, just like there is no consensus on the clinical effects of IMH. As a general precaution, it is recommended to take daily 150 mg og iodine for those who are not pregnant and planning pregnancy, and 250 mg of iodine for the pregnant and breastfeeding women (24). Pregnant women with hypothyroidism are recommended to measure TSH levels every 4 weeks in the first half of pregnancy and at least once between the 26th and 32nd weeks (25). There is no definitive treatment method in the treatment of IMH, and iodine supplementation is generally

recommended. There is not enough evidence for the use of levothyroxine and there are conflicting results (26).

While the European Thyroid Association (ETA) states that IMH treatment can be considered in the first trimester, the American Thyroid Association (ATA) does not recommend any specific treatment (27). Only 2 randomized controlled trials have investigated the effects of levothyroxine treatment on IMH. In one of these studies, 526 pregnant women with IMH were included in the study. Control groups, treated with levothyroxine and not treated with levothyroxine groups were compared. Children born later were screened with comprehensive tests until the age of 5, and no significant neurodevelopmental difference was observed between the two groups (28). The other study was conducted with 411 pregnant women with IMH and it was determined that levothyroxine treatment did not create a significant difference in cognitive functions in children (29). However, in these two studies, the fact that the treatment was given in late gestational weeks was considered a limitation. Contrary to these studies, Auso et al. was observed in an animal model study evaluating IMH, that early levothyroxine treatment affected the neurodevelopment of offspring born to hypothyroxinemic mothers (30). A recent review focused on the negative effects of IMH on children's cognitive and psychosocial development, and recommended iodine supplementation as a precaution (31). Similarly, two different reviews have stated that IMH negatively affects pregnancy and newborn health. In addition, levothyroxine treatment was not thought to be beneficial. (32,33). For this reason, more studies are needed on the treatment of IMH with levothyroxine.

In a study investigating the effect of iodine supplementation on IMH, iodine supplements were given to pregnant women during the late pregnancy period, between the 4th and 6th and between the 10th-12th weeks. In this study, no neurodevelopmental delay was observed in the children of pregnant women who received iodine supplementation between the 4th and 6th weeks compared to the other two groups (34). Although levothyroxine treatment in the treatment of IMH is controversial, there is a consensus on iodine supplementation (26).

CONCLUSION

IMH is a frequently encountered problem in the clinic practice. Iodine deficiency is generally defined as the biggest risk factor. There is no consensus on its consequences and treatment for pregnant and baby health. This creates confusion among clinicians. Considering the effects of thyroid hormones on the fetal brain, serious concerns arise. However, the effects of IMH on pregnancy and the fetus have not been definitively demonstrated. The number of studies on treatment is limited and the effectiveness of levothyroxine treatment has not been proven, however, iodine

supplementation is recommended. As a result, IMH is a problem that should be taken into account during pregnancy and care should be taken regarding its diagnosis and treatment. Additionally, more research is needed on the effects and treatment of IMH on pregnant and fetal health.

Ethics Committee Approval: Ethics committee permission was not required for the research to be combined and distributed appropriately. Not received.

Author Contributions:

Concept: ZK, Design: ZK, Supervision: ZK, Data Collection and/or Processing: ZK, Analysis and/or Interpretation: ZK, Writing: ZK.

Declaration of Interests: The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The author received no financial support for the research and/or authorship of this article.

REFERENCES

1. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol. 2017;13(10):610-622.
2. Furnica RM, Lazarus JH, Gruson D, Daumerie C. Update on a new controversy in endocrinology: isolated maternal hypothyroxinemia. J Endocrinol Invest. 2015;38(2):117-123.
3. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21(10):1081-125.
4. Dosiou C, Medici M. Management of Endocrine Disease: Isolated maternal hypothyroxinemia during pregnancy: knowns and unknowns. Eur J Endocrinol. 2017;176(1):R21-R38.
5. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med. 1994;331(16):1072-1078.
6. Glinoer D. Pregnancy and iodine. Thyroid. 2001;11(5):471-481.
7. Furnica RM, Gruson D, Lazarus JH, Maiter D, Bernard P, Daumerie C. First trimester isolated maternal hypothyroxinaemia: adverse maternal metabolic profile and impact on the obstetrical outcome. Clin Endocrinol (Oxf). 2017;86(4):576-583.
8. Gowachirapant S, Melse-Boonstra A, Winichagoon P, Zimmermann MB. Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient

pregnant women. Matern Child Nutr. 2014;10(1):61-71.

9. Knight BA, Shields BM, Hattersley AT, Vaidya B. Maternal hypothyroxinaemia in pregnancy is associated with obesity and adverse maternal metabolic parameters. Eur J Endocrinol. 2016;174(1):51-57.
10. Wang S, Teng WP, Li JX, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. J Endocrinol Invest. 2012;35(3):322-325.
11. Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. Obstet Gynecol. 2007;109(5):1129-1135.
12. Hamm MP, Cherry NM, Martin JW, Bamforth F, Burstyn I. The impact of isolated maternal hypothyroxinemia on perinatal morbidity. J Obstet Gynaecol Can. 2009;31(11):1015-1021.
13. Chen L, Yang H, Ye E, Lin Z, Peng M, Lin H, et al. Insignificant Effect of Isolated Hypothyroxinemia on Pregnancy Outcomes During the First and Second Trimester of Pregnancy. Front Endocrinol (Lausanne). 2020 ;16(11):528146.
14. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol. 2008;112(1):85-92.
15. Su X, Zhao Y, Cao Z, Yang Y, Duan T, Hua J. Association between isolated hypothyroxinaemia in early pregnancy and perinatal outcomes. Endocr Connect. 2019;8(4):435-441.
16. Yang X, Yu Y, Zhang C, Zhang Y, Chen Z, Dubois L, et al. The Association Between Isolated Maternal Hypothyroxinemia in Early Pregnancy and Preterm Birth. Thyroid. 2020;30(12):1724-1731.
17. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SM, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. J Clin Endocrinol Metab. 2013;98(11):4382-90.
18. Gong X, Liu A, Li Y, Sun H, Li Y, Li C, et al. The impact of isolated maternal hypothyroxinemia during the first and second trimester of gestation on pregnancy outcomes: an intervention and prospective cohort study in China. J Endocrinol Invest. 2019;42(5):599-607.
19. Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, Li T, et al. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in

China. J Clin Endocrinol Metab. 2011;96(10):3234-41.

20. Lavado-Autric R, Ausó E, García-Velasco JV, Arufe Mdel C, Escobar del Rey F, Berbel P, et al. Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. J Clin Invest. 2003;111(7):1073-82.
21. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clin Endocrinol (Oxf). 2010;72(6):825-9.
22. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf). 2003;59(3):282-288.
23. Craig WY, Allan WC, Kloza EM, Pulkkinen AJ, Waisbren S, Spratt DI, et al. Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. J Clin Endocrinol Metab. 2012;97(1):E22-8.
24. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;27(3):315-389.
25. Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. J Clin Endocrinol Metab. 2010;95(7):3234-3241.
26. López-Muñoz E, Mateos-Sánchez L, Mejía-Terrazas GE, Bedwell-Cordero SE. Hypothyroidism and isolated hypothyroxinemia in pregnancy, from physiology to the clinic. Taiwan J Obstet Gynecol. 2019;58(6):757-763.
27. Taylor PN, Muller I, Nana M, Velasco I, Lazarus JH. Indications for treatment of subclinical hypothyroidism and isolated hypothyroxinaemia in pregnancy. Best Pract Res Clin Endocrinol Metab. 2020;34(4):101436.
28. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. N Engl J Med. 2017;376(9):815-825.
29. Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med. 2012;366(6):493-501.
30. Ausó E, Lavado-Autric R, Cuevas E, Del Rey FE, Morreale De Escobar G, Berbel P. A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. Endocrinology. 2004;145(9):4037-4047.

31. Grossklaus R, Liesenkötter KP, Doubek K, Völzke H, Gaertner R. Iodine Deficiency, Maternal Hypothyroxinemia and Endocrine Disrupters Affecting Fetal Brain Development: A Scoping Review. Nutrients. 2023;15(10):2249.
32. Han Y, Gao X, Wang X, Zhang C, Gong B, Peng B, et al. A Systematic Review and Meta-Analysis Examining the Risk of Adverse Pregnancy and Neonatal Outcomes in Women with Isolated Hypothyroxinemia in Pregnancy. Thyroid. 2023;33(5):603-614.
33. Zhuo L, Wang Z, Yang Y, Liu Z, Wang S, Song Y. Obstetric and offspring outcomes in isolated maternal hypothyroxinaemia: a systematic review and meta-analysis. J Endocrinol Invest. 2023;46(6):1087-1101.
34. Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, Graells M, et al. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. Thyroid. 2009;19(5):511-9.

ODU TIP DERGİSİ/ODU MEDICAL JOURNAL (ODU MED J)
August 2024;11(2):99-114

DERLEME / REVIEW
DOI: 10.56941/odutip.1442818

Progress in Utilizing Chitosan-Based Nanoparticles for Pulmonary Drug Administration

Gamze Mercan[1], Zümrüt Varol Selcuk[2]

[1] Hacettepe University, Department of Nanotechnology and Nanomedicine, Ankara, Turkiye

[2] Ordu University, Department of Mathematics and Science Education, Ordu, Turkiye

Received: 25 February 2024, Accepted: 29 August 2024, Published online: 31 August 2024

Abstract

The escalating prevalence of respiratory ailments poses a significant global public health challenge, ranking among the primary causes of mortality worldwide. Notably, diseases such as asthma, chronic obstructive pulmonary disease, pneumonia, cystic fibrosis, and lung cancer, alongside the emergence of respiratory diseases, notably those induced by the coronavirus family, have contributed substantially to global fatalities in the past two decades. Consequently, numerous studies have been undertaken to enhance the effectiveness of therapeutic interventions against these diseases, with a particular emphasis on nanomedicine-driven pulmonary drug delivery. As a result, the development of nanocarriers has emerged as a promising avenue to surmount the constraints associated with traditional therapies, aiming to elevate drug bioavailability at the intended site while minimizing undesired side effects. Within this domain, nanoparticles fashioned from chitosan (CS) exhibit distinct advantages over alternative nanocarriers owing to the inherent biological properties of chitosan, including its anti-inflammatory, antimicrobial, and mucoadhesive attributes. Furthermore, CS nanoparticles have demonstrated the potential to augment drug stability, extend the duration of action, refine drug targeting, regulate drug release kinetics, optimize the dissolution of poorly soluble drugs, and enhance the cell membrane permeability of hydrophobic drugs. These unique properties position CS nanoparticles as a promising candidate for optimizing drug performance following pulmonary administration. Consequently, this review endeavors to elucidate the potential of chitosan nanoparticles in the realm of pulmonary drug delivery, shedding light on how their intrinsic biological characteristics can ameliorate the treatment landscape of pulmonary diseases. Emphasis is placed on delineating the synergistic interplay between chitosan nanoparticles and the encapsulated drug, thereby offering insights into the prospective advancements in treating respiratory ailments.

Key Words: Lung diseases, Pulmonary, Drug delivery, Chitosan, Nanoparticles

Akciğer Hastalıklarında Kitosan Tabanlı Nanopartiküllerin İlaç Taşıyıcı Sistemlerin Uygulamasındaki Gelişmeler

Özet

Solunum yolu hastalıklarının giderek artan yaygınlığı, dünya genelinde önemli bir küresel halk sağlığı sorunu teşkil ederek dünya genelindeki başlıca ölüm nedenleri arasında yer almaktadır. Özellikle son iki on yılda astım, kronik obstrüktif akciğer hastalığı, pnömoni, kistik fibrozis ve akciğer kanseri gibi hastalıkların yanı sıra koronavirüs ailesi tarafından tetiklenen solunum yolu hastalıkları gibi hastalıklar, küresel ölümlere büyük ölçüde katkıda bulunmuştur. Bu nedenle, bu hastalıklara yönelik terapötik müdahalelerin etkinliğini artırmaya yönelik birçok çalışma yapılmış, bu çalışmaların özellikle nanotıp destekli akciğer ilaç dağıtımına odaklandığı gözlemlenmiştir. Bu bağlamda, nanonakliyecilerin geliştirilmesi, geleneksel tedavilerle ilişkilendirilen kısıtlamaları aşmak için umut vaat eden bir yol olarak ortaya çıkmış ve böylece amaçlanan bölgede ilaç biyoyararlılığını artırmayı ve istenmeyen yan etkileri en aza indirmeyi hedeflemiştir. Kitosan (CS) kullanılarak şekillendirilen nanopartiküller, kitosanın doğal biyolojik özelliklerine dayalı olarak diğer nanonakliyecilere göre önemli avantajlar sunmaktadır. Bu avantajlar arasında anti-enflamatuar, antimikrobiyal ve mukoadhezif özellikler yer almaktadır. Ayrıca, CS nanopartiküller, ilaç kararlılığını artırma, etki süresini uzatma, ilaç hedeflemeyi iyileştirme, ilaç salınım kinetiğini düzenleme, düşük çözünürlüğe sahip ilaçların çözünürlüğünü artırma ve hidrofobik ilaçların hücre zarı geçirgenliğini artırma potansiyeline sahiptir. Bu benzersiz özellikler, CS nanopartiküllerini akciğer uygulaması sonrası ilaç performansını optimize etmek için umut vadeden bir aday olarak konumlandırmaktadır. Bu nedenle, bu inceleme, kitosan nanopartiküllerinin akciğer ilaç dağıtımı alanındaki potansiyelini aydınlatmayı amaçlamakta ve kitosanın içsel biyolojik özelliklerinin solunum yolu hastalıklarının tedavi alanını nasıl iyileştirebileceğine dair anlayış sunmaktadır. Ayrıca, CS nanopartiküllerinin içinde bulunduğu ilaç ile olan etkileşimi ayrıntılı olarak ele alarak solunum yolu hastalıklarının tedavisindeki olası ilerlemelere dair bir perspektif sunulmaktadır.

Anahtar Kelimeler: Akciğer hastalıkları, Akciğer, İlaç dağıtımı, Kitosan, Nanopartiküller

Suggested Citation: Mercan G., Selcuk ZV. Progress in Utilizing Chitosan-Based Nanoparticles for Pulmonary Drug Administration. ODU Med J, 2024;11(2): 99-114.

Address for correspondence/reprints:

Gamze Mercan

Telephone number: +90 (312) 338 16 38

E-mail: gmercn@gmail.com

INTRODUCTION

Lung diseases rank among the top 10 global causes of mortality, with Chronic Obstructive Pulmonary Disease (COPD), lower respiratory tract infections, and lung cancer standing as the third, fourth, and sixth leading causes of death, respectively (1). The advent of the COVID-19 pandemic has further exacerbated respiratory-related fatalities, with the surge in severe respiratory symptoms and associated complications among individuals infected with SARS-CoV-2 (1,2). Additionally pandemic control measures, such as social distancing and lockdowns, may have contributed to delays in diagnosing and treating non-coronavirus-related lung diseases, elevating the risks of complications and mortality associated with these conditions (3).

Consequently, there has been a heightened focus on the research and development of Pulmonary Drug Delivery Systems (PDDS) in recent years to optimize the treatment of lung diseases. PDDS offers several advantages, including targeted local treatment, maintaining high drug concentrations in the lungs for enhanced therapeutic efficacy, controlled drug release, and improved patient compliance (4). However, delivering drugs to the lungs presents significant challenges, necessitating the overcoming of mechanical, chemical, and immunological barriers of the respiratory tract (5,6). Various strategies, including nanostructured carriers, have been developed to address these challenges, capitalizing on their reduced size and increased surface-to-volume ratio to facilitate effective drug absorption and mitigate lung clearance (7,8,9).

Among nanostructures, polymeric nanoparticles, particularly those made from chitosan (CS), have gained widespread attention due to their biocompatibility, biodegradability, low toxicity, and scalability (10,11,12,13). CS, a natural polymer, stands out for drug delivery applications, especially in pulmonary delivery, owing to its inherent properties, such as mucoadhesive potential, and antimicrobial, anti-inflammatory, antioxidant, and wound-healing activities (14,15). Furthermore, the FDA has recognized CS as

"GenerallyRecognized as Safe" (GRAS), approving its use in tissue engineering and drug delivery devices (16).

CS nanoparticles exhibit the capacity to enhance drug stability, prolong action duration, control drug release, optimize dissolution of poorly soluble drugs, and increase cell membrane permeability for hydrophobic drugs. Additionally functionalization of CS nanoparticles can enhance adhesion to lung cells, enabling targeted drug delivery and minimizing systemic side effects (17). This advancement in drug delivery technology holds significant promise for treating chronic lung diseases like asthma and COPD, as well as improving drug delivery for bacterial and fungal infections and lung cancer.

Several studies support the potential of CS nanoparticles in diverse applications, including improving drug transport in a murine asthma model (18), enhancing in vivo lung deposition for COPD treatment (19), inhibiting *P. aeruginosa* biofilm (20), reducing inflammatory responses in cystic fibrosis (CF) (21), improving drug selectivity in lung cancer cells (22), increasing antituberculostatic drug concentration in the lung (15), and reducing systemic toxicity in severe COVID-19 infections (23,24,25).

This comprehensive review delves into the advantages and prospects of CS nanoparticles as pulmonary drug delivery systems, encompassing small molecule drugs, proteins/peptides, and genes for treating local lung diseases. The data collection spanned the years 2013 to 2023 and involved sources such as Scopus, Web of Science, Science Direct, PubMed, and Espacenet.

Challenges and Opportunities in Pulmonary Drug Delivery

The pulmonary route stands out as a promising avenue for drug administration, offering advantages over conventional dosage forms by allowing a reduction in the administered dose compared to oral and parenteral routes. Key characteristics of the pulmonary route, such as a substantial surface area (100 m^2), abundant blood supply, high permeability of the thin peripheral epithelial layer (0.2–0.7 μm), low enzymatic activity, and the avoidance of first-pass metabolism, contribute to its efficacy (26). Despite these advantages, challenges exist in harnessing the full therapeutic potential of pulmonary drug delivery, both for local and systemic treatments.

A significant obstacle in pulmonary drug delivery is the intricate clearance mechanisms that drugs encounter upon inhalation, acting as primary barriers to drug absorption. Mucociliary clearance, a crucial defense mechanism of the lung, entraps inhaled molecules in the mucus layer, impacting their solubility, diffusion across epithelial layers, and binding to cell surfaces or

receptors. Drugs unable to penetrate the mucus layer face removal through mucociliary clearance, emphasizing the importance of crossing this barrier to reach the alveolar epithelial layer (27). Particle properties, including size and surface area, play a vital role in determining the efficiency of drug delivery systems, prompting investigations into the use of (CS) nanoparticles. CS, known for its mucoadhesive properties, facilitates drug penetration through the mucus layer by interacting with mucin (28-29).

Pulmonary surfactant, a lipoprotein complex produced by alveolar cells, can enhance drug adhesion and agglutination, potentially increasing drug clearance from the lungs (30). Recent studies, however, suggest that pulmonary surfactant is not an insurmountable barrier and can serve as an effective vehicle for delivering both hydrophobic and hydrophilic compounds deep into the lungs (31,32).

Pulmonary macrophages present another challenge to drug efficacy in the lungs, particularly for particles in the size range of 0.5 to 5.0 µm, which are prone to internalization through endocytosis. Despite this challenge, recent research has identified pulmonary macrophages as a therapeutic target, particularly in the treatment of tuberculosis. For instance, Pawde and colleagues46 developed mannose-functionalized CS nanoparticles containing clofazimine for treating drug-resistant tuberculosis. The mannose-decorated nanoparticles facilitated increased recognition by macrophages, enhancing uptake and enabling targeted drug delivery to the site of Mycobacterium tuberculosis infection. This underscores the potential for overcoming challenges and leveraging opportunities in pulmonary drug delivery systems.

Physicochemical and Biological Properties of Chitosan

CS is a linear amino polysaccharide characterized by the repetition of 2-amino-2-deoxy-β-(1,4)-d-glucosamine and 2-acetamide-2-deoxy-β-(1,4)-d-glucosamine units, resulting from the partial deacetylation of chitin under alkaline conditions. Chitin, the precursor of CS, is composed of the polymer poly (β-(1,4)-N-acetyl-D-glucosamine) and is abundantly present in the exoskeleton of crustaceans, insects, arthropods, and the cell walls of fungi. Notably, marine chitin derived from sources such as shrimp, lobster, and crab stands as the primary commercially available source of CS (33,34).

CS stands as a linear polycationic polymer with free acetamide groups and hydroxyl functions attached to the glucopyranose rings. This structure, formed by the partial deacetylation of chitin, exhibits susceptibility to nucleophilic attacks. Selective modification of the free amino groups in CS results in a diverse range of

functionalities, distinguishing it from chitin. CS, derived primarily from marine chitin found in crustaceans, insects, arthropods, and fungi, offers superior hydrophilicity and reactivity compared to chitin. Additionally while chitin faces limitations due to its low aqueous solubility and reactivity, CS demonstrates enhanced hydrophilicity, excellent degradability, and biocompatibility (14,35).

CS is soluble in dilute acidic solutions, with solubility influenced by factors such as degree of deacetylation (DDA) and molecular weight (MW). However, exceeding the polymer's pKa results in deprotonation, causing CS to lose its positive charge and precipitate. The choice of acid for solubilization is critical, affecting physicochemical parameters like solubility, viscosity, ionic strength, and stability. Acetic acid is commonly used for adequate solubility, while citric acid and formic acid are alternative options. Acid selection can impact solution viscosity, ionic strength, and stability, affecting interactions with other compounds. Furthermore, acid type can influence CS nanoparticle formation through electrostatic interactions (36-41).

The crystallinity of CS, characterized by the crystallinity index (CI), involves the ratio of crystalline to amorphous fractions. CS exhibits semi-crystalline and polymorphic behavior, with CI influencing properties like swelling, porosity, hydration, and absorption. Molecular weight categorizes CS as low, medium, or high, impacting viscosity and solubility. Commercially available CS typically falls within the 50 to 2000 kDa range. The degree of deacetylation (DDA) plays a crucial role in determining CS's physicochemical properties, affecting solubility, viscosity, mechanical behavior, biodegradation, mucoadhesion, and antimicrobial activity. Reports indicate that mucoadhesive and antibacterial properties increase with higher DDA (42,43).

CS possesses various biological activities, including antimicrobial, antioxidant, anti-inflammatory, and anticancer properties. The antimicrobial mechanism involves interactions between positively charged CS molecules and negatively charged bacterial cell membranes, disrupting biofilms and causing cellular component leakage. Antioxidant activity involves the removal of free radicals, with CS exhibiting greater properties at lower molecular weights and higher DDA. Immunostimulatory effects result from the presence of N-acetyl-D-glucosamine groups, stimulating inflammatory cells and promoting cytokine production. CS also demonstrates anticancer activity by inhibiting proliferation, inducing apoptosis, and activating the immune system. CS's flexible structure, attributed to free protonable amino groups, enables easy modification and functionalization, making it a versatile polymer for nanoparticle development (17,44).

Preparation of Chitosan-Based Nanoparticles

Numerous methods have been devised for the synthesis of CS nanoparticles, with key approaches involving emulsification, precipitation, and ionic or covalent crosslinking, often implemented in combination (45). The initial method, utilizing covalent crosslinking with glutaraldehyde, was later discarded due to toxicity concerns and drug integrity issues (46-47).

Precipitation Methods

Phase Inversion Precipitation: Involves emulsification using an aqueous CS solution, stabilizer (poloxamer), and organic phase, followed by high-pressure homogenization and low-pressure evaporation for nanoparticle precipitation (48).

Desolvation: Entails coalescence of water-in-oil emulsions, promoting nanoparticle precipitation. Organic solvents and high-energy homogenization limit widespread use, and resultant nanoparticles are typically larger (31,44).

Widely adopted for its simplicity, cost-effectiveness, environmental friendliness, and scalability. Electrostatic interactions between CS's positively charged amino groups and negatively charged polyanions, like sodium tripolyphosphate (TPP), form nanospheres. Particle size can be adjusted by varying the CS/TPP ratio. Although advantageous, it may yield larger nanoparticles with high polydispersity, and pH changes can destabilize the system (45).

Based on covalent crosslinking, this method utilizes reverse micelles as nanoreactors. Crosslinkers, such as glutaraldehyde, connect CS chains to form interconnected polymer aggregates. The technique offers controlled particle size distribution, producing smaller nanoparticles (<100 nm) compared to ionic gelation. However, glutaraldehyde's cytotoxicity prompts the exploration of alternative crosslinking agents like genipin (46-48).

Considered environmentally friendly, it involves dissolving CS in aqueous acetic acid and passing the solution through a nozzle with hot air. Parameters like nozzle size, flow rate, and temperature influence nanoparticle properties. Drawbacks include longer processing time, larger particle size, and suitability issues for thermosensitive drugs (49-50).

CS can serve as a coating for various nanostructures such as liposomes, solid lipid nanoparticles, and polymeric nanoparticles. Integration can occur during or after nanoparticle preparation, with CS solution dripped onto nanoparticle suspensions. Coating mechanisms involve entanglement of polymer chains or electrostatic interaction between CS and nanoparticle surfaces (41-45).

Chitosan-Based Nanoparticles for Pulmonary Delivery

The utilization of CS nanoparticles for pulmonary delivery encounters challenges, primarily stemming from their proclivity to aggregate and undergo exhalation. To surmount these challenges and establish a stable, solid formulation, particle engineering techniques like freeze-drying and spray-drying have emerged as promising strategies. Incorporating carriers such as lactose and mannitol becomes crucial to producing dry inhalable powders, ensuring an optimal mean aerodynamic diameter for effective deposition in the alveoli, and preventing nanoparticle aggregation (48).

Given CS's intrinsic properties, including mucoadhesion, anti-inflammatory, and antimicrobial activities, CS nanoparticles offer significant advantages for local drug delivery to the lungs. These nanoparticles not only augment the antiviral (e.g., anti-SARS-CoV-2) and antibacterial (e.g., against M. tuberculosis) activities of encapsulated drugs but also facilitate drug penetration through the mucosal layer. Moreover, they enhance the anti-inflammatory effects of the drug and promote increased interaction/internalization in specific cells, such as macrophages and tumor cells.

Due to its unique properties and numerous advantages, several studies have been conducted to investigate the pulmonary delivery of drugs encapsulated in CS-based nanoparticles. A summary of key findings is presented in Table 1-2 (37-48).

Table 1. CS-based nanoparticles for pulmonary drug delivery

Disease	Drug	Limitations	Carrier	Main Results
Asthma	Ferulic Acid	Low bioavailability and short half-life	Hyaluronic acid-coated CS NP	Improved drug interaction and transport across the mucus layer; increased therapeutic efficacy
	Budesonide	Low bioavailability	CS-coated PLGA NP	Improved bioavailability and in vivo lung deposition in animal model
	Baicalein	Low bioavailability	CS NP	Nanoparticles control the immune-allergy-inflammatory response of asthma in mice
	Montelukast	Significant hepatic metabolism after oral administration	CS NP	DPI formulation showed Optimum deposition in the deep lung
COPD	Budesonide	Low aqueous solubility and bioavailability	CS NP	Enhancement of drug solubility
	Amikacin	Poor lung penetration after endovenous administration	PEG-CS NP combined with black phosphorus quantum dots	Improved mucus penetration and antibacterial activity
Pulmonary fibrosis	Nifedipine	Low bioavailability	CS-PLGA NP	Reduced markers of pulmonary fibrosis and oxidative stress
IPF	msFGFR2c	Low bioavailability	Phosphoryl-choline-CS NP	Enhanced antifibrotic efficacy, reduced inflammatory cytokines, decreased pulmonary fibrosis score and collagen deposition

Table 2. (Table 1, continuation)

Disease	Drug	Limitations	Carrier	Main Results
CF	Ciprofloxacin	Microbial resistance	ALG-lyase-functionalized CS NP	Higher inhibitory effect on P. aeruginosa biofilm
	wtCFTR-mRNA	Low stability; low transfection efficiency	CS-lecithin oil-core nanocapsules	Restored CFTR function in the cystic fibrosis cell line
	Antisense oligonucleotide (ASO)	Low stability	CS/ASO nanocomplex	Significant downregulation of ENaC activity in human respiratory epithelial cells
	Tobramycin	High frequency of administration; ototoxic and nephrotoxic effects; bacterial resistance	SLPICS-functionalized ALG/CS NP	Inhibition of P. aeruginosa in vitro; reduction in inflammatory response; improvement in interaction with CF mucus
Pulmonary fibrosis	Nifedipine	Low bioavailability	CS-PLGA NP	Reduced markers of pulmonary fibrosis and oxidative stress
PF	msFGFR2c	Low bioavailability	Phosphoryl-choline-CS NP	Enhanced antifibrotic efficacy, reduced inflammatory cytokines, decreased pulmonary fibrosis score and collagen deposition
CF	Ciprofloxacin	Microbial resistance	ALG-lyase-functionalized CS NP	Higher inhibitory effect on P. aeruginosa biofilm
	wtCFTR-mRNA	Low stability; low transfection efficiency	CS-lecithin oil-core nanocapsules	Restored CFTR function in the cystic fibrosis cell line
	Antisense oligonucleotide (ASO)	Low stability	CS/ASO nanocomplex	Significant downregulation of ENaC activity in human respiratory epithelial cells
	Tobramycin	High frequency of administration; ototoxic and nephrotoxic effects; bacterial resistance	SLPICS-functionalized ALG/CS NP	Inhibition of P. aeruginosa in vitro; reduction in inflammatory response; improvement in interaction with CF mucus
	Ciprofloxacin	Microbial resistance	DNase-I-functionalized CS NP	Prolonged microbial inhibition, prevention of biofilm formation and biofilm dispersal potential
Lung cancer	Resveratrol	Low solubility	CS/lecithin nanocomplex	Enhanced antitumor activity; increased selectivity in A549 cells
	aPD-L1	Low stability; unwanted adverse effects	CS/aPD-L1 nanocomplex	Improved lung adhesion and permeation; enhanced therapeutic efficacy
Tuberculosis	Bedaquiline	Prolonged treatment; unwanted adverse effects	CS NP	Reduction in toxic effects; Increased drug concentration in the lungs
	Linezolid	Unwanted adverse effects	CS NPs	Improved deep lung deposition in vitro
Pneumonia	Gallium.Ga(III)	Nephrotoxicity	Hyaluronic acid-CS NP	Improvement in Ga(III) persistence in the lungs and preventing its accumulation in the kidney
	Gentamicin	Low bioavailability; unwanted adverse effects	CS/Fucoidan NP	Improved antibacterial activity; reduced systemic toxicity
RSV	Oxymatrine	Enzymatic degradation; poor lung penetration	CS-coated liposomes	Enhanced distribution and retention of oxymatrine in lung tissue in vivo
COVID-19	Silymarin and curcumin	Low penetration and adsorption in the lungs	CS-coated BSA NP	Reduced inflammation; enhanced antiviral activity in vitro

Asthma

Asthma is a complex respiratory disease characterized by irreversible airway obstruction, hyperresponsiveness, and chronic inflammation. Conventional treatments involve bronchodilators and glucocorticosteroids, but high doses can be clinically ineffective and harmful (18). Dhayanandamoorthy et al. developed CS nanoparticles loaded with ferulic acid (FA) and functionalized with hyaluronic acid (HA) for asthma prophylaxis. These nanoparticles, called FACHA, were aerosolized using a vibrating mesh nebulizer. In mouse models of ovalbumin-induced asthma, FACHA nanoparticles attenuated inflammation, hypersensitivity, and airway remodeling. Compared to free FA, FACHA nanoparticles exhibited superior therapeutic indices, attributed to HA-functionalized CS promoting better deposition and an improved therapeutic index of HA (19).

Budesonide (BUD), a poorly bioavailable drug used in asthma treatment, was loaded into CS-poly(lactic-co-glycolic acid) (PLGA) nanoparticles by Ahmad et al. The BUD-loaded nanoparticles (BUD-NP) demonstrated lung deposition and penetration. Inhalation of BUD-NP resulted in higher Cmax and AUC compared to oral and intravenous treatment groups. The improvement in BUD absorption was linked to the induction of intercellular tight junction openings within the lung epithelium facilitated by CS (20).

CS nanoparticles were also employed for the pulmonary delivery of baicalein, a flavonoid with anti-inflammatory properties. Baicalein-CS nanoparticles controlled eosinophilic inflammation, airway hyperresponsiveness, and immune-allergic responses in mouse models of asthma. The nanoparticles downregulated IL-5 levels, contributing to better-managed inflammation (49).

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a progressive inflammatory lung disease resulting in decreased lung function. Anti-inflammatory therapies, including corticosteroids like BUD, are commonly used. BUD-loaded CS nanoparticles (CS NP) were developed using ionic gelation with poly(vinyl alcohol) (PVA) as a surfactant. The spherical nanoparticles exhibited improved drug release in vitro, demonstrating potential for enhanced therapeutic outcomes in COPD.121 Black phosphorus quantum dots (BPQDs) associated with PEGylated CS nanospheres were used to deliver amikacin (AM) for treating pulmonary infections in COPD patients. The nanostructure exhibited mucoadhesive properties, facilitating mucus penetration and resulting in higher drug release due to the rapid degradation of BPQDs. This approach alleviated airflow obstruction in a COPD mice model (40-42).

Pulmonary Fibrosis

Pulmonary fibrosis involves the remodeling and destruction of lung tissue. Nifedipine, a calcium channel blocker, loaded into CS-PLGA nanoparticles, demonstrated promise for treating pulmonary fibrosis. The nanoparticles exhibited a spherical shape, improved drug release, enhanced lung deposition, and increased bioavailability. Engineered nanoparticles reduced lung fibrotic and oxidative stress markers, demonstrating potential therapeutic benefits (23). Phosphorylcholine-coated CS nanoparticles (PPCs-NPs) were developed to encapsulate the mutant soluble ectodomain of fibroblast growth factor receptor-2 IIIc (msFGFR2c) protein, targeting excessive myofibroblast differentiation in idiopathic pulmonary fibrosis (IPF). The nanoparticles significantly reduced α-smooth muscle actin (α-SMA) expression, a marker of myofibroblast differentiation. In vivo studies showed increased msFGFR2c bioavailability, improved therapeutic efficacy, and enhanced rat survival rates (24). These studies highlight the potential of CS nanoparticles in addressing various respiratory conditions, providing targeted and controlled drug delivery for improved therapeutic outcomes.

Cystic Fibrosis (CF)

CF is characterized by impaired mucociliary clearance due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leading to mucus retention, bacterial infection, inflammation, and airway obstruction. Patel et al. investigated ciprofloxacin-loaded alginate lyase functionalized-CS nanoparticles against mucoid P. aeruginosa biofilm. The alginate lyase disrupted bacterial mucus, enhancing ciprofloxacin delivery. The nanoparticles had suitable properties for pulmonary drug delivery, demonstrating antimicrobial and anti-biofilm potential (20).

Lung Cancer

Chemotherapy remains the primary treatment for advanced lung cancer, but traditional drugs face limitations like lack of targetability, low bioavailability, and severe side effects (21). CS nanoparticles are explored for cancer therapy due to their mucoadhesiveness, controlled release, targeting, and increased permeability into tumor cells. Kamel et al. developed CS-doped self-assembled lecithin-based cationic nanoparticles (LeciPlex) loaded with resveratrol, aiming to improve solubility and anticancer efficacy (22). The study reported enhanced anticancer effects, low toxicity, and increased selectivity against the A549 lung cancer cell line (23).

In another study, CS nanoparticles loaded with anti-programmed cell death protein ligand 1 (aPD-L1) were prepared for inhalation to treat lung cancer. CS facilitated transmucosal delivery, promoting the rapid accumulation of

aPD-L1 in lung metastasis. CS acted as an adjuvant for aPD-L1, inducing potent cell-mediated immune responses and reducing the number of metastases in the lungs (48).

These studies showcase the potential of CS nanoparticles in addressing challenges associated with CF and lung cancer, providing targeted and effective drug delivery strategies.

CONCLUSION

Due to the rising mortality associated with respiratory diseases like COVID-19, tuberculosis, and lung cancer, there has been a growing emphasis on developing innovative systems for delivering drugs to the lungs. In this context, nanostructured carriers, particularly CS nanoparticles, have gained attention as a promising alternative. The progress in pulmonary drug delivery using CS has been noteworthy, demonstrating significant achievements.

CS, widely acknowledged as a renewable resource, second only to cellulose, possesses distinctive properties, including being non-toxic, biocompatible, and biodegradable. These attributes provide a competitive edge over other biodegradable polymers, with mucoadhesive, anti-inflammatory, and antimicrobial activities. The antimicrobial properties of CS can be harnessed to combat resistance, such as in P. aeruginosa infections, while its anti-inflammatory nature may aid in reducing inflammation in severe acute respiratory syndrome. This review critically examines the advancements of CS-based nanoparticles as an inhaled drug delivery system.

These nanoparticles exhibit considerable potential for clinical use, offering benefits like improved local drug delivery, minimized side effects, enhanced therapeutic activity, and prolonged drug release. The promising results evaluated in this review highlight the ability of CS nanoparticles, when administered via inhalation, to address the significant challenge of drug clearance from the lungs. Several in vivo studies have reported an increase in drug deposition in the lungs, attributed to the crucial mucoadhesive property of CS, facilitating drug penetration through the mucus layer. Furthermore, CS nanoparticles optimize biopharmaceutical parameters, particularly solubility, contributing to increased bioavailability, with some studies reporting a reduction in systemic toxicity.

Moreover, CS nanoparticles enhance the therapeutic activity of drugs, particularly in terms of antibacterial activity against CF-related pathogens, antiviral activity against SARS-CoV-2, and anti-inflammatory activity needed for treating conditions like COPD, IPF, and CF. Collectively, these observed benefits position CS as a polymer with the most promising properties for the development of

nanocarriers for pulmonary drug delivery applications.

Nevertheless, further studies are imperative to establish scalable processes for CS nanoparticle preparation. Additionally surface engineering of CS nanoparticles using specific ligands should be explored to actively target these particles to specific lung sites. Comprehensive investigations into the pharmacokinetics, preclinical toxicity, and biodistribution parameters of CS nanoparticles are essential steps to move closer to conducting clinical trials.

Ethics Committee Approval: Ethics committee permission was required for the research to be combined and distributed appropriately. not received.

Author Contributions:

Concept: Design: Literature search: Data Collection and Processing: Analysis or Interpretation: Written by: GM, ZVS.

Declaration of Interests: None of the authors have potential conflicts of interest to be disclosed.

Funding: No financial support was received for this research.

REFERENCES

1. Frick C, Rumgay H, Vignat J, et al. Quantitative estimates of preventable and treatable deaths from 36 cancers worldwide: A population-based study. Lancet Glob. Health. 2023;11:e1700–e1712.
2. Sung H, Ferlay J, Siegel R.L, , et al. Global Cancer Statistics. 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J. Clin.. 2021; 71:209–249.
3. Zhong L, Li Y, Xiong L, et al. Small molecules in targeted cancer therapy: Advances challenges and future perspectives. Signal Transduct. Target. Ther. 2021; 6: 201.
4. Riley R.S, June C.H, Langer R, et al. Delivery technologies for cancer immunotherapy. Nat. Rev. Drug Discov.. 2019; 18: 175–196.
5. Schaue D, McBride W.H. Opportunities and challenges of radiotherapy for treating cancer. Nat. Rev. Clin. Oncol.. 2015;12:527–540.
6. Bariwal J, Ma H, Altenberg G.A, et al. Nanodiscs: A versatile nanocarrier platform for cancer diagnosis and treatment. Chem. Soc. Rev. 2022;51:1702–1728.
7. Cheng Z, Li M, Dey R, et al. Nanomaterials for cancer therapy: Current progress and perspectives. J. Hematol. Oncol. 2021; 14: 85.
8. Zeng L, Gowda B.H.J, Ahmed M.G, , et al. Advancements in nanoparticle-based

treatment approaches for skin cancer therapy. Mol. Cancer. 2023;22:10.

9. Pei Z, Chen S, Ding L, et al. Current perspectives and trend of nanomedicine in cancer: A review and bibliometric analysis. J. Control. Release. 2022; 352:211–241.
10. Wang Y, Zhang K, Qin X, et al. Biomimetic Nanotherapies: Red Blood Cell Based Core-Shell Structured Nanocomplexes for Atherosclerosis Management. Adv. Sci. 2019; 6: 1900172.
11. Deng G, Sun Z, Li S, et al. Cell-Membrane Immunotherapy Based on Natural Killer Cell Membrane Coated Nanoparticles for the Effective Inhibition of Primary and Abscopal Tumor Growth. ACS Nano. 2018; 12: 12096–12108.
12. Wei X, Gao J, Fang R.H, et al. Nanoparticles camouflaged in platelet membrane coating as an antibody decoy for the treatment of immune thrombocytopenia. Biomaterials. 2016; 111:116–123.
13. Li J, Ai Y, Wang L, et al. Targeted drug delivery to circulating tumor cells via platelet membrane-functionalized particles. Biomaterials. 2016; 76: 52–65.
14. Solari F.A, Krahn D, Swieringa F, et al. Multi-omics approaches to study platelet mechanisms. Curr. Opin. Chem. Biol. 2023; 73: 102253.
15. Sekhon U.D.S, Swingle K, Girish A, et al. Platelet-mimicking procoagulant nanoparticles augment hemostasis in animal models of bleeding. Sci. Transl. Med. 2022; 14: eabb8975.
16. Gay L.J, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat. Rev. Cancer. 2011; 11: 123–134.
17. Lavergne M, Janus-Bell E, Schaff M, et al. Platelet Integrins in Tumor Metastasis: Do They Represent a Therapeutic Target? Cancers. 2017; 9: 133.
18. Liang Y, Mak JC. Inhaled therapies for asthma and chronic obstructive pulmonary disease. Curr Pharm Des. 2021;27(12):1469-1481.
19. Dhayanandamoorthy Y, Antoniraj MG, Kandregula CAB, Kandasamy R. Aerosolized hyaluronic acid decorated, ferulic acid loaded chitosan nanoparticle: A promising asthma control strategy. Int J Pharm. 2020;591:119958.
20. Ning S, Zhang T, Lyu M, et al. A type I AIE photosensitiser-loaded biomimetic nanosystem allowing precise depletion of cancer stem cells and prevention of cancer recurrence after radiotherapy. Biomaterials. 2023; 295: 122034.
21. Zheng X, Song X, Zhu G, Pan D, Li H, Hu J, et al. Nanomedicine combats drug resistance in lung cancer. Adv Mater. 2024;36(3):2308977.

22. Narmani A, Jafari SM. Chitosan-based nanodelivery systems for cancer therapy: Recent advances. Carbohydr Polym. 2021;272:118464.
23. Butcher K, Kannappan V, Kilari RS, Morris MR, McConville C, Armesilla AL, Wang W. Investigation of the key chemical structures involved in the anticancer activity of disulfiram in A549 non-small cell lung cancer cell line. BMC Cancer. 2018;18(1):1-12.
24. Gao C, Wu Z, Lin Z, et al. Polymeric capsule-cushioned leukocyte cell membrane vesicles as a biomimetic delivery platform. Nanoscale. 2016;8: 3548–3554.
25. Diakos C.I, Charles K.A, McMillan D.C, et al. Cancer-related inflammation and treatment effectiveness. Lancet. Oncol. 2014; 15: e493–e503.
26. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature. 2008; 454: 436–444.
27. Wynn T.A, Vannella K.M. Macrophages in Tissue Repair Regeneration and Fibrosis. Immunity. 2016; 44: 450–462.
28. Chan J.D, Lai J, Slaney C.Y, et al. Cellular networks controlling T cell persistence in adoptive cell therapy. Nat. Rev. Immunol. 2021; 21: 769–784.
29. Restifo N.P, Dudley M.E, Rosenberg S.A. Adoptive immunotherapy for cancer: Harnessing the T cell response. Nat. Rev. Immunol. 2012; 12: 269–281.
30. Siska P.J, Rathmell J.C. T cell metabolic fitness in antitumor immunity. Trends Immunol. 2015; 36: 257–264.
31. Kang M, Hong J, Jung M, et al. T-Cell-Mimicking Nanoparticles for Cancer Immunotherapy. Adv. Mater.. 2020; 32: e2003368.
32. Liu T, Zhou Z, Zhang M, et al. Cuproptosis-immunotherapy using PD-1 overexpressing T cell membrane-coated nanosheets efficiently treats tumor. J. Control. Release. 2023: 362; 502–512.
33. Wang W, Wu F, Mohammadniaei M, et al. Genetically edited T-cell membrane coated AIEgen nanoparticles effectively prevents glioblastoma recurrence. Biomaterials. 2023; 293: 121981.
34. O'Brien K.L, Finlay D.K. Immunometabolism and natural killer cell responses. Nat. Rev. Immunol. 2019; 19: 282–290.
35. Wu S.Y, Fu T, Jiang Y.Z, et al. Natural killer cells in cancer biology and therapy. Mol. Cancer. 2020;19 : 120.
36. Zhang L, Zhang Y, Wang X, et al. A Trojan-Horse-Like Biomimetic Nano-NK to Elicit an Immunostimulatory Tumor Microenvironment for Enhanced GBM Chemo-Immunotherapy. Small. 2023; 19: e2301439.

37. Galipeau J, Sensébé L. Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities. Cell Stem Cell. 2018; 22: 824–833.
38. Lan T, Luo M, Wei X. Mesenchymal stem/stromal cells in cancer therapy. J. Hematol. Oncol. 2021; 14:195.
39. Timaner M, Letko-Khait N, Kotsofruk R, et al. Therapy-Educated Mesenchymal Stem Cells Enrich for Tumor-Initiating Cells. Cancer Res.. 2018; 78: 1253–1265.
40. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2016;138(1):16-27.
41. Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy?. Int J Chron Obstruct Pulmon Dis. 2018;13:2587-2601.
42. Larj MJ, Bleecker ER. Therapeutic responses in asthma and COPD: corticosteroids. Chest. 2004;126(2 Suppl):138S-149S.
43. Yang N, Ding Y, Zhang Y, et al. Surface Functionalization of Polymeric Nanoparticles with Umbilical Cord-Derived Mesenchymal Stem Cell Membrane for Tumor-Targeted Therapy. ACS Appl. Mater. Interfaces. 2018; 10: 22963–22973.
44. Gao C, Lin Z, Jurado-Sánchez B, et al. Stem Cell Membrane-Coated Nanogels for Highly Efficient In Vivo Tumor Targeted Drug Delivery. Small. 2016; 12: 4056–4062.
45. Park J.Y, Park J.Y, Jeong Y.G, et al. Pancreatic Tumor-Targeting Stemsome Therapeutics. Adv. Mater. 2023; 35:e2300934.
46. Chen Q, Zhang L, Li L, et al. Cancer cell membrane-coated nanoparticles for bimodal imaging-guided photothermal therapy and docetaxel-enhanced immunotherapy against cancer. J. Nanobiotechnol. 2021; 19: 449.
47. Zeng Y, Li S, Zhang S, et al. Cell membrane coated-nanoparticles for cancer immunotherapy. Acta Pharm. Sin. B. 2022; 12: 3233–3254.
48. Zacaron TM, Silva MLSE, Costa MP, Silva DME, Silva AC, Apolônio ACM, et al. Advancements in chitosan-based nanoparticles for pulmonary drug delivery. Polymers (Basel). 2023;15(18):3849.
49. Li Z, Cai H, Li Z, et al. A tumor cell membrane-coated self-amplified nanosystem as a nanovaccine to boost the therapeutic effect of anti-PD-L1 antibody. Bioact. Mater.2023; 21: 299–312.
50. Xiong J, Wu M, Chen J, et al. Cancer-Erythrocyte Hybrid Membrane-Camouflaged Magnetic Nanoparticles with Enhanced Photothermal-Immunotherapy for Ovarian Cancer. ACS Nano. 2021; 15: 19756–19770.

51. Cui J, Zhang F, Yan D, Han T, Wang L, Wang D, Tang B.Z. “Trojan Horse” Phototheranostics: Fine-Engineering NIR-II AIEgen Camouflaged by Cancer Cell Membrane for Homologous-Targeting Multimodal Imaging-Guided Phototherapy. Adv. Mater. 2023; 35: e2302639.